PDL DRUG REVIEW

Proprietary Name: Azstarys®
Common Name: serdexmethylphenidate & dexmethylphenidate
PDL Category: Stimulants-Methylphenidate

Comparable Products	Preferred Drug List Status
Dexmethylphenidate	Preferred with Conditions

Summary

Pharmacology/Usage: Azstarys® contains dexmethylphenidate (a CNS stimulant) and serdexmethylphenidate (a prodrug of dexmethylphenidate). Each capsule contains a fixed molar ratio of 30% dexmethylphenidate and 70% serdexmethylphenidate. The mode of therapeutic action in ADHD is not known.

Azstarys® is a Schedule II controlled substance. It contains dexmethylphenidate HCl, a Schedule II controlled substance, and serdexmethylphenidate, a Schedule IV controlled substance. CNS stimulants, including Azstarys®, have a high potential for abuse. Azstarys® may produce physical dependence and tolerance from continued therapy.

Indication: For the treatment of attention deficit hyperactivity disorder (ADHD) in patients 6 years of age and older.

There is no pregnancy category for this medication; however, the risk summary indicates that there are no available data on use in pregnant women to evaluate for a drug-associated risk of major birth defects, miscarriage, or other adverse maternal or fetal outcomes. Published studies and post marketing reports on methylphenidate use during pregnancy have not identified a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes. There may be risks to the fetus associated with the use of CNS stimulants during pregnancy. CNS stimulants, such as Azstarys®, can cause vasoconstriction and thereby decrease placental perfusion. No fetal and/or neonatal adverse reactions have been reported with the use of therapeutic doses of methylphenidate during pregnancy; however, premature delivery and low birth weight infants have been reported in amphetamine-dependent mothers. The safety and efficacy of use have not been established in pediatric patients less than 6 years of age.

Dosage Form: Capsules containing serdexmethylphenidate/dexmethylphenidate: 26.1mg/5.2mg, 39.2mg/7.8mg, 52.3mg/10.4mg

Recommended Dosage: Prior to initiating treatment with Azstarys®, assess for the presence of cardiac disease (i.e. perform a careful history, family history of sudden death or ventricular arrhythmia, and physical exam).

Assess for the risk of misuse prior to prescribing and monitor for signs of abuse and dependence while on therapy. Maintain careful prescription records, educate patients about abuse, monitor for signs of abuse and overdose, and periodically re-evaluate the need for Azstarys® use.

For pediatric patients 6 to 12 years of age, the recommended starting dose is 39.2mg/7.8mg QAM. The dosage may be increased after one week to a dosage of 52.3mg/10.4mg QD or decreased after one week to a dosage of 26.1mg/5.2mg QD, depending on response and tolerability. The maximum recommended dosage is 52.3mg/10.4mg QD.

For adults and pediatric patients 13 to 17 years of age, the recommended starting dose is 39.2mg/7.8mg QAM. Increase the dosage after one week to a dosage of 52.3mg/10.4mg QD, which is the maximum recommended dosage.

Pharmacological treatment of ADHD may be required for extended periods. Periodically re-assess the long-term use of Azstarys,® and adjust dosage as needed.

Administer with or without food. Azstarys® capsules may be taken whole or opened and the entire contents sprinkled into 50ml of water or over 2 tablespoons of applesauce. Consume all the drug/food mixture immediately or within 10 minutes of mixing; do not store for future use.

If switching from other methylphenidate products, discontinue that treatment and titrate with Azstarys® using the titration schedule described above. Do not substitute Azstarys® for other methylphenidate products on a milligram-per-milligram basis because these products have different pharmacokinetic profiles from Azstarys® and may have different methylphenidate base composition.

If paradoxical aggravation of symptoms or other adverse reactions occur, the dosage should be reduced, or if necessary, the drug should be discontinued. Azstarys® should be periodically discontinued to assess the pediatric patient's condition and need for ongoing treatment. If improvement is not observed after appropriate dosage adjustment over a one-month period, the drug should be discontinued.

There is no experience with the use of Azstarys® in patients with hepatic impairment or in patients with renal impairment. Since renal clearance is not an important route of serdexmethylphenidate or methylphenidate elimination, renal impairment is expected to have little effect on the pharmacokinetics of Azstarys®.

Drug Interactions: Do not administer Azstarys® concomitantly with MAOIs or within 14 days after discontinuing MAOI treatment.

Azstarys® may decrease the effectiveness of drugs used to treat hypertension. Monitor blood pressure and adjust the dosage of the antihypertensive drug, as needed.

Concomitant use of halogenated anesthetics and Azstarys® may increase the risk of sudden blood pressure and heart rate increase during surgery. Avoid the use of Azstarys® in patients being treated with anesthetics on the day of surgery.

Combined use of methylphenidate with risperidone when there is a change, whether an increase or decrease, in dosage of either or both medications may increase the risk of extrapyramidal symptoms (EPS). Monitor for signs of EPS.

Box Warning: Azstarys® has a box warning regarding abuse and dependence. CNS stimulants, including Azstarys®, other methylphenidate-containing products, and amphetamines, have a high potential for abuse and dependence. Assess the risk of abuse prior to prescribing and monitor for signs of abuse and dependence while on therapy.

Common Adverse Drug Reactions: *Listed % incidence for adverse drug reactions= reported % incidence for drug (methylphenidate; ≥5% of the methylphenidate group and at least twice the rate of the placebo group).* The most frequently reported adverse events included decreased appetite, decreased weight, nausea, abdominal pain, dyspepsia, vomiting, insomnia, anxiety, affect lability, irritability, dizziness, increased blood pressure, and tachycardia.

A short-term study that included pediatric patients 6 to 12 years of age with ADHD was comprised of a 3-week, open-label, dose optimization phase in which all patients received Azstarys®, followed by a 1-week, double-blind, controlled phase in which patients were randomized to continue Azstarys® or switch to placebo. Because of the study design, the reported adverse reaction rates cannot be used to predict the rates that may be expected in clinical practice.

CNS stimulants, including Azstarys®, other methylphenidate-containing products, and amphetamines, have a high potential for abuse and dependence. Assess the risk of abuse prior to prescribing and monitor for signs of abuse and dependence while on therapy.

Sudden death, stroke, and myocardial infarction have been reported in adults with CNS stimulant treatment at recommended doses. Sudden death has been reported in pediatric patients with structural cardiac abnormalities and other serious heart problems taking CNS stimulants at recommended doses for ADHD. Avoid use in patients with known structural cardiac abnormalities, cardiomyopathy, serious heart rhythm abnormalities, coronary artery disease, and other serious heart problems. Further assess patients who develop exertional chest pain, unexplained syncope, or arrhythmias during Azstarys® treatment.

CNS stimulants cause an increase in blood pressure (mean increase about 2 to 4mmHg) and heart rate (mean increase about 3 to 6 beats per minute). Some individuals may have larger increases. Monitor all patients for hypertension and tachycardia.

CNS stimulants may exacerbate symptoms of behavior disturbance and thought disorder in patients with a pre-existing psychotic disorder. CNS stimulants may induce a manic or mixed mood episode in patients. Prior to starting treatment, screen patients for risk factors for developing a manic episode. In addition, CNS stimulants, at recommended doses, may cause psychotic or manic symptoms in patients without a prior history of psychotic illness or mania. If such symptoms occur, consider discontinuing Azstarys®.

Prolonged and painful erections, sometimes requiring surgical intervention, have been reported with methylphenidate products, in both pediatric and adult patients. Priapism was not reported with drug initiation but developed after some time on the drug, often subsequent to an increase in dose. Priapism has also appeared during a period of drug withdrawal (drug holidays or during discontinuation). Patients who develop abnormally sustained or frequent and painful erections should seek immediate medical attention.

CNS stimulants used to treat ADHD, including Azstarys®, are associated with peripheral vasculopathy, including Raynaud's phenomenon. Signs and symptoms are usually intermittent and mild; however, very rare sequelae include digital ulceration and/or soft tissue breakdown. Effects of peripheral vasculopathy, including Raynaud's phenomenon, were observed in post-marketing reports at different times and at therapeutic doses in all age groups throughout the course of treatment. Signs and symptoms generally improve after reduction in dose or discontinuation of drug. Careful observation for digital changes is necessary during treatment with ADHD stimulants.

CNS stimulants have been associated with weight loss and slowing of growth rate in pediatric patients. In a long-term, open-label safety study with Azstarys® conducted in pediatric patients 6 to 12 years of age with ADHD, there was a lower than expected increase in height and weight compared to pediatric patients of the same age and sex, on average. Closely monitor growth (height and weight) in pediatric patients treated with CNS stimulants, including Azstarys®. Patients who are not growing or gaining height or weight as expected may need to have their treatment interrupted.

Contraindications: In patients:

- With known hypersensitivity to serdexmethylphenidate, methylphenidate, or other components of the product. Bronchospasm, rash, and pruritus have been reported in patients who received Azstarys®. Hypersensitivity reactions such as angioedema and anaphylactic reactions have been reported in patients treated with other methylphenidate products.
- Receiving concomitant treatment with monoamine oxidase inhibitors (MAOIs), or within 14 days following discontinuation of treatment with an MAOI, because of the risk of hypertensive crisis.

Manufacturer: Corium, Inc

Analysis: The efficacy of Azstarys® for the treatment of ADHD in pediatric patients 6 to 12 years of age was assessed in a randomized, double-blind, placebo-controlled, parallel group, analog classroom study. The pediatric patients (N=150) in this study met Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5) criteria for a primary diagnosis of ADHD (combined, inattentive, or hyperactive/impulsive presentation) confirmed by the Mini International Neuropsychiatric Interview for Children and Adolescents (MINI-KID).

After washout of previous ADHD medication, subjects entered an open-label dose-optimization period (3 weeks) with an initial dosage of 39.2mg/7.8mg QAM. The dose could be titrated, until an optimal dose or the maximum dosage of 52.3mg/10.4mg QD was reached. At the end of the optimization period, subjects were randomly assigned into a 1-week parallel group treatment period to receive the individually optimized dose of Azstarys® or placebo.

At the end of the 1-week treatment period, raters assessed the attention and behavior of the subjects in a laboratory classroom setting over a period 13 hours using the Swanson, Kotkin, Agler, M-Flynn, and Pelham (SKAMP) rating scale. SKAMP is a validated 13-item teacher-rated scale that assesses manifestations of ADHD in a classroom setting. On this day, the dose was administered in the morning immediately after breakfast.

The primary efficacy endpoint was the mean change from baseline (pre-dose at randomization visit) of the SKAMP-Combined scores averaged across the test day (not including baseline score), with assessments conducted at 0.5, 1, 2, 4, 8, 10, 12, and 13 hours post-dose. Results suggested that the mean change from baseline in the SKAMP-Combined scores, averaged across the test day, was statistically significantly lower (indicating improvement) with Azstarys® as compared with placebo. Results can be seen in the table below, which was adapted from the prescribing information.

	Treatment group	N	Mean Baseline Score	LS Mean Change from Baseline	Placebo-subtracted difference
Study 1	Azstarys®	74	17.9	-4.87	-5.4
	Placebo	76	17.9	0.54	

The efficacy of 52.3mg/10.4mg Azstarys® in adults and pediatric patients 13 to 17 years of age was established by pharmacokinetic bridging between Azstarys® (52.3mg/10.4mg) and dexmethylphenidate ER capsules.

Place in Therapy: Azstarys®, which contains dexmethylphenidate and serdexmethylphenidate (a prodrug of dexmethylphenidate), is indicated for the treatment of ADHD in patients 6 years of age and older. As with other CNS stimulants for ADHD, Azstarys® has a box warning regarding abuse and dependence. Assess the risk of abuse prior to prescribing and monitor for signs of abuse and dependence while on therapy. In a randomized, double-blind, placebo-controlled analog classroom study that included pediatric patients 6 to 12 years of age who met DSM-5 criteria for ADHD, the mean change from baseline in the SKAMP-Combined scores, averaged across the test day (primary outcome) was statistically significantly lower (improved) with Azstarys® compared to placebo. This product offers physicians another treatment option for ADHD.

There is no evidence at this time to support that Azstarys® is safer or more effective than the other currently preferred, more cost-effective medications. It is therefore recommended that Azstarys® remain non-preferred and require prior authorization and be available to those who are unable to tolerate or who have failed on preferred medications.

PDL Placement: ☐ **Preferred**
☒ **Non-Preferred with Conditions**

References

[1] Azstarys [package insert]. Grand Rapids, MI: Corium, Inc; 2021.