Drug Monograph

Drug Name: **Azstarys™ (serdexmethylphenidate/dexmethylphenidate) capsule**
Drug Class: **Central Nervous System: ADHD, Methylphenidate, Long Acting**
Prepared For: MO HealthNet
Prepared By: Conduent

☒ **New Criteria** ☐ **Revision of Existing Criteria**

Executive Summary

Purpose:	The purpose of this monograph is to provide a review of new therapy to determine whether the reviewed drug should be made available on an open access basis to prescribers, require a clinical edit or require prior authorization for use.
Dosage Forms:	Azstarys is available in a 26.1 mg/5.2 mg, a 39.2 mg/7.8 mg, and a 52.3 mg/10.4 mg capsule.
Manufacturer:	Distributed by: Corium, Inc., Grand Rapids, MI 49512.
Summary of Findings:	Azstarys was studied in a Phase 3 randomized, double-blind, placebo-controlled, analog classroom study. In this study of 150 patients 6 to 12 years of age with ADHD, Azstarys significantly improved ADHD symptoms with a single dose, as measured by the primary endpoint, the change from baseline in Swanson, Kotkin, Agler, M-Flynn, and Pelham Rating Scale – Combined (SKAMP-C) scores averaged over a 13-hour laboratory classroom day [Placebo subtracted difference: -5.4 (95% CI: -7.1, -3.7)]. The efficacy of Azstarys 52.3 mg/10.4 mg in adults and pediatric patients 13 to 17 years of age was established by pharmacokinetic bridging between Azstarys and dexmethylphenidate hydrochloride extended-release capsules.
Status Recommendation:	☐ Clinical Edit ☐ PA Required ☐ Open Access ☒ PDL
Type of PA Criteria:	☐ Appropriate Indications ☒ Non-Preferred ☐ No PA Required ☐ Preferred

Purpose

The purpose of this monograph is to provide a review of new therapy to determine whether the reviewed drug should be considered a prior authorization drug, a clinical edit drug or an open access drug. While prescription expenditures are increasing at double-digit rates, payers are evaluating ways to control these costs by influencing prescriber behavior and guide appropriate medication usage. This review will assist in the achievement of qualitative and economic goals related to health care resource utilization. Restricting the use of certain medications can reduce costs by requiring documentation of appropriate indications for use, and where appropriate, encourage the use of less expensive agents within a drug class.

Introduction [1,2]

Attention deficit/hyperactivity disorder (ADHD) effects and estimated 6.1 million children in the U.S. between the ages of 2 and 17 years. It is a neuropsychiatric disorder usually diagnosed in childhood that often persists into adulthood. The prevalence of ADHD among children is approximately 9.4% and ranges from 2.5% to 4.4% among adults, although prevalence estimates vary on the basis of differences in research methodologies, the various groups being described, and the changes in diagnostic criteria over time. Symptoms of ADHD affect cognitive, academic, occupational, behavioral, emotional, and social functioning. American Academy of Pediatrics (AAP) guidelines from 2019 recommend that school-aged children (6 to 12 years of age) be treated with medications for ADHD in combination with parent training in behavior management or behavioral classroom interventions. For most patients treated with medication, stimulants are used as first-line therapy, with a variety of short-acting and long-acting formulations available.

Dosage Form [3]

Azstarys is available in a 26.1 mg/5.2 mg, a 39.2 mg/7.8 mg, and a 52.3 mg/10.4 mg capsule.

Manufacturer [3]

Distributed by: Corium, Inc., Grand Rapids, MI 49512.

Indication(s) [3]

Azstarys is indicated for the treatment of ADHD in patients ≥6 years of age.

Clinical Efficacy [3,4,5] (mechanism of action/pharmacology, comparative efficacy)

Serdexmethylphenidate (SDX) is a prodrug of dexmethylphenidate (d-MPH). Dexmethylphenidate HCl is a central nervous system (CNS) stimulant. The mode of therapeutic action in ADHD is not known.

Pharmacokinetics:

Absorption	Bioavailability: 3% (SDX); t_{max}= 2 hours (combination); 8 hours (SDX alone); t_{max} is lengthened in the presence of food (4-4.5 hours)
Metabolism	Prodrug likely converted by enzymes in the gastrointestinal (GI) tract; d-MPH is metabolized primarily via de-esterification
Excretion	SDX: 62% (renal), 37% (fecal); methylphenidate (MPH): 90% (renal)
Half-life	t 1/2=5.7 hours (SDX)); 11.7 hours (MPH)

Clinical Trials Experience

STUDY DESIGN (NCT03292952)	Multicenter, dose-optimized, randomized, double-blind, placebo-controlled, parallel group, analog classroom study (N=150)
INCLUSION CRITERIA	• Pediatric patients 6-12 years of age • Must meet Diagnostic and Statistical Manual of Mental Disorders-Fifth Edition (DSM-5) criteria for a primary diagnosis of ADHD per clinical evaluation and confirmed by the Mini International Neuropsychiatric Interview for Children and Adolescents (MINI-KID) • Must have a score of at least 3 (mildly ill) on the clinician-administered Clinical Global Impressions-Severity (CGI-S) scale
EXCLUSION CRITERIA	• Diagnosis of bipolar I or II disorder, major depressive disorder, conduct disorder, obsessive-compulsive disorder, any history of psychosis, autism spectrum disorder, disruptive mood dysregulation disorder (DMDD), intellectual disability, Tourette's Syndrome, confirmed genetic disorder with cognitive and/or behavioral disturbances • Evidence of any chronic disease of the CNS such as tumors, inflammation, seizure disorder, vascular disorder, potential CNS related disorders that might occur in childhood, or history of persistent neurological symptoms attributable to serious head injury • Current (within the last month) psychiatric diagnosis other than specific phobia, motor skills disorders, oppositional defiant disorder, sleep disorders, elimination disorders, adjustment disorders, learning disorders, communication disorders, school phobia, or separation anxiety • History of attempted suicide or clinically significant suicidal ideation or subject has a Columbia-Suicide Severity Rating Scale (C-SSRS) score for suicidal ideation ≥2 • Clinically significant unstable medical abnormality, chronic disease, or a history of a clinically significant abnormality of the cardiovascular, gastrointestinal (GI), respiratory, hepatic, or renal systems, or a disorder or history of a condition that may interfere with drug absorption, distribution, metabolism, or excretion of study drug • History or presence of abnormal electrocardiograms (ECGs)
TREATMENT REGIMEN	• The study consisted of a Screening Period, an Open-Label Dose Optimization Phase, a Double-Blind Treatment Phase and a Follow-Up Visit, as follows: ○ Screening Period: Subjects underwent a screening period up to 49 days prior to entering into the Open-Label Dose Optimization Phase. Subjects then underwent a washout of previous ADHD medications. ○ Open-Label Dose Optimization Phase (3 weeks): During the Dose Optimization Phase, subjects initiated dosing at 39.2 mg/7.8 mg once daily in the morning and then were titrated up or down on a weekly basis to doses of 26.1 mg/5.2 mg, 39.2 mg/7.8 mg, or 52.3 mg/10.4 mg until an optimal dose based on tolerability and best individual dose-response in the opinion of the Investigator. The maximum dose was 52.3 mg/10.4 mg per day. ○ Double-Blind Treatment Phase: Eligible subjects were randomized to receive single daily doses of Azstarys or placebo for 7 days according to a randomization schedule. The dose of Azstarys given in the Treatment Phase was the same as the optimized dose of Azstarys at the end of the Dose Optimization Phase. All subjects received their assigned treatment daily for 7 days. The dose was the same at each day of the Treatment Period. At the end of the 1-week treatment period, raters evaluated the attention and behavior of the subjects in a laboratory classroom setting over a period of 13 hours

<table>
<tr><td></td><td>using the Swanson, Kotkin, Agler, M-Flynn, and Pelham (SKAMP) rating scale.
○ Follow-Up Visit: 3 ±2 days after administration of the last dose of the Treatment Phase, subjects entered a Follow-Up Visit to evaluate safety parameters.</td></tr>
<tr><td>RESULTS</td><td>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.

The mean change from baseline in the SKAMP-Combined scores, averaged across the test day, was statistically significantly lower (indicating improvement) with Azstarys compared to placebo.

<table>
<tr><th>Study Number</th><th>Treatment Group</th><th>N</th><th>Mean Baseline Score* (SD)</th><th>LS Mean Change from Baseline** (SE)</th><th>Placebo-Subtracted Difference*** (95% CI)</th></tr>
<tr><td rowspan="2">Study 1</td><td>Azstarys (26.1/15.2, 39.2/7.8, 52.3/10.4 mg/day)</td><td>74</td><td>17.9 (9.2)</td><td>-4.87 (0.62)</td><td rowspan="2">-5.4
(-7.1, -3.7)</td></tr>
<tr><td>Placebo</td><td>76</td><td>17.9 (10.4)</td><td>0.54 (0.70)</td></tr>
</table>
Abbreviations: SD=standard deviation; SE=standard error; LS Mean=least-squares mean; CI=confidence interval
* Baseline score assessed at pre-dose on the practice classroom day/randomization visit after 2 days of active drug washout
**Classroom day least-squares mean change from baseline over hours 0.5, 1, 2, 4, 8, 10, 12, and 13.
***Difference (active drug minus placebo) in least-squares mean change from baseline.

The efficacy of 52.3 mg/10.4 mg in Azstarys in adults and pediatric patients 13 to 17 years of age was established by pharmacokinetic bridging between Azstarys (52.3 mg/10.4 mg) and dexmethylphenidate hydrochloride extended-release capsules.</td></tr>
<tr><td>SAFETY</td><td>Discussed in the Adverse Effects section below.</td></tr>
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Contraindications [3,4]

- Hypersensitivity to SDX, MPH, or product components
- Concurrent treatment with a monoamine oxidase inhibitor (MAOI), or use of an MOAI within the preceding 14 days

Warnings and Precautions [3,4]

- Serious cardiovascular events: Avoid use in patients with known structural cardiac abnormalities, cardiomyopathy, serious heart arrhythmias, or coronary artery disease.
- Blood pressure and heart rate increases: Monitor blood pressure and pulse.
- Psychiatric Adverse Reactions: Evaluate for bipolar disorder prior to Azstarys use.
- Priapism: Immediate medical attention should be sought if signs or symptoms of prolonged penile erections or priapism are observed.
- Peripheral vasculopathy, including Raynaud's phenomenon: Careful observation for digital changes is necessary during treatment with ADHD stimulants.
- Long-term suppression of growth: Monitor height and weight at appropriate intervals in pediatric patients.

Adverse Effects [3,4]

Most common, ≥5 % (and at least twice the rate of placebo)
Decreased appetite
Decreased weight
Nausea
Abdominal pain
Dyspepsia
Vomiting
Insomnia
Anxiety
Affect lability
Irritability
Dizziness
Increased blood pressure
Tachycardia

Drug Interactions [3,4]

- MAOIs: Concomitant use of MAOIs and CNS stimulants can cause hypertensive crisis with potential outcomes of: death, stroke, myocardial infarction, aortic dissection, ophthalmological complications, eclampsia, pulmonary edema, and renal failure.
- Antihypertensive drugs: Azstarys may decrease the effectiveness of drugs used to treat hypertension.
- Halogenated anesthetics: Concomitant use of halogenated anesthetics and Azstarys may increase the risk of sudden blood pressure and heart rate increase during surgery.
- Risperidone: Combined use of MPH 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).

Dosage and Administration [3,4]

- Pediatric patients 6 to 12 years: Recommended starting dosage is 39.2 mg/7.8 mg orally once daily in the morning. Dosage may be increased to 52.3 mg/10.4 mg daily or decreased to 26.1 mg/5.2 mg daily after one week. Maximum recommended dosage is 52.3 mg/10.4 mg once daily.
- Adult and pediatric patients 13 to 17 years: Recommended starting dosage is 39.2 mg/7.8 mg orally once daily in the morning. Increase dosage after one week to 52.3 mg/10.4 mg once daily.
- Administer with or without food.
- Swallow capsules whole or open and sprinkle onto applesauce or add to water.
- Do **not** substitute for other MPH products on a milligram-per-milligram basis.

Cost

Generic Name	Brand Name	Manufacturer	Dose	Cost**/ Month
Serdexmethylphenidate/ dexmethylphenidate	Azstarys™	Corium, Inc.	39.2 mg/7.8 mg orally each morning	$387
Dexmethylphenidate ER	Focalin XR®	Novartis, various	5 mg to 40 mg orally each morning	$380 (5 mg brand); $187 (5 mg generic)

** Wholesale Acquisition Cost

Conclusion

Azstarys is a combination of serdexmethylphenidate (a prodrug of dexmethylphenidate) and dexmethylphenidate, both of which are CNS stimulants. It is indicated for the treatment of ADHD in patients ≥6 years of age. The efficacy of Azstarys was established in a randomized, double-blind, placebo-controlled, parallel group, analog classroom study with 150 participants ages 6 to 12 years. The study was conducted in four phases: Screening Period, Open-Label Dose Optimization Phase (3 weeks), Double-Blind Treatment Phase, and Follow-Up Visit.
The primary efficacy endpoint was the mean change from baseline of the SKAMP-Combined scores averaged across the test day. This mean change from baseline was statistically significantly lower with Azstarys compared to placebo. Adverse events include: decreased appetite, decreased weight, nausea, abdominal pain, dyspepsia, vomiting, anxiety, affect lability, irritability, dizziness, increased blood pressure, and tachycardia. Although Azstarys is similar to other branded agents for ADHD, the utilization of Azstarys will be determined by the extent that prescribers believe that it is differentiated from the other long-acting stimulants on the market.

Recommendation

This drug is being considered for inclusion in the state specific Preferred Drug List (PDL) as non-preferred.

References

1) Wolraich ML, Hagan JF, Allan C, et al. AAP SUBCOMMITTEE ON CHILDREN AND ADOLESCENTS WITH ATTENTION-DEFICIT/HYPERACTIVE DISORDER. Clinical Practice Guideline for the Diagnosis, Evaluation, and Treatment of Attention-Deficit/Hyperactivity Disorder in Children and Adolescents. *Pediatrics*. 2019;144(4):e20192528
2) IPD Analytics. Azstarys New Drug Review: Azstarys. March 2021.
3) Azstarys [package insert]. Grand Rapids, MI: Corium, Inc.; August 2021.
4) Clinical Pharmacology [drug reference database]. Available at: https://www.clinicalkey.com/pharmacology/. Accessed: September 17, 2021.

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