OXTELLAR XR® (oxcarbazepine) extended-release tablets, for oral use

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 U.S. Approval: 2000

Recent Major Changes

Warnings and Precautions (5.4) 12/2015

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 old

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 800 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 30 mL/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 (2.6, 12.3)

Dosage Forms and Strengths

Extended-release tablets: 150 mg, 300 mg and 600 mg

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FULL PRESCRIBING INFORMATION

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

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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

<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>
</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 (8.6)].

2.5 Dosage Modifications in Geriatric Patients

In geriatric patients, consider initiating therapy at the lower end of the usual dose range (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 (8.5)].

2.6 Dosage Recommendations for Concomitant Antiepileptic Drugs

Enzyme inducing antiepileptic drugs such as carbamazepine, phenobarbital, and phenytoin decrease plasma levels of Oxtellar XR®. Consider using Oxtellar XR® in combination with non-inducing AEDs when possible. If Oxtellar XR® is used in combination with enzyme inducing AEDs, monitor patients closely for decreased effectiveness [see Drug Interactions (7.1)].

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 Hypersensitivity

Clinically significant hypersensitivity (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 within the first 3 months of treatment. However, clinically significant hypersensitivity may develop more than a year after initiating therapy. Most immediate-release oxcarbazepine-treated patients who developed hypersensitivity 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).Polyneuropathic changes, such as peripheral hypoesthesia, may be associated with the marketing use of immediate-release oxcarbazepine.

Among treated patients in a controlled trial of adjunctive therapy with Oxtellar XR® 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. Eight of 51 patients with clinical 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 (1.1%). Monitoring serum sodium concentrations in patients developing 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®. In particular, 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®, immediately 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

In some patients reporting AED-induced hypersensitivity reactions to carbamazepine that appear to have 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 may also experience hypersensitivity reactions with Oxtellar XR®. If the patient experiences rash, pruritus, or any unusual skin changes or if the skin changes are severe, 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 treated with immediate-release oxcarbazepine use. The median time of onset for these events 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 estimated from post-marketing surveillance reports. Generally, 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® and prescribing prednisone. Association with HLA-B*1502

Patients carrying the HLA-B*1502 allele may be at increased risk for SJS/TEN with Oxtellar XR® treatment. Human Leukocyte Antigen (HLA) allele B*1502 increases the risk for developing SJS/TEN in patients taking oxcarbazepine. The chemical structures of immediate-release oxcarbazepine and Oxtellar XR® are similar. However, no correlation between HLA-B*1502 and oxcarbazepine-induced SJS/TEN has been discovered. Testing for the presence of the HLA-B*1502 allele should be considered in patients with ancestry in genetically at-risk populations, prior to initiating treatment with Oxtellar XR®. The use of Oxtellar XR® should be avoided in patients positive for HLA-B*1502 unless the benefits clearly outweigh the risks. Consideration should also be given to avoid the use of other drugs associated with SJS/TEN in HLA-B*1502 positive patients, when alternative therapies are otherwise equally acceptable. Screening

is not generally recommended in patients from populations in which the prevalence of HLA-B*1502 is low, or in current Oxtellar XR® users, as the risk of SJS/TEN is largely confined to the first few months of therapy, regardless of HLA-B*1502 status. The use of HLA-B*1502 screening has been proposed for any individual in whom SJS/TEN is suspected, for the emergence or worsening of depression, suicidal thoughts or behavior, and/or any unusual changes in mood or behavior.

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

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

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.

5.7 Multi-Organs Hypersensitivity

Multi-organ hypersensitivity reactions have occurred in close temporal association (median time to onset of symptoms was 5–7 days) range early to the initiation of immediate-release oxcarbazepine therapy in both 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. 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., elevated liver function test abnormalities), renal (e.g., proteinuria, nephritis, oliguria), renal failure, musculoskeletal pain and joint swelling, myalgia, arthritis, asthma, 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 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, monohydrated oxcarbazepine (MHD), may gradually decrease throughout pregnancy. Oxtellar XR® 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 (5.8)]

Serious Dermal Reactions [see Warnings and Precautions (5.3)]

Serious Behavior and Ideation [see Warnings and Precautions (5.4)]

Multi-Organ Hypersensitivity [see Warnings and Precautions (5.7)]

Hematologic Reactions [see Warnings and Precautions (5.8)]
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 (≥ 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

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

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

Adverse Reactions Associated with Discontinuation of 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

<table>
<thead>
<tr>
<th>Immediate-Release Oxcarbazepine Dosage (mg/day)</th>
<th>Placebo N=166 %</th>
</tr>
</thead>
<tbody>
<tr>
<td>OXC 600 N=163</td>
<td></td>
</tr>
<tr>
<td>OXC 1200 N=171</td>
<td></td>
</tr>
<tr>
<td>OXC 2400 N=126</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Body as a Whole</th>
<th>Fatigue</th>
<th>Asthenia</th>
<th>Edema Legs</th>
<th>Weight Increase</th>
<th>Feeling Abnormal</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>15</td>
<td>12</td>
<td>15</td>
<td>7</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>3</td>
<td>6</td>
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<td><strong>Cardiovascular System</strong></td>
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<td>Hypotension</td>
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</table>

**Digestive System**

<table>
<thead>
<tr>
<th>Nausea</th>
<th>Vomiting</th>
<th>Pain Abdominal</th>
<th>Diarrhea</th>
<th>Dyspepsia</th>
<th>Constipation</th>
<th>Gastritis</th>
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<tbody>
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<td>15</td>
<td>25</td>
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<td><strong>Musculoskeletal System</strong></td>
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</table>

**Metabolic and Nutritional Disorders**

| Hypotension | 0       | 1      | 2      | 0 |

**Nervous System**

<table>
<thead>
<tr>
<th>Headache</th>
<th>Dizziness</th>
<th>Somnolence</th>
<th>Ataxia</th>
<th>Nystagmus</th>
<th>Gait Abnormal</th>
<th>Insomnia</th>
<th>Tremor</th>
<th>Nervousness</th>
<th>Agitation</th>
<th>Coordination Abnormal</th>
<th>EEG Abnormal</th>
<th>Speech Disorder</th>
<th>Confusion</th>
<th>Cranial Injury NOS</th>
<th>Dymetria</th>
<th>Thinking Abnormal</th>
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**Skin and Appendages**

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**Special Senses**

<table>
<thead>
<tr>
<th>Diplopia</th>
<th>Vertigo</th>
<th>Vision Abnormal</th>
<th>Accommodation Abnormal</th>
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* Events in at Least 2% of Patients Treated with 2400 mg/day of Immediate-Release Oxcarbazepine and Numerically More Frequent than in the Placebo Group
8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy
Oxetil XRP® plasma concentrations may decrease during pregnancy [see Warnings and Precautions (5.9)].

Pregnancy Category C

There is no adequate and well-controlled clinical studies of Oxetil XRP® in pregnant women; however, Oxetil XRP® 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 Oxetil XRP® is a human teratogen. Oxetil XRP® 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 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 maternally toxic (decreased body weight gain, clinical signs), but there is no evidence to indicate that this effect 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 rabbits were dosed orally with oxcarbazepine (55, 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 in utero exposure to Oxetil XRP®, physicians are advised to discourage aspiration of pregnant women taking Oxetil XRP® for 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 Labor and Delivery

The effect of Oxetil XRP® on labor and delivery in humans has not been evaluated.

8.3 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 in nursing infants from the oxcarbazepine, a decision should be made whether to discontinue nursing or to discontinue the drug in the nursing women, taking into account the importance of the drug to the mother.

8.4 Pediatric Use

The short term safety and effectiveness of Oxetil XRP® 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 Oxetil XRP® in adults that included pharmacokinetic sampling [see Clinical Studies (14.1)];

2) A pharmacokinetic study of Oxetil XRP® 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)].

Oxetil XRP® 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.

8.5 Geriatric Use

Following administration of single (300 mg) and multiple (600 mg/day) doses of immediate-release oxcarbazepine to elderly volunteers, 60-85 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)].

8.6 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 Oxetil XRP® 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 Oxetil XRP® 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 Oxetil XRP®.

8.7 Hepatic Impairment

The pharmacokinetics of oxcarbazepine and MHD has not been evaluated in severe hepatic impairment, and caution should be exercised in these patients. [see Clinical Pharmacology (12.3)].

9 DRUG ABUSE AND DEPENDENCE

9.2 Abuse

The abuse potential of Oxetil XRP® has not been evaluated in human studies. Oxetil XRP® 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 doses taken were approximately 24,000 mg. All patients recovered with symptomatic treatment.

Treatment and Management

There is no specific antidote for Oxetil XRP® 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

Oxetil XRP® is an antiepileptic drug (AED). Oxetil XRP® extended-release tablets contain oxcarbazepine for once-a-day oral administration.

Table 5: AED Drug Interactions with Oxcarbazepine

<table>
<thead>
<tr>
<th>AED (Coadministered (daily dose)</th>
<th>IR-Oxcarbazepine (daily dose)</th>
<th>Influence of IR-Oxcarbazepine on AED Concentration Mean Change [90% Confidence Interval]</th>
<th>Influence of AED on MHD Concentration (Mean Change, 90% Confidence Interval)</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbamazepine (400 – 2000 mg)</td>
<td>900 mg n.c.</td>
<td>40% decrease [Cl: 17% decrease, 57% decrease]</td>
<td>Consider initiating Oxetil XRP® at a higher dose.</td>
<td>Monitor and titrate dose to desired clinical effect (see 2.6)</td>
</tr>
<tr>
<td>Phenobarbital (100 – 500 mg)</td>
<td>600 – 1800 mg n.c.</td>
<td>14% increase [Cl: 2% decrease, 24% increase]</td>
<td>25% decrease [Cl: 3% decrease, 48% decrease]</td>
<td>Consider initiating Oxetil XRP® at a higher dose. Monitor and titrate dose to desired clinical effect (see 2.6)</td>
</tr>
<tr>
<td>Phenytoin (250 – 500 mg)</td>
<td>600 – 1800 &gt;1200-2400 mg n.c.</td>
<td>up to 40% increase [Cl: 12% decrease, 68% increase]</td>
<td>30% decrease [Cl: 3% decrease, 48% decrease]</td>
<td>Consider initiating Oxetil XRP® at a higher dose. Monitor and titrate dose to desired clinical effect (see 2.6)</td>
</tr>
<tr>
<td>Valproic Acid (400 – 2800 mg)</td>
<td>600-1800 n.c.</td>
<td>18% decrease [Cl: 13% decrease, 40% decrease]</td>
<td>Monitor: Dose adjustment of Oxetil XRP® may not be needed.</td>
<td></td>
</tr>
</tbody>
</table>
Oxcarbazepine is white to yellow crystalline powder. Oxcarbazepine is sparingly soluble in chloroform (30-100 mL/g). In aqueous media over pH range 1-8, oxcarbazepine is practically insoluble and its solubility is 40 mL/g (0.04 mL/g at pH 7.0, 25°C. The molecular formula of oxcarbazepine is C_{19}H_{17}N_{2}O_5, and its molecular weight is 352.27. 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, 600 mg tablets only), magnesium stearate, methacrylic acid copolymer, microcrystalline cellulose, polyethylene glycol, 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, electro-physiological studies indicate that they produce blockade of voltage-sensitive sodium channels, resulting in stabilization of hyperexcited neuronal channels, 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 receptor systems 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 chronic, spontaneously recurring focal seizures in Rhesus monkeys with aluminum implants. No development of tolerance (i.e., attenuation of anticonvulsant 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.

13. CLINICAL STUDIES

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Oxcarbazepine is rapidly reduced by cytosolic enzymes in the liver to MHD, which is primarily excreted by the kidneys. More than 95% of a dose of immediate-release oxcarbazepine appears in the urine either as glucuronides of oxcarbazepine and MHD. The pharmacokinetics of oxcarbazepine and MHD have not been evaluated in severe hepatic impairment on the basis of the following studies in patients with hepatic impairment. For oxcarbazepine and MHD, the pharmacokinetics and metabolism of immediate-release oxcarbazepine and MHD were evaluated in healthy volunteers and heparically impaired subjects after a single 900 mg oral dose. Mild-to-severe 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)].

13.2 Pregnancy

Due to physiological changes during pregnancy, MHD plasma levels may gradually decrease throughout pregnancy. The use of oxcarbazepine in pregnant women should be carefully considered. The effect of pregnancy on the pharmacokinetics and metabolism of oxcarbazepine and MHD has not been evaluated in pregnant women. In a study of 12 healthy volunteers, the mean plasma concentration of oxcarbazepine was not significantly different from that observed in healthy nonpregnant controls [seeUse in Specific Populations (8.1)]. In addition, oxcarbazepine and MHD induce a subgroup of the cytochrome P450 3A family (CYP3A4) and P-gp, which may influence the pharmacokinetics and metabolism of other drugs. Results demonstrated that the pharmacokinetics of oxcarbazepine and its pharmacologically active 10-monohydroxy metabolite (MHD) have little or no capacity to function as inhibitors of the major cytochrome P450 enzyme systems responsible for the metabolism of other drugs. No significant interactions of oxcarbazepine or MHD with brain neurotransmitter or receptor systems have been demonstrated. The pharmacokinetics and metabolism of immediate-release oxcarbazepine and MHD are qualitatively similar in healthy male and female subjects [see Use in Specific Populations (8.1)].

14. ADVERSE REACTIONS

14.1 Postmarketing Surveillance

Oxcarbazepine and MHD are rapidly reduced by cytosolic enzymes in the liver to MHD, which is primarily excreted by the kidneys. More than 95% of a dose of immediate-release oxcarbazepine appears in the urine either as glucuronides of 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)].

15. TOXICOLOGY

15.1 Carcinogenesis

Oxcarbazepine and MHD are rapidly reduced by cytosolic enzymes in the liver to MHD, which is primarily excreted by the kidneys. More than 95% of a dose of immediate-release oxcarbazepine appears in the urine either as glucuronides of 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)].
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 triads 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>
<thead>
<tr>
<th>Median seizure frequency during 8-week baseline period (per 28 days)</th>
<th>Median seizure frequency during 16-week treatment period (per 28 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 (N=121)</td>
<td>7.0</td>
<td>5.0</td>
<td>-28.7 %</td>
<td>0.000</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>
</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>
</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 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

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.

• 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 (5.7)].

• 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.
RA-OXT-V2
Revised: December 2015