The Pharmacokinetic Profile of Oxtellar XR®: Supporting Once-Daily Dosing

Oxtellar XR is an extended-release tablet formulation of oxcarbazepine (OXC), an analogue of carbamazepine (CBZ), indicated for the treatment of partial-onset seizures in patients 6 years of age and older.[1,2] CBZ is the benchmark antiepileptic drug (AED) for efficacy in partial-onset seizures.[2] However, OXC is metabolized differently than CBZ and demonstrates a differentiated pharmacokinetic profile that simplifies its clinical use.[2]

While the precise mechanism by which OXC exerts its antiseizure effect is unknown, it had been shown that pharmacologic activity is driven primarily through its metabolite, 10-monohydroxy metabolite (MHD).[1] In vitro electrophysiological research has demonstrated that both OXC and MHD work by binding to and blocking sodium channels, thereby diminishing high-frequency, repetitive nerve impulses that may cause seizures through stabilization of hyperexcited neurons and inhibition of repetitive neuronal firing and propagation of electrical impulses (**Figure 1**).[1] Evidence also suggests that OXC and MHD may increase potassium conductance and modulation of high-voltage activated calcium channels.[1]

Oxtellar XR leverages the proven OXC mechanism of action with a unique formulation that allows for once-daily dosing in both adult and pediatric patients with partial-onset seizures. Oxtellar XR tablets are formulated with Solutrol®, a matrix delivery system that was designed to enable poorly soluble compounds to be delivered reproducibly and completely.[1,2,4] Solutrol extended-release technology is composed of drug and solubilizing agents that are evenly distributed through the polymer matrix and are released from the hydrated polymer by diffusion and erosion, ensuring that the drug is released evenly and in a controlled manner, providing level OXC delivery over 24 hours.[1,2,4] **Figure 2** illustrates the steady absorption of metabolite MHD with demonstrated low fluctuation of plasma concentrations over 24 hours in healthy adults.[1,2,4]

INDICATION

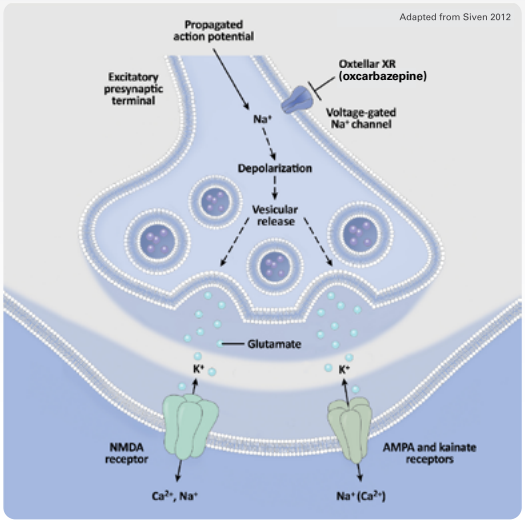
Oxtellar XR® is indicated for the treatment of partial-onset seizures in patients 6 years of age and older.

CONTRAINDICATIONS

Oxtellar XR is contraindicated in patients with a known hypersensitivity to oxcarbazepine,or to any of the components of Oxtellar XR, or to eslicarbazepine acetate. Reactions have included anaphylaxis and angioedema.

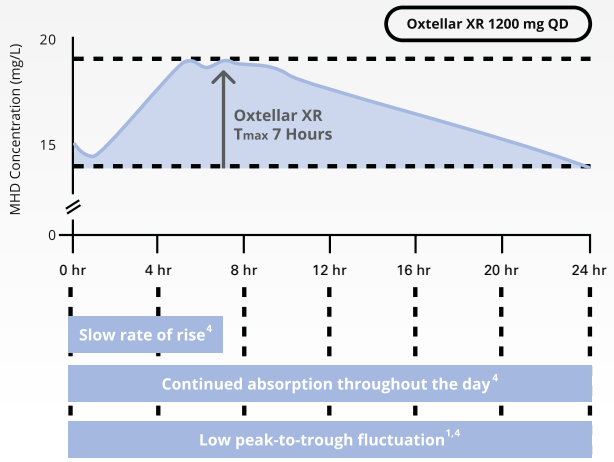
Please refer to the full Prescribing Information for complete information on Oxtellar XR, or visit www.OxtellarXRhcp.com and see additional Important Safety Information throughout.

FIGURE 1. PROPOSED MECHANISM OF ACTION OF OXCARBAZEPINE[1,3]



NMDA: N-methyl-D-aspartate
AMPA: α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid

FIGURE 2. MHD PLASMA CONCENTRATIONS IN HEALTHY ADULTS AT STEADY STATE SHOW STEADY 24-HOUR ABSORPTION WITH LOW FLUCTUATION[1,2,4]



ONCE-DAILY
Oxtellar XR®
(oxcarbazepine) extended-release tablets
600 mg 300 mg 150 mg

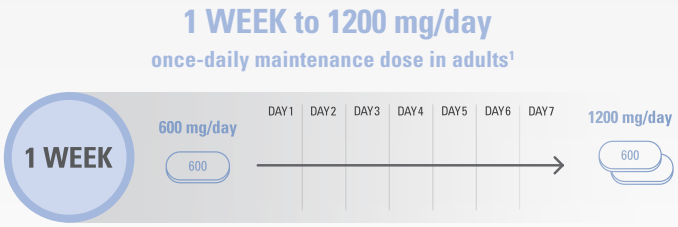
In addition to consistent absorption over 24 hours, when Oxtellar XR is given once daily to adults with partial-onset seizures, steady-state plasma concentrations of MHD are reached within 5 days, providing a 1-week titration period to reach maintenance dosing.[1] More precise adult dosing and administration information is presented in **Figure 3**.

With differentiated reductive metabolism and a patented delivery technology, Oxtellar XR offers adult and pediatric patients with partial-onset seizures an even and controlled rate of drug absorption that supports convenient once-daily dosing.

FIGURE 3. OXTELLAR XR DOSING IN ADULT PATIENTS WITH PARTIAL-ONSET SEIZURES[1]

Adult Patients[1]

- Initiate treatment at a dosage of 600 mg/day given orally once daily for 1 week. Subsequent dosage increases can be made at weekly intervals in 600 mg/day increments[1]
- Maintain at 1200 mg/day to 2400 mg/day once daily[1]



Administration[1]

- Patients should take Oxtellar XR on an EMPTY STOMACH at least 1 hour before or at least 2 hours after meals
- Oxtellar XR tablets should be swallowed whole. Do not cut, crush, or chew the tablets
- Lower-strength tablets (150 mg tablets) are available for pediatric patients or patients with difficulty swallowing
- See full Prescribing Information for patients with severe renal impairment, taking other AEDs, or taking contraceptives

IMPORTANT SAFETY INFORMATION (continued)

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.

To receive more information about Oxtellar XR or for access to resources to help manage your patients' partial-onset seizures, sign up here.

Please refer to the full Prescribing Information for complete information on Oxtellar XR, or visit www.OxtellarXRhcp.com and see additional Important Safety Information throughout.

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IMPORTANT SAFETY INFORMATION (continued)

WARNINGS & PRECAUTIONS (continued)

- 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.
- Approximately 25% to 30% of patients who have had hypersensitivity reactions to carbamazepine 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.
- Withdrawal of Oxtellar XR should be done gradually to minimize the potential of increased seizure frequency and status epilepticus.
- Multi-organ hypersensitivity reactions have occurred in patients on oxcarbazepine therapy. Some 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 an alternative etiology cannot be established, discontinue Oxtellar XR.
- 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 may gradually decrease throughout pregnancy. An increase in seizure frequency may occur. Monitor patients carefully during pregnancy and through the postpartum period.
- Exacerbation of or new onset primary generalized seizures has been reported with immediate-release oxcarbazepine. The risk is seen especially in children, but may also occur in adults. Discontinue Oxtellar XR if it occurs.
- Data on a limited number of pregnancies from pregnancy registries suggest that oral clefts and ventricular septal defects are associated with oxcarbazepine monotherapy use.

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 or discontinuation of enzyme inducers may be necessary.
- In adult 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.
- Use of Oxtellar XR with certain hormonal contraceptives may decrease hormone plasma levels and render these contraceptives less effective. Additional or alternative non-hormonal forms of contraception are recommended.

ADVERSE REACTIONS

The most commonly observed adverse reactions (≥ 5% and more frequent than placebo) seen in adults 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%). Adverse reactions in pediatric patients are similar to those seen in adults.

Please refer to Full Prescribing Information for Oxtellar XR.

References:

1. Oxtellar XR. Package insert. Supernus Pharmaceuticals Inc. **2.** French JA, Baroldi P, Brittain ST, Johnson JK; for PROSPER Investigators Study Group. Efficacy and safety of extended-release oxcarbazepine (Oxtellar XR™) as adjunctive therapy in patients with refractory partial-onset seizures: a randomized controlled trial. *Acta Neural Scand.* 2014;129(3):143-153. **3.** Bialer M, White SH. Key factors in the discovery and development of new antiepileptic drugs. *Nat Rev Drug Discov.* 2010;9(1):68-82. **4.** Data on file. Supernus Pharmaceuticals, Inc.

Supernus® Pharmaceuticals