MPR

PRESCRIBING ALERT®

Dear Healthcare Professional,

At *MPR* we strive to bring you important drug information in a concise and timely manner. In keeping with this goal, we are pleased to provide you with this PRESCRIBING ALERT with detailed information on Oxtellar XR™ (oxcarbazepine) extended-release tablets, manufactured by Supernus Pharmaceuticals, Inc.

Oxtellar XR is the first and only FDA-approved extended-release formulation of oxcarbazepine. Taken once daily, Oxtellar XR is indicated as adjunctive therapy of partial seizures in adults and children 6 years to 17 years of age. The consistent release of oxcarbazepine allows for continued absorption of oxcarbazepine and its active metabolite, 10-monohydroxy metabolite, over 24 hours.[1]

Oxtellar XR is available as 150 mg, 300 mg, and 600 mg extended-release tablets. Oxtellar XR allows for once-daily dosing convenience. When converting from Trileptal® (oxcarbazepine) to Oxtellar XR, higher doses of Oxtellar XR may be necessary.[1]

INDICATION

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

IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS

- Oxtellar XR is contraindicated in patients with a known hypersensitivity to oxcarbazepine or to any of its components.

WARNINGS & PRECAUTIONS

- Clinically significant hyponatremia (sodium <125 mmol/L) may develop during treatment. Measurement and laboratory tests of serum sodium concentrations should be considered for patients during maintenance treatment with Oxtellar XR, particularly if the patient is receiving other medications known to decrease serum sodium levels. Discontinuation of oxcarbazepine treatment may be clinically required.
- Rare cases of anaphylaxis and angioedema involving the larynx, glottis, lips, and eyelids have been reported in patients after taking the first or subsequent doses of oxcarbazepine. Angioedema associated with laryngeal edema can be fatal. If a patient develops any of these reactions after treatment with Oxtellar XR, the drug should be discontinued and an alternative treatment started. Do not rechallenge these patients with Oxtellar XR.
- Inform patients who have had hypersensitivity reactions to carbamazepine that approximately 25% to 30% of them will experience hypersensitivity reactions with Oxtellar XR. Patients with a history of hypersensitivity reactions to carbamazepine should ordinarily be treated with Oxtellar XR only if the potential benefit justifies the potential risk. Discontinue Oxtellar XR immediately if signs or symptoms of hypersensitivity develop.
- Serious dermatological reactions, including Stevens-Johnson syndrome and toxic epidermal necrolysis, have been reported in association with oxcarbazepine use. Should a patient develop a skin reaction while using Oxtellar XR, consideration should be given to discontinuing its use. (Please see WARNINGS section of complete prescribing information.)
- Anyone considering prescribing Oxtellar XR must balance the risk of suicidal thoughts or behavior with the risk of untreated illness. Epilepsy and many other illnesses for which antiepileptic drugs are prescribed are themselves associated with morbidity and mortality and an increased risk of suicidal thoughts and behavior. Should suicidal thoughts and behavior emerge during Oxtellar XR treatment, the prescriber needs to consider whether the emergence of these symptoms in any given patient may be related to the illness being treated.

(Important Safety Information continued on next page)

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

- Withdrawal of Oxtellar XR should be done gradually to minimize the potential of increased seizure frequency.
- Multi-organ hypersensitivity reactions have occurred in patients being treated with oxcarbazepine therapy. While 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 disorders. If this reaction is suspected, discontinue Oxtellar XR and initiate an alternative treatment.
- Rare reports of hematologic events such as pancytopenia, agranulocytosis, and leukopenia have been seen in patients treated with oxcarbazepine and discontinuation of therapy should be considered if any evidence of these hematologic events develop.
- Due to physiological changes during pregnancy, plasma concentrations of the active metabolite of oxcarbazepine, the 10-monohydroxy derivative, may gradually decrease throughout pregnancy. Monitor patients carefully during pregnancy and through the postpartum period because the active metabolite concentrations or levels may increase after delivery. It is recommended that patients taking Oxtellar XR be enrolled in the NAAED Pregnancy Registry.

DOSING CONSIDERATIONS

- Enzyme inducing antiepileptic drugs such as carbamazepine, phenobarbital, and phenytoin decrease the exposure to MHD, the active metabolite of Oxtellar XR. Dosage increases may be necessary.
- In patients with severe renal impairment, 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.
- Concurrent use of Oxtellar XR with hormonal contraceptives and other oral or implant contraceptives may decrease plasma levels and render these contraceptives less effective. Additional non-hormonal forms of contraception are recommended.

ADVERSE REACTIONS

The most commonly observed (≥5%) adverse reactions seen in association with Oxtellar XR and more frequent than in placebo-treated patients were (1200 mg, 2400 mg, v placebo): dizziness (20%, 41%, v 15%), somnolence (12%, 14%, v 9%), headache (8%, 15%, v 7%), balance disorder (5%, 7%, v 5%), tremor (5%, 1%, v 2%), vomiting (6%, 15%, v 9%), diplopia (10%, 13%, v 4%), asthenia (3%, 7%, v 1%), and fatigue (6%, 3%, v 1%).

Please refer to the full Prescribing Information for Oxtellar XR.

More information about Oxtellar XR is available in the current edition of *MPR*.

Sincerely,

Madonna Krawczyk, PharmD
Director of Clinical Communications
MPR Custom Programs

REFERENCE

1. Oxtellar XR [prescribing information]. Rockville, MD: Supernus Pharmaceuticals, Inc.; October 2012.

SPN.OXT.2013-0086 10/13

Oxtellar XR™

(oxcarbazepine) extended-release tablets

℞

Tablets not actual size.

Company: Supernus Pharmaceuticals, Inc.

Active Ingredient: Oxcarbazepine; 150 mg, 300 mg, 600 mg extended-release tablets.

Indications: Adjunctive therapy in the treatment of partial seizures in adults and in children 6–17 years of age.

Adults: >17 years of age: Initially 600 mg once daily for 1 week; dose increases can be made at weekly intervals in 600 mg increments to achieve the recommended daily dose: 1200-2400 mg/day. Renal impairment (CrCL <30 mL/min): start at 300 mg per day and increase slowly. Geriatric patients: start at lower dose (300 mg or 450 mg per day) and increase slowly. In conversion of oxcarbazepine immediate-release to Oxtellar XR, higher doses of Oxtellar XR may be necessary.

Children: Target dose is based upon weight. Titrate to target dose over 2-3 weeks. Initiate with 8-10 mg/kg once per day. Increase in weekly increments of 8-10 mg/kg once daily, not to exceed 600 mg, to achieve target daily dose.

Contraindications: Known hypersensitivity to oxcarbazepine or to any of its components.

Warnings/Precautions: Hyponatremia; monitor sodium as recommended. Anaphylactic reactions and angioedema; discontinue if occurs. Past history of hypersensitivity reaction to carbamazepine; only use based upon risk benefit. Serious dermatological reactions; discontinue if observed. Suicidal behavior and ideation; monitor for symptoms. Withdraw gradually. Multi-organ hypersensitivity; discontinue if suspected. Hematologic reactions; discontinue if suspected.

Drug Interactions: Phenytoin, carbamazepine, and phenobarbital coadministration decreases blood levels of an active metabolite; greater dose may be required. May decrease the effectiveness of hormonal contraceptives; additional non-hormonal forms of contraception recommended.

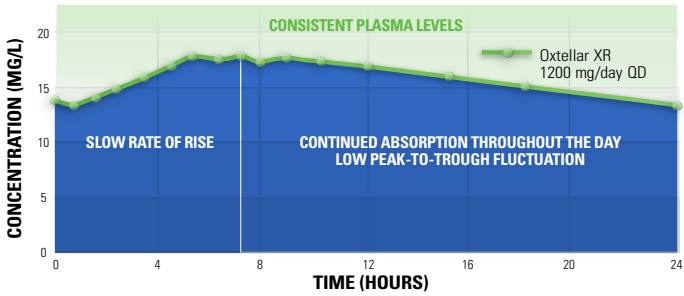
Specific Populations: Pregnancy; monitor patients. Plasma levels of active metabolite may be decreased. Based on animal data, may cause fetal harm. Severe hepatic impairment; not recommended.

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

How Supplied: Tablets—100/bottle.

Taken once daily, Oxtellar XR is the first and only FDA-approved extended-release formulation of oxcarbazepine[1]

OXTELLAR XR 24-HOUR PLASMA CONCENTRATIONS



- Oxtellar XR releases oxcarbazepine over a 24-hour period, achieving the indicated plasma concentrations of the active metabolite 10-monohydroxy derivative after administration of the 1200 mg/day dose[2]

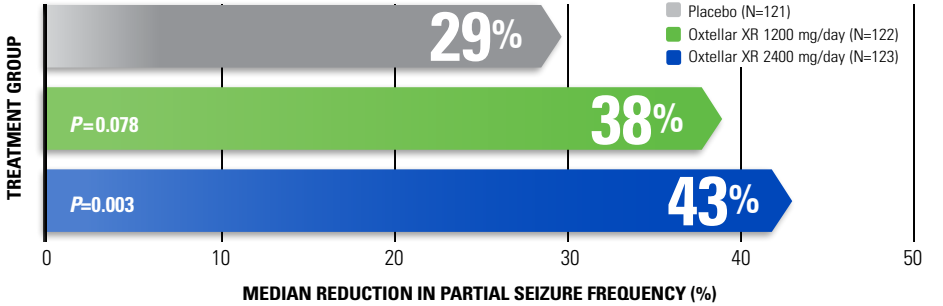
Source: Data on file.[2]

Please refer to the full Prescribing Information for Oxtellar XR and the Important Safety Information on pages 3 and 4.

(continued on next page)

[✓] Oxtellar XR™ (oxcarbazepine) significantly reduces partial seizure frequency[1]

REDUCTION* IN PARTIAL SEIZURE FREQUENCY–PRIMARY ENDPOINT, INTENTION-TO-TREAT POPULATION



- Although the 1200 mg/day-placebo contrast did not reach statistical significance, concentration-response analysis revealed that the 1200 mg/day dose is an effective dose[1]
- Oxtellar XR is approved for 1200 mg/day to 2400 mg/day[1]

*Reduction = median percent reduction, treatment phase, as adjunctive therapy in controlled phase 3 clinical trial of refractory epilepsy.

Source: Oxtellar XR [prescribing information].[1]

[✓] Oxtellar XR has an established safety profile[1]

■ Adverse events occurred more frequently than placebo[1]

ADVERSE EVENTS OCCURRING IN ≥5% OF PATIENTS

	Placebo (N=121)	Oxtellar XR 1200 mg/day (N=122)	Oxtellar XR 2400 mg/day (N=123)
Dizziness	15%	20%	41%
Headache	7%	8%	15%
Vomiting	9%	6%	15%
Somnolence	9%	12%	14%
Diplopia	4%	10%	13%
Asthenia	1%	3%	7%
Balance Disorder	5%	5%	7%
Fatigue	1%	6%	3%
Tremor	2%	5%	1%

- Cognitive adverse events were similar to placebo[2]
- Incidence of nausea was similar to placebo: 12% (2400 mg/day), 12% (1200 mg/day), and 12% (placebo)[2]
- Incidence of hyponatremia was similar to placebo: 0.8% (2400 mg/day), 1.6% (1200 mg/day), and 1.7% (placebo)[2]
- Incidence of neurologic and ophthalmologic adverse events in the 2400 mg/day and 1200 mg/day groups was lower than what would generally be expected with Trileptal® (oxcarbazepine)[2]

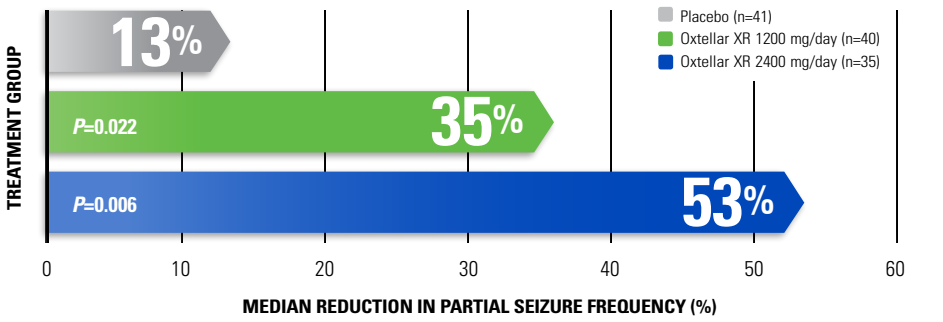
Source: Oxtellar XR [prescribing information][1]; Data on file.[2]

Please refer to the full Prescribing Information for Oxtellar XR and the Important Safety Information on pages 3 and 4.

(continued on next page)

Oxtellar XR significantly reduced partial seizure frequency in a subset of patients in North America[2]

REDUCTION* IN PARTIAL SEIZURE FREQUENCY–POST HOC ANALYSIS OF NORTH AMERICAN SUBSET



Results based on a post hoc analysis of a subset of partial seizure patients in North America.

*Reduction = median percent reduction, treatment phase, as adjunctive therapy in controlled phase 3 clinical trial of refractory epilepsy.

Source: Data on file.[2]

Oxtellar XR offers once-a-day convenience[1]

- When converting from Trileptal® to Oxtellar XR, higher doses of Oxtellar XR may be necessary[1]
- Oxtellar XR should be taken as a single daily dose on an empty stomach[1]
  - Patients should take Oxtellar XR at least 1 hour before or at least 2 hours after meals
  - When Oxtellar XR is taken with food, adverse reactions are more likely to occur because of increased peak plasma concentration levels
- Oxtellar XR tablets should be swallowed whole. Do not cut, crush, or chew the tablets[1]
  - Lower strength tablets (150 mg) are available for pediatric patients or patients with difficulty swallowing

INDICATION

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

IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS

- Oxtellar XR is contraindicated in patients with a known hypersensitivity to oxcarbazepine or to any of its components.

WARNINGS & PRECAUTIONS

- Clinically significant hyponatremia (sodium <125 mmol/L) may develop during treatment. Measurement and laboratory tests of serum sodium concentrations should be considered for patients during maintenance treatment with Oxtellar XR, particularly if the patient is receiving other medications known to decrease serum sodium levels. Discontinuation of oxcarbazepine treatment may be clinically required.
- Rare cases of anaphylaxis and angioedema involving the larynx, glottis, lips, and eyelids have been reported in patients after taking the first or subsequent doses of oxcarbazepine. Angioedema associated with laryngeal edema can be fatal. If a patient develops any of these reactions after treatment with Oxtellar XR, the drug should be discontinued and an alternative treatment started. Do not rechallenge these patients with Oxtellar XR.

Please refer to the full Prescribing Information for Oxtellar XR and the Important Safety Information on pages 3 and 4.

(continued on next page)

- Inform patients who have had hypersensitivity reactions to carbamazepine that approximately 25% to 30% of them will experience hypersensitivity reactions with Oxtellar XR. Patients with a history of hypersensitivity reactions to carbamazepine should ordinarily be treated with Oxtellar XR only if the potential benefit justifies the potential risk. Discontinue Oxtellar XR immediately if signs or symptoms of hypersensitivity develop.
- Serious dermatological reactions, including Stevens-Johnson syndrome and toxic epidermal necrolysis, have been reported in association with oxcarbazepine use. Should a patient develop a skin reaction while using Oxtellar XR, consideration should be given to discontinuing its use. (Please see WARNINGS section of complete prescribing information.)
- Anyone considering prescribing Oxtellar XR must balance the risk of suicidal thoughts or behavior with the risk of untreated illness. Epilepsy and many other illnesses for which antiepileptic drugs are prescribed are themselves associated with morbidity and mortality and an increased risk of suicidal thoughts and behavior. Should suicidal thoughts and behavior emerge during Oxtellar XR treatment, the prescriber needs to consider whether the emergence of these symptoms in any given patient may be related to the illness being treated.

  Patients, their caregivers, and families should be informed that antiepileptic drugs increase the risk of suicidal thoughts and behavior and should be advised of the need to be alert for the emergence or worsening of the signs and symptoms of depression, any unusual changes in mood or behavior, or the emergence of suicidal thoughts, behavior, or thoughts about self-harm. Behaviors of concern should be reported immediately to healthcare providers.
- Withdrawal of Oxtellar XR should be done gradually to minimize the potential of increased seizure frequency.
- Multi-organ hypersensitivity reactions have occurred in patients being treated with oxcarbazepine therapy. While 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 disorders. If this reaction is suspected, discontinue Oxtellar XR and initiate an alternative treatment.
- Rare reports of hematologic events such as pancytopenia, agranulocytosis, and leukopenia have been seen in patients treated with oxcarbazepine and discontinuation of therapy should be considered if any evidence of these hematologic events develop.
- Due to physiological changes during pregnancy, plasma concentrations of the active metabolite of oxcarbazepine, the 10-monohydroxy derivative, may gradually decrease throughout pregnancy. Monitor patients carefully during pregnancy and through the postpartum period because the active metabolite concentrations or levels may increase after delivery. It is recommended that patients taking Oxtellar XR be enrolled in the NAAED Pregnancy Registry.

DOSING CONSIDERATIONS

- Enzyme inducing antiepileptic drugs such as carbamazepine, phenobarbital, and phenytoin decrease the exposure to MHD, the active metabolite of Oxtellar XR. Dosage increases may be necessary.
- In patients with severe renal impairment, 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.
- Concurrent use of Oxtellar XR with hormonal contraceptives and other oral or implant contraceptives may decrease plasma levels and render these contraceptives less effective. Additional non-hormonal forms of contraception are recommended.

ADVERSE REACTIONS

The most commonly observed (≥ 5%) adverse reactions seen in association with Oxtellar XR and more frequent than in placebo-treated patients were (1200 mg, 2400 mg, v placebo): dizziness (20%, 41%, v 15%), somnolence (12%, 14%, v 9%), headache (8%, 15%, v 7%), balance disorder (5%, 7%, v 5%), tremor (5%, 1%, v 2%), vomiting (6%, 15%, v 9%), diplopia (10%, 13%, v 4%), asthenia (3%, 7%, v 1%), and fatigue (6%, 3%, v 1%).

Please refer to the full Prescribing Information for Oxtellar XR.

REFERENCES

1. Oxtellar XR [prescribing information]. Rockville, MD: Supernus Pharmaceuticals, Inc.; October 2012.
2. Data on file. Supernus Pharmaceuticals, Inc., Rockville, MD.

SPN.OXT.2013-0086 10/13