OXTELLAR XR (oxcarbazepine) extended-release tablets

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)

DOSE 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 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)

DOSE 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)

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)

ADVERSE REACTIONS

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

DRUG INTERACTIONS

- Phenytoin, Carbamazepine, and Phenytoin Carboxamides: Avoid concomitant use of Oxtellar XR™ and Phenytoin. Use of Withdrawal of Oxtellar XR™ should be reduced by 50% (7.2)

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™: Withdraw gradually (5.6)
- Multi-Organ Hypersensitivity: Discontinue if suspected (5.7)
- Hematologic Reactions: Discontinue if suspected (5.8)

DRUG ABUSE AND DEPENDENCE

- Pregnancy: Plasma levels of active metabolite may be decreased. Monitor patients. Based on animal data, may cause fetal harm. (5.9, 8.1).

OVERDOSAGE

- 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

PATIENT COUNSELING INFORMATION

- See 17 for PATIENT COUNSELING INFORMATION and Medication Guide
- Revised: October 2012

Full Prescribing Information:

- 1 INDICATIONS AND USAGE
- 2 DOSAGE AND ADMINISTRATION
- 3 DOSAGE FORMS AND STRENGTHS
- 4 CONTRAINDICATIONS
- 5 WARNINGS AND PRECAUTIONS
- 6 ADVERSE REACTIONS
- 7 DRUG INTERACTIONS

Full Prescribing Information:

- Oxtellar XR™ is indicated as adjunctive therapy of partial seizures in adults and in children 6 years to 17 years of age.
- 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).
- 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.
- In pediatric patients 6 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>
<thead>
<tr>
<th>Weight</th>
<th>Target Daily Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>20 kg to 29 kg</td>
<td>900 mg per day</td>
</tr>
<tr>
<td>29.1 kg to 39 kg</td>
<td>1200 mg per day</td>
</tr>
<tr>
<td>Greater than 39 kg</td>
<td>1800 mg per day</td>
</tr>
</tbody>
</table>

- 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-monoxyhydroxy 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 (5.5)].

- 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 (12.5)].
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 CONTRAINICATIONS
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 dosages 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 or restricted. Post-marketing cases of symptomatic hyponatremia have been reported during post-market 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 and 1800 mg, respectively, experienced low serum sodium concentrations (125 and 126 mEq/L), respectively, 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 low enough to lower sodium concentrations to Low (<135 mEq/L) were observed for 3 months (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, unsteadiness, confusional state). 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 patients treated with immediate-release oxcarbazepine who have a history of hypersensitivity reactions to carbamazepine may also 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 in 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 treatment with immediate-release oxcarbazepine use. The median time of onset for reported cases was 19 days. Such reactions may be very severe, requiring hospitalization with very rare reports of fatal outcome. Recurrence of the serious skin reactions may be life threatening, and some patients have required discontinuation from treatment. The overall incidence of serious skin reactions, including SJS and TEN, in trials compared to placebo was 7.9 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, 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>
<thead>
<tr>
<th>Indication</th>
<th>Placebo Patients with Events per 1,000 Patients</th>
<th>Drug Patients with Events per 1,000 Patients</th>
<th>Relative Risk: Incidence of Events in Drug Patients/Incidence in Placebo Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epilepsy</td>
<td>1.0</td>
<td>3.4</td>
<td>3.5</td>
</tr>
<tr>
<td>Psychiatric</td>
<td>5.7</td>
<td>8.5</td>
<td>1.5</td>
</tr>
<tr>
<td>Other</td>
<td>1.0</td>
<td>1.8</td>
<td>1.9</td>
</tr>
<tr>
<td>Total</td>
<td>2.4</td>
<td>4.3</td>
<td>1.8</td>
</tr>
</tbody>
</table>

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.

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), skin and soft tissue (e.g., dermatitis, pemphigus, purpura, necrosis), muscle and joint (e.g., joint swelling, myalgia, arthralgia, asthma), nervous system (e.g., leukopenia, encephalopathy), respiratory (e.g., dyspnea, pulmonary edema, asthma, bronchospasm, interstitial lung disease), hepatic portal 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 for an increased risk of seizures. In clinical trials, the risk of seizures was similar for the epilepsy and psychiatric indications.

6 ADVERSE REACTIONS

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

- Hypnotenamia [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)]
- 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 another drug 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.
Adverse Reactions Associated with Discontinuation of Oxtellar XR™ Adjunctive Therapy with Oxtellar XR™ in Pediatric Patients 4 to 16 Years Old Previously Treated

nausea (3.7%), diplopia (3.2%), and somnolence (2.4%). Oxtellar XR™ were similar to those seen in adults.

Oxcarbazepine and Oxtellar XR™ were not examined in the same trial, adverse event frequencies in placebo with concomitant AEDs and that were numerically more common in the patients treated with ≥2% of adult patients with epilepsy treated with immediate-release oxcarbazepine or placebo with concomitant AEDs 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.

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 ≥2%) were: dizziness (9.8%), vomiting (5.3%), nausea (3.7%), diplopia (3.2%), and somnolence (2.4%).

Adjuvantive 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 Oxtellar XR™ with Concomitant AEDs in Adults*  

<table>
<thead>
<tr>
<th>Immediate-Release Oxcarbazepine Dosage (mg/day)</th>
<th>OXC 600 N = 163</th>
<th>OXC 1200 N = 171</th>
<th>OXC 2400 N = 126</th>
<th>Placebo N = 166</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>%</td>
<td>%</td>
<td>%</td>
<td>%</td>
</tr>
<tr>
<td><strong>Body as a Whole</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>15</td>
<td>12</td>
<td>15</td>
<td>7</td>
</tr>
<tr>
<td>Fatigue</td>
<td>6</td>
<td>3</td>
<td>6</td>
<td>5</td>
</tr>
<tr>
<td>Edema Legs</td>
<td>2</td>
<td>1</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Weight Increase</td>
<td>1</td>
<td>2</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td><strong>Cardiovascular System</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypotension</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td><strong>Digestive System</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>15</td>
<td>25</td>
<td>29</td>
<td>10</td>
</tr>
<tr>
<td>Vomiting</td>
<td>13</td>
<td>25</td>
<td>36</td>
<td>5</td>
</tr>
<tr>
<td>Pain Abdominal</td>
<td>10</td>
<td>13</td>
<td>11</td>
<td>5</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>5</td>
<td>6</td>
<td>7</td>
<td>6</td>
</tr>
<tr>
<td>Dysepsia</td>
<td>5</td>
<td>6</td>
<td>6</td>
<td>2</td>
</tr>
<tr>
<td>Constipation</td>
<td>2</td>
<td>2</td>
<td>6</td>
<td>4</td>
</tr>
<tr>
<td>Gastritis</td>
<td>2</td>
<td>1</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td><strong>Metabolic and Nutritional Disorders</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyponotamia</td>
<td>3</td>
<td>1</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td><strong>Musculoskeletal System</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Muscle Weakness</td>
<td>1</td>
<td>2</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Sprains and Strains</td>
<td>0</td>
<td>2</td>
<td>2</td>
<td>1</td>
</tr>
</tbody>
</table>

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

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.

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, hematemeses, hemorrhage rectum, hemmorhoids, 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, hypoproteinemia, liver enzymes elevated, serum transaminase increased.

Musculoskeletal System: hypotonia 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, hypoaesthesia, hypokinesia, hyporeflexia, hypotonia, hysteria, libido decreased, libido increased, manic reaction, migraine, muscle contractions involuntary, nervousness, neuropsy, ocu-lo-cerebral reactions, panic disorder, paralysies, paraplegia, personality disorder, psychosis, plosis, stupor, tetany.

Respiratory System: asthma, bronchitis, coughing, dyspepsia, epistaxis, laryngismus, pleurisy.

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

Special Senses: accommodation abnormal, cataract, conjunctival hemorrhage, edema eye, hemianopia, mydriasis, ophthalmia externa, photophobia, scotoma, state of transplantion, tinnitus, xerophallacia.

Urogenital and Reproductive System: dysuria, hematuria, intermenstrual bleeding, leukorrhea, meningitis, 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 (6.7)].
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

<table>
<thead>
<tr>
<th>AED</th>
<th>Coadministered (daily dose)</th>
<th>IR-oxcarbazepine (daily dose)</th>
<th>Influence of IR-oxcarbazepine on AED Concentration (90% Confidence Interval)</th>
<th>Influence of AED on MHD Concentration (90% Confidence Interval)</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbamazepine</td>
<td>900 mg</td>
<td>nc</td>
<td>40% decrease [Cl: 17% decrease, 57% decrease]</td>
<td>Consider initiating Oxtellar XR™ at a higher dose.</td>
<td></td>
</tr>
<tr>
<td>Phenytoin</td>
<td>600 – 1800 mg</td>
<td>14% increase [Cl: 2% increase, 24% increase]</td>
<td>25% decrease [Cl: 12% decrease, 51% decrease]</td>
<td>Monitor and titrate dose to desired clinical effect (see 2.6)</td>
<td></td>
</tr>
<tr>
<td>Phenytoin</td>
<td>250 – 500 mg</td>
<td>up to 40% increase</td>
<td>30% decrease [Cl: 3% decrease, 46% decrease]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Valproic Acid</td>
<td>600-1800 mg</td>
<td>nc</td>
<td>18% decrease [Cl: 13% decrease, 40% decrease]</td>
<td>Monitor, Dose adjustment of Oxtellar XR™ may not be needed.</td>
<td></td>
</tr>
</tbody>
</table>

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 [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 [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 animal studies. This fact, and the results of the animal studies described, 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 (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 [MHD] 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 maternal 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 MHD 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 MHD 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 MHD on a mg/m² basis).

To provide information regarding the effects of uterine exposure to Oxtellar XR™, physicians are advised to recommend that pregnant patients taking Oxtellar XR™ enroll in the NAEEF 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 [Clinical Studies (14.1)].
2) A pharmacokinetic study of Oxtellar XR™ in pediatric patients ages 4 to 16 years [Clinical Pharmacology (12.3)], and
3) Safety and efficacy studies with the immediate-release formulation in adults and pediatric patients [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 [Dosage and Administration (2.5)].

8.5 Renal Impairment

There is a linear correlation between creatinine clearance and the renal clearance of MHD. [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 [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 [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. [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-dibenzo(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 6, 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 C₂₅H₂₄N₂O₂ 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-monoxygen hydroxymetabolite (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 anticonvulsive effects of the drug. No significant interactions of oxcarbazepine or MHD with brain neurotransmitter or modulator receptor sites have been demonstrated.

12.2 Pharmacokinetics

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.

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 120% higher by 25% by 29% to 32% than 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 tablets), the pharmacokinetics of MHD are not influenced by the presence of food. 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 responsible for most antiepileptic activity. Following oral administration, oxcarbazepine is absorbed and extensively metabolized to its pharmacologically active 10-monoxygen hydroxymetabolite (MHD), which is primarily metabolized further to glucuronides of MHD (49%) or as unchanged MHD (27%); the inactive DHD 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 less than 4% of an administered dose. The inactive DHD accounts for less than 4% of an administered dose. The maximum plasma concentration and AUC values of oxcarbazepine and MHD do not bind to alpha-1-acid glycoprotein. No significant interactions of oxcarbazepine or MHD with brain neurotransmitter or modulator receptor sites have been demonstrated.

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 oxcarbazepine 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 with 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 heptically 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

Drug interaction biological changes during pregnancy, MHD plasma levels may gradually decrease throughout pregnancy [see Use in Specific Populations (8.1)].

Drug Interaction Studies

In Vito: 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 demonstrated that oxcarbazepine and its pharmacologically active 10-monoxygen metabolite (MHD) have little or no capacity to function as inhibitors or inhibitors of the hepatic P450 enzymes or inhibitors of the hepatic P450 enzymes or inhibitors of the hepatic P450 enzymes or inhibitors of the hepatic P450 enzymes or inhibitors of the hepatic P450 enzymes or inhibitors of the hepatic P450 enzymes or inhibitors of the hepatic P450 enzymes or inhibitors of the hepatic P450 enzymes or inhibitors of the hepatic P450 enzymes or inhibitors of the hepatic P450 enzymes or inhibitors of the hepatic P450 enzymes. In addition, coadministration of immediate-release oxcarbazepine with the oral contraceptive has been evaluated in severe hepatic impairment, and therefore it is not recommended in these patients [see Use in Specific Populations (8.6)].

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-glucuronontransferase 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-glucuronotransferase, it is unlikely to have an effect on drugs that are mainly eliminated by conjugation through UDP-glucuronontransferase (e.g., diazepam, lamotrigine).

In addition, oxcarbazepine and MHD induce a subgenus 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:

Drug interaction biological changes during pregnancy, MHD plasma levels may gradually decrease throughout pregnancy [see Use in Specific Populations (8.1)].

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 49% [90% CI: 22-63] in one study and 52% [90% CI: 38-62] in another study. The mean AUC values of LNG were decreased by 48% [90% CI: 22-63] in one study and 52% [90% CI: 38-62] in another study. The mean AUC values of LNG were decreased by 48% [90% CI: 22-63] in one study and 52% [90% CI: 38-62] 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: 20-32]. Verapamil produced a decrease of 20% [90% CI: 16-22] of the plasma levels of MHD after coadministration with immediate-release oxcarbazepine.

Other Interactions

Clopidogrel, erythromycin and dextropropoxyphene had no effect on the pharmacokinetics of oxcarbazepine 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 hepatic 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 hepatic adenomas 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 hepatic 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, 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 chromosome aberrations and polychromatolytic in 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 lung 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, estrus cyclicality 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 an 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 mg or 2400 mg/day) or placebo.

Table 6 presents the primary efficacy results by treatment group.

<table>
<thead>
<tr>
<th>Oxtellar XR™</th>
<th>Median seizure frequency during 8-week baseline period (per 29 days)</th>
<th>Median seizure frequency during 16-week treatment period (per 29 days)</th>
<th>Median percent change in seizure frequency</th>
<th>Seizure frequency percent change effect size</th>
<th>P value vs placebo*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>7.0</td>
<td>5.0</td>
<td>-28.7%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oxtellar XR™ 1200mg/day (N=122)</td>
<td>6.0</td>
<td>4.3</td>
<td>-38.2%</td>
<td>9.5%</td>
<td>0.078</td>
</tr>
<tr>
<td>Oxtellar XR™ 2400mg/day (N=123)</td>
<td>6.0</td>
<td>3.7</td>
<td>-42.9%</td>
<td>14.2%</td>
<td>0.003</td>
</tr>
</tbody>
</table>

*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 600 mg per day, 1200 mg per day and 2400 mg per day (dosed twice daily) in a randomized, double-blind, placebo-controlled trial. All doses resulted in a statistically significant reduction in seizure frequency 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 (5.6)].

- 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