Pediatric Focused Safety Review: Oxtellar XR™ (oxcarbazepine extended-release) Pediatric Advisory Committee Meeting March 24, 2015

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Outline

• Background Information
• Relevant Labeling
• Drug Use Trends
• Safety
• Summary
Background Drug Information
Oxtellar XR™
(oxcarbazepine extended-release)

- **Drug:** Oxtellar XR™
- **Formulations:** 150, 300 and 600 mg extended-release tablets
- **Sponsor:** Supernus Pharmaceuticals, Inc.
- **Original Market Approval and Pediatric Labeling Change:**
  October 19, 2012
- **Therapeutic Category:** Anti-epileptic medication
- **Indication:** Adjunctive treatment of partial seizures in adults and pediatric patients 6 years of age and older
- **Previous PAC review:** oxcarbazepine immediate-release, November 16, 2006
Background Drug Information, continued

Oxtellar XR™
(oxcarbazepine extended-release)

• **Current Postmarketing Requirements under the Pediatric Research and Equity Act (PREA):**
  – Two pharmacokinetic (PK) and tolerability trials in pediatric patients:
    • 1 month to 6 months of age
    • 6 months to 4 years of age
  – Two safety and efficacy trials in pediatric patients as adjunctive treatment of partial seizures:
    • 1 month up to 2 years of age
    • 2 years up to 6 years of age
1 INDICATIONS AND USAGE
Oxtellar XR™ is an anti-epileptic drug indicated for the adjunctive treatment of partial seizures in patients 6 years of age and older.

2 DOSAGE AND ADMINISTRATION
2.3 Dosing for Pediatric Patients 6 to 17 years of age

<table>
<thead>
<tr>
<th>Weight</th>
<th>Titrated Target Daily Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>20 to 29 kg</td>
<td>900 mg per day</td>
</tr>
<tr>
<td>29.1 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>
Relevant Labeling, continued
Oxtellar XR™
(oxcarbazepine extended-release)

4 CONTRAINDICATIONS
• Known hypersensitivity to oxcarbazepine or any of its components

5 WARNINGS AND PRECAUTIONS
5.1 Hyponatremia
5.2 Anaphylactic Reactions and Angioedema
5.3 Hypersensitivity Reactions in Patients with Hypersensitivity to Carbamazepine
5.4 Serious Dermatologic Reactions
5.5 Suicidal Behavior and Ideation
5.6 Withdrawal of AEDs
5.7 Multi-organ Hypersensitivity
5.8 Hematologic Reactions
5.9 Risk of Seizures in the Pregnant Patient
5.10 Laboratory Tests – Changes in T4 w/o changes in T3 or TSH
Relevant Labeling, continued

Oxtellar XR™
(oxcarbazepine extended-release)

6 ADVERSE REACTIONS
6.1 Clinical Trials Experience

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

Incidence of adverse events was similar to that in adults.
8 USE IN SPECIFIC POPULATIONS
8.4 Pediatric Use
The short term safety and effectiveness of Oxtellar XR™ in pediatric patients ages 6 to 16 years with partial onset seizures is supported by:

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

12 CLINICAL PHARMACOLOGY
12.3 Pharmacokinetics
PK data supports weight based dosing in pediatric patients ages 4 to 16 years of age. Tablet is inappropriate for pediatric patients under 6 because of the size.

14 CLINICAL STUDIES
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.
Drug Utilization Data: Oxcarbazepine

Nationally estimated number of patients that received a dispensed prescription for oxcarbazepine from U.S. outpatient retail pharmacies, stratified by patient age*, August 2013 through July 2014

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Patients (N)</th>
<th>Share (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oxcarbazepine</td>
<td>619,318</td>
<td>100%</td>
</tr>
<tr>
<td>0-16 years</td>
<td>152,362</td>
<td>24.6%</td>
</tr>
<tr>
<td>&lt; 1 year</td>
<td>3,984</td>
<td>2.6%</td>
</tr>
<tr>
<td>2-5 years</td>
<td>21,444</td>
<td>14.1%</td>
</tr>
<tr>
<td>6-16 years</td>
<td>131,364</td>
<td>86.2%</td>
</tr>
<tr>
<td>17+ years</td>
<td>473,109</td>
<td>76.4%</td>
</tr>
<tr>
<td>Unspecified age</td>
<td>815</td>
<td>0.1%</td>
</tr>
</tbody>
</table>

*Subtotals may not sum exactly due to rounding. Because of patients aging during the study period, patients may be counted more than once in the individual age categories. For this reason, summing across age groups is not advisable and will result in overestimates of patient counts.

Pediatric Drug Utilization: Oxcarbazepine

Nationally estimated number of pediatric patients (0-16 years) that received a dispensed prescription for Oxcarbazepine from U.S. outpatient retail pharmacies

Oxcarbazepine Utilization Data
Prescribing Specialty\textsuperscript{1} and Diagnosis\textsuperscript{2}
August 2009 through July 2014, Aggregate

• **Top Prescribing Specialties**
  (% of total outpatient retail prescriptions dispensed)
  – Psychiatry (34% of prescriptions)
  – Neurology (31% of prescriptions)
  – Pediatrics accounted for 3% of total prescriptions

• **Top Diagnosis**
  – Epilepsy NOS (ICD-9 code 345.9) was the top diagnosis captured in pediatric patients across all pediatric age groups based on U.S. office-based physician survey data

\textsuperscript{1}IMS, National Prescription Audit (NPA). August 2009 to July 2014. Extracted November 2014
Selection of Pediatric FAERS Cases
August 1, 2009 to July 31, 2014

Total pediatric reports with a serious outcome (n=203)
Pediatric reports with an outcome of death (n=8)

Excluded Reports (n=50)
(Including 7 deaths)
- Duplicate Reports (n=45)
- Transplacental exposure (n=4)
- Adult (n=1)

Pediatric case series
(n=153, 1 death)

2 additional deaths since last PAC review, 11/2006
Deaths\(n=3\) Oxcarbazepine
November 16, 2006 to July 31, 2014

- 14-year-old female died after self-inflicted gunshot wound to the head  
  - On oxcarbazepine for 2 years; levetiracetam for one year prior to the event. Both medications stopped 2 weeks before the event. Bupropion and other unidentified meds were in the GI tract at autopsy.

- 13-year-old female acutely ingested multiple drugs, had a cardiorespiratory arrest and died  
  - Drugs included zolpidem, olanzapine, lorazepam, quetiapine, temazepam, oxcarbazepine, fluoxetine, and trazodone. Combined effect of drugs assessed as the cause of death.

- 4-year-old female with hydrocephalus, shunt and history of seizures died in her sleep  
  - Had been on oxcarbazepine for 3.5 years prior to the event. Autopsy lists cause of death as “maternal trauma.”
Serious Non-Fatal Unlabeled Adverse Events Oxcarbazepine

Event of Special interest - Hypothyroidism
Search: January 14, 2000 to July 31, 2014

Events occurring in more than three cases
Search: August 1, 2009 to July 31, 2014
Event of Special Interest: Hypothyroidism
Oxcarbazepine

- Search included data from the approval date of oxcarbazepine immediate release
- Labeling for oxcarbazepine immediate-release includes hypothyroidism in Section 6.2, Adverse Events, Post-Marketing and Other Experience
- Oxtellar XR™ does not include hypothyroidism in Section 6.2
- 9 of 26 cases required further review after excluding:
  - 6 cases reporting laboratory changes without clinical symptoms of hypothyroidism (in labeling)
  - 11 cases reporting other confounding products, reported twice or exposure not timed to the event
Hypothyroidism, continued (n=9) Oxcarbazepine

- All cases reported low T4 without reported changes in TSH.
- Five patients, ages 4 to 15 years, reported typical hypothyroid symptoms such as fatigue, weight gain and constipation. Patients improved with levothyroxine and continued oxcarbazepine.
- Two patients, age 5 and 8 years reported to have decreased growth. Growth improved after oxcarbazepine was stopped.
- 12-year-old male with Sturge-Weber syndrome reported to have decreased growth. Patient treated with levothyroxine, oxcarbazepine was continued and repeat T4 was normal.
- 5-year-old female reported to have weight gain and a puffy face after starting oxcarbazepine. Oxcarbazepine was continued. No further information on treatment was provided.
Serious Non-Fatal **Unlabeled** Adverse Events
Oxcarbazepine

Reported in more than 3 cases

- **Product Substitution** (n=33)
- **Drug Ineffective** (n=20)
- **Decreased Appetite** (n=4)
- **Hallucination** (n=4)

*Unlabeled events are underlined on this slide and subsequent slides*
Serious Non-Fatal Unlabeled Adverse Events, continued, Oxcarbazepine

**Product Substitution** (n=33)

- Related to either to generic substitution or change from name brand to generic.
- No cases described an adverse event related to conversion from IR to XR or vice versa.
- No product quality issues were identified.
Serious Non-Fatal Unlabeled Adverse Events, continued, Oxcarbazepine

Drug Ineffective (n=20)

- Two cases described increased seizures with drug ineffective
  - 13-year-old male experienced multiple seizures while on oxcarbazepine for 6 months. Dose increased but event not resolved at the time of the report.
  - 2-year-old female had increased seizures after a refill of the suspension. Improper storage was suspected. Dose increased and no further seizures reported.

- 13-year-old female with undetectable blood level after refill of suspension. Change in behavior, decreased appetite and lethargy were noted. Dose was increased and the symptoms resolved.

- Fourteen cases described oxcarbazepine as ineffective when used in combination with multiple AEDs.

- Single cases: use of an expired product, coincidental use with other ineffective products for other indications, off-label treatment of migraines.
Serious Non-Fatal Unlabeled Adverse Events, continued, Oxcarbazepine

Decreased Appetite (n=4)

- Two cases were reported in patients with subependymal giant cell astrocytoma who were treated with oxcarbazepine and everolimus. Decreased appetite is listed in labeling as a common adverse reaction for everolimus.

- 4-year-old female with encephalopathy due to valproic acid toxicity reported decreased appetite. Clinical condition and not oxcarbazepine may have accounted for the symptoms.

- 13-year-old female was also reported under drug ineffective. This patient had undetectable blood levels of oxcarbazepine.
Serious Non-Fatal Unlabeled Adverse Events, continued, Oxcarbazepine

**Hallucinations (n=4)**

- 3-year-old female on Trileptal for several years developed hallucinations when switched to generic product. Hallucinations resolved after generic product was discontinued.

- 9-year-old female on oxcarbazepine for 1 month developed hallucinations and tiredness. Symptoms resolved after oxcarbazepine was stopped.

- 15-year-old female on risperidone, aripiprazole, sertraline and methylphenidate and oxcarbazepine developed hallucinations, loss of vision in one eye, itching and possible seizure. All concomitant products labeled for seizures. Sertraline and methylphenidate are labeled for hallucinations.

- 3-year-old male ingested 300 mg oxcarbazepine, 10 mg buspirone and 60 mg amphetamine salts. Observed in hospital with no significant sequelae but reported hallucinations after discharge that self resolved.
Serious Non-Fatal Labeled Adverse Events, Oxcarbazepine

Events reported more than three times

5 WARNINGS AND PRECAUTIONS
Abnormal Behavior*
Blister (SJS)
Confusional State
Lethargy
Pyrexia*
Rash*
Stevens-Johnson Syndrome (SJS)
Thrombocytopenia

6 ADVERSE REACTIONS
Abdominal Pain
Aggression
Condition Aggravated
Dizziness
Fatigue
Feeling Abnormal
Hypotonia
Insomnia
Somnolence
Urticaria
Vomiting

*also classified as an adverse reaction
Summary of Safety Reviews
Oxtellar XR™
(oxcarbazepine extended-release)

- This concludes the pediatric focused safety review of FAERS reports
- FDA recommends updating Section 6.2, Adverse Events, Postmarketing and Other Experience, of Oxtellar XR labeling to include hypothyroidism
- No other potential safety signals were identified
- FDA recommends continued routine monitoring
- Does the committee concur?
ACKNOWLEDGEMENTS

Division
Billy Dunn, MD
Eric Bastings, MD
Norman Hershkowitz, MD, PhD
Steven Dinsmore, MD

OPT
Judith Cope, MD, MPH
Dianne Murphy, MD
Robert “Skip” Nelson, MD, PhD
Amy Odegaard, MPH
Pam Weinel, MS, MBA, RN

DPMH
Lynne Yao, MD
Denise Pica-Branco, PhD
Hari Cheryl Sachs, MD

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Mohamed Mohamoud, PharmD, MPH, BCPS
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Judy Staffa, PhD, Rph