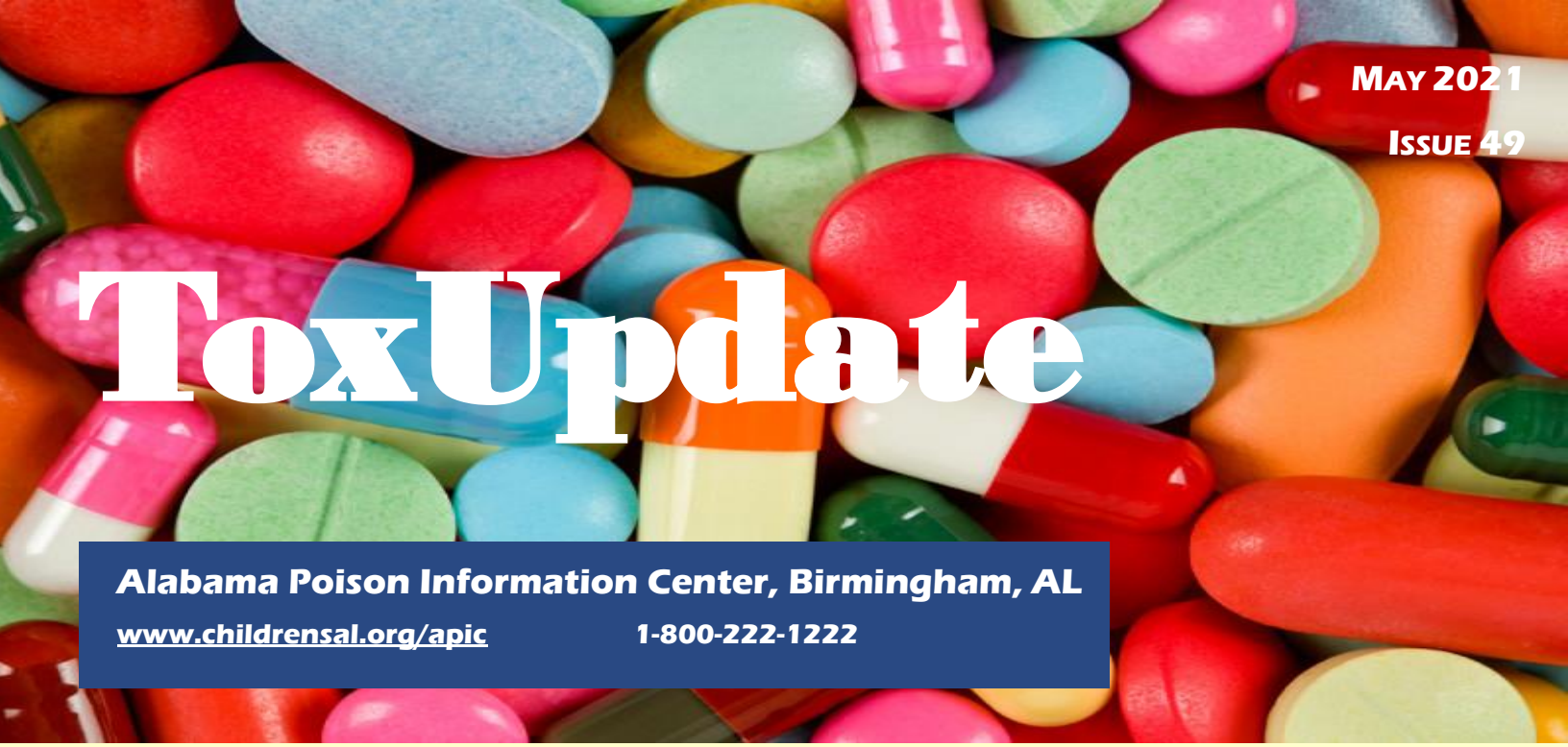

May 2021
Issue 49

# ToxUpdate

**Alabama Poison Information Center, Birmingham, AL**
www.childrensal.org/apic 1-800-222-1222

## Caplyta®: A New Second-Generation Antipsychotic for Schizophrenia

*By Brandon Watson, Samford University PharmD Candidate*

Schizophrenia is a severe mental illness that is primarily treated with antipsychotics. Second-generation antipsychotics (SGAs) are typically preferred over first-generation due lower risk for extrapyramidal symptoms (EPS), though they do have a higher risk for metabolic symptoms. SGAs can bind to many receptors, so their adverse effect profile is dependent on the binding affinity specific SGAs have on these receptors. Caplyta (lumateperone) is a new SGA that was approved in December 2019 for the treatment of schizophrenia.

Similar to other SGAs, Caplyta is theorized to exhibit its therapeutic effect in schizophrenia through antagonistic effects on 5-$HT_{2A}$ and $D_2$ receptors. Caplyta has a high affinity for 5-$HT_{2A}$ receptors, moderate affinity for $D_2$ and $\alpha_1$ receptors, and low affinity for muscarinic and histaminergic receptors. This low affinity could mean that Caplyta has lower instances of adverse effects related to these receptors compared to some other SGAs. Some of the most common adverse effects seen in clinical trials were somnolence/sedation, nausea, dry mouth, and dizziness. There are also warnings about the risk of neuroleptic malignant syndrome (NMS), EPS, metabolic symptoms, and seizures. However, there is some evidence that Caplyta may have lower incidence of EPS and metabolic symptoms compared to other SGAs.

Caplyta is available as a 42 mg capsule that comes in boxes of 30 capsules. The recommended dosage is one capsule daily with food, and titration is not needed. Caplyta is a CYP3A4 substrate, so coadministration with CYP3A4 inducers or inhibitors is not recommended. Caplyta is also not recommended for patients with moderate to severe hepatic impairment, due to these patients being at risk for a 2- to 3-fold increase in hepatic impairment while on Caplyta. There is no safety date available for use in children. Caplyta can potentially cause EPS in neonates when taken by pregnant patients during the third trimester.

(Continued on Page 3)

ALABAMA POISON INFORMATION CENTER
800-222-1222

### Special Interest Articles

- Caplyta®
- Azstarys™
- Xcopri®

***Did you know?***

The CDC says only 1,893 Americans tested positive for influenza this past flu season. The previous flu season had 290,000 positive cases. Of those flu cases from last season, 198 children died from influenza-related causes. So far this season, only one child has died.

# Azstarys™: Novel Drug for Attention Deficit Hyperactivity Disorder

*By Brianna Deraney, Samford University PharmD Candidate*

***"Because of the different pharmacokinetic properties and base compositions, Azstarys should not be substituted on a milligram per milligram basis with other methylphenidate products.[2]"***

The FDA has recently approved a novel stimulant medication for attention deficit hyperactivity disorder (ADHD), Azstarys, that will be available Summer 2021. Azstarys is a combination of extended-release serdexmethylphenidate (SDX) with immediate-release dexmethylphenidate (d-MPH).[1] It is a fixed ratio of 30% d-MPH and 70% SDX. The three capsule strengths available are 26.1/5.2 mg, 39.2/7.8 mg, and 52.3/10.4 mg. Because of the different pharmacokinetic properties and base compositions, Azstarys should not be substituted on a milligram per milligram basis with other methylphenidate products.[2] SDX is the prodrug of d-MPH and is converted to d-MPH after absorption in the GI tract, providing both immediate symptom control with d-MPH and gradual release for symptom control throughout the day with SDX. It is the first medication to use the prodrug SDX with d-MPH. Azstarys is taken once daily and is approved for ages 6 and older. The recommended starting dose is 39.2/7.8 mg once daily in the morning and the maximum dose is 52.3/10.4 mg once daily for both pediatric and adult patients. The most common adverse effects seen in clinical trials were headache, upper abdominal pain, insomnia, and pharyngitis.[1]

In trials, the time to peak concentration under fasting conditions was around 2 hours. However, when given with food, the time to peak concentration was around 4-4.5 hours

Overdose signs and symptoms can result in CNS stimulation and sympathomimetic effects and can include diarrhea, nausea, vomiting, agitation, anxiety, tremors, hyperreflexia, muscle twitching, seizures, euphoria, confusion, delirium, hallucinations, sweating, flushing, headache, hyperpyrexia, tachycardia, palpitations, cardiac arrhythmias, hypotension or hypertension, tachypnea, mydriases, dryness of mucous membranes, and rhabdomyolysis.[3]


*References*

1. FDA Oks Novel Dual-Action Stimulant Med for ADHD. Medscape Medical News. March 8, 2021. https://www.medscape.com/viewarticle/947075 (Accessed March 31, 2021).
2. Serdexmethylphenidate/Dexmethylphenidate. POISINDEX® System (electronic version). IBM Watson Health, Greenwood Village, Colorado, USA. Available at: https://www.micromedexsolutions.com/ (Accessed April 7, 2021).
3. AZSTARYS™. KemPharm Grand Rapids, MI. March 2021. https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/212994s000lbl.pdf (Accessed March 31, 2021).

## Caplyta Continued from Page 1

The toxic dose of Caplyta has not yet been established, and no cases of overdose have been reported. Symptoms of overdose would be anticipated to be similar to adverse effects seen at therapeutic doses, as well as, overdose symptoms seen in other SGAs. This could include symptoms such as CNS depression, anticholinergic effects, and seizures. Due to the lack of information related to toxicity, any patient who takes more than the recommended dose of Caplyta and experience symptoms should be evaluated by a healthcare facility. Extra factors that are important in a potential overdose of Caplyta include hepatic impairment, pregnancy, concomitant use of a CYP3A4 inhibitor, and if the patient is a child.

*References*


1. Lumateperone. POISINDEX® System (electronic version). IBM Watson Health, Greenwood Village, Colorado, USA. Available at: https://www.micromedexsolutions.com/ (Accessed March 31, 2021).
2. CAPLYTA® [package insert]. Intra-Cellular Therapies, Inc., New York, NY. 2019. https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/209500s000lbl.pdf. (Accessed March 31, 2021).
3. Greenwood J, Acharya RB, Marcellus V, Rey JA. Lumateperone: A Novel Antipsychotic for Schizophrenia. Ann Pharmacother. 2021 Jan;55(1):98-104.
4. Lieberman JA, Davis RE, Correll CU, Goff DC, Kane JM, Tamminga CA, Mates S, Vanover KE. ITI-007 for the Treatment of Schizophrenia: A 4-Week Randomized, Double-Blind, Controlled Trial. Biol Psychiatry. 2016 Jun 15;79(12):952-61.


# Xcopri® in Adults with Uncontrolled Focal Seizures

*By Laura Read RPh, CSPI, Alabama Poison Information Center*

In November 2019, the U.S. Food and Drug Administration approved Xcopri ®(Cenobamate) for the treatment of focal aware or simple partial seizures in adults. In one clinical trial, a 56% decrease from baseline in seizure frequency was seen versus placebo with a 22% reduction in frequency. Cenobamate regulates slowly inactivating sodium ion channels, but also regulates a persistent sodium channel current and is a positive modulator of the gamma-aminobutyric acid ion channel. Cenobamate slows the brain cells change from inactivated to resting; however, the exact mechanism of action remains unknown.

Common side effects for cenobamate are dizziness, somnolence, diplopia, headache, and fatigue. Adverse events that have led to treatment cessation are ataxia, dizziness, nystagmus, and vertigo. One trial result showed that adjunctive treatment with cenobamate in patients that took lamotrigine, carbamazepine, and oxcarbazepine had at least one adverse event. Cenobamate is generally well tolerated and the side effects to the medication may be related to titration of dosing done too rapidly (> 200 mg per day) or when used with other antiepileptic drugs with similar mechanism of action, such as another voltage-gated sodium channel blocker.

Serious side effects of cenobamate include Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) and QT shortening. As with other antiepileptic drugs, withdrawal should be done gradually to prevent seizure occurrence (over a two-week period). The dosage range of cenobamate is between 200 mg and 400 mg daily depending on the individual's health history. Cenobamate is usually started at lower doses and increased over the range of 11- 19 weeks. Acute overdose has not been reported at this time, but overdose effects are expected to be an extension of the adverse effects seen at therapeutic doses.

*References*


1. Cenobamate. POISINDEX® System (electronic version). IBM Watson Health, Greenwood Village, Colorado, USA. Available at: https://www.micromedexsolutions.com/ (Accessed March 15, 2021).
2. Xcopri® [package insert]. SK Life Science, Paramus, NJ. 2020. https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/212839s000lbl.pdf. (Accessed March 15, 2021).
3. Cenobamate. Epilepsy Foundation. https://www.epilepsy.com/medications/cenobamate. (Accessed March 15, 2021).
4. Mudigoudar, B, Wheless, J. Safety of adjunctive treatment with cenobamate in patients with uncontrolled focal seizures. Lancet Neurol. 2020;19:288. doi:10.1016/S1474-4422(20)30069-7