HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use AZSTARYS safely and effectively. See full prescribing information for AZSTARYS.

AZSTARYS (serdexmethylphenidate and dexmethylphenidate) capsules, for oral use, CII
Initial U.S. Approval: 2021

WARNING: ABUSE, MISUSE, AND ADDICTION
***See full prescribing information for complete boxed warning*.**

AZSTARYS has a high potential for abuse and misuse, which can lead to the development of a substance use disorder, including addiction. Misuse and abuse of CNS stimulants, including AZSTARYS, can result in overdose and death (5.1, 9.2, 10):

Before prescribing AZSTARYS

Educate patients and their families about these risks, proper storage of the drug, and proper disposal of any unused drug.

frequently monitor for signs and symptoms of abuse, misuse, and addiction.

----------RECENT MAJOR CHANGES----------

Boxed Warning	10/2023
Dosage and Administration (2.1, 2.3, 2,5)	10/2023
Warnings and Precautions (5.1, 5.2, 5.8, 5.9, 5.10)	10/2023

----------INDICATIONS AND USAGE----------

AZSTARYS is a central nervous system (CNS) stimulant indicated for

FULL PRESCRIBING INFORMATION: CONTENTS*

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1. INDICATIONS AND USAGE
2. DOSAGE AND ADMINISTRATION
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5.1 Abuse, Misuse,

Adults and Pediatric Patients 13 to 17 years of age

The recommended starting dosage of AZSTARYS is 39.2 mg serdexmethylphenidate/7.8 mg dexmethylphenidate once daily in the morning.
Increase the dosage after one week to a dosage of 52.3 mg serdexmethylphenidate/10.4 mg dexmethylphenidate per day, depending on response and tolerability.
Maximum recommended dosage is 52.3 mg serdexmethylphenidate/10.4 mg dexmethylphenidate once daily.

2.3 Administration Instructions

Administer AZSTARYS orally once daily in the morning with or without food *[see Clinical Pharmacology (12.3)]*.

AZSTARYS capsules may be taken whole, or opened and the entire contents sprinkled into 50 mL 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 *[see Clinical Pharmacology (12.3)]*.

2.4 Switching from Other Methylphenidate Products

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 *[see Description (11), Clinical Pharmacology (12.3)]*.

2.5 Dosage Reduction and Discontinuation

If paradoxical aggravation of symptoms or other adverse reactions occur, reduce dosage or, if necessary, discontinue AZSTARYS. If improvement is not observed after appropriate dosage adjustment over a one-month period, discontinue AZSTARYS.

3 DOSAGE FORMS AND STRENGTHS

AZSTARYS capsules are available as:

26.1 mg/5.2 mg (serdexmethylphenidate/dexmethylphenidate) – blue cap/grey body, imprinted with "286" on cap and "KP415" on the body
39.2 mg/7.8 mg (serdexmethylphenidate/dexmethylphenidate) – dark blue cap/grey body, imprinted with "429" on cap and "KP415" on the body
52.3 mg/10.4 mg (serdexmethylphenidate/dexmethylphenidate) – orange cap/grey body, imprinted with "5612" on cap and "KP415" on the body

4 CONTRAINDICATIONS

AZSTARYS is contraindicated in patients:

with known hypersensitivity to serdexmethylphenidate, methylphenidate, or other components of AZSTARYS. Bron

5.4 Psychiatric Adverse Reactions

Exacerbation of Pre-Existing Psychosis

CNS stimulants may exacerbate symptoms of behavior disturbance and thought disorder in patients with a pre-existing psychotic disorder.

Induction of a Manic Episode in Patients with Bipolar Disorder

CNS stimulants may induce a manic or mixed mood episode in patients. Prior to initiating AZSTARYS treatment, screen patients for risk factors for developing a manic episode (e.g., comorbid or history of depressive symptoms or a family history of suicide, bipolar disorder, or depression).

New Psychotic or Manic Symptoms

CNS stimulants, at the recommended dosage, may cause psychotic or manic symptoms (e.g., hallucinations, delusional thinking, or mania) in patients without a prior history of psychotic illness or mania. In a pooled analysis of multiple short-term, placebo-controlled studies of CNS stimulants, psychotic or manic symptoms occurred in approximately 0.1% of CNS stimulant-treated patients, compared to 0% of placebo-treated patients. If such symptoms occur, consider discontinuing AZSTARYS.

5.5 Priapism

Prolonged and painful erections, sometimes requiring surgical intervention, have been reported with methylphenidate use

5.7 Long-Term Suppression of Growth in Pediatric Patients

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 *[see Adverse Reactions (6.1)]*.

Closely monitor growth (weight and height) in AZSTARYS-treated pediatric patients. Pediatric patients who are not growing or gaining height or weight as expected may need to have their treatment interrupted.

5.8 Acute Angle Closure Glaucoma

There have been reports of angle closure glaucoma associated with methylphenidate treatment.

Although the mechanism is not clear, AZSTARYS-treated patients considered at risk for acute angle closure glaucoma (e.g., patients with significant hyperopia) should be evaluated by an ophthalmologist.

5.9 Increased Intraocular Pressure and Glaucoma

There have been reports of an elevation of intraocular pressure (IOP) associated with methylphenidate treatment *[see Adverse Reactions (6.2)]*.

Prescribe AZSTARYS to patients with open-angle glaucoma or abnormally increased IOP only if the benefit of treatment is considered to outweigh the risk. Closely monitor AZSTARYS-treated patients with a history of abnormally increased IOP or open angle glaucoma.

5.10 Motor and Ve

CNS stimulants, including methylphenidate, have been associated with the onset or exacerbation of motor and verbal tics. Worsening of Tourette's syndrome has also been reported *[see Adverse Reactions (6.2)]*.

Before initiating AZSTARYS, assess the family history and clinically evaluate patients for tics or Tourette's syndrome. Regularly monitor AZSTARYS-treated patients for the emergence or worsening of tics or Tourette's syndrome, and discontinue treatment if clinically appropriate.

6 ADVERSE REACTIONS

The following are discussed in more detail in other sections of the labeling:

Abuse, Misuse, and Addiction *[see Boxed Warning, Warnings and Precautions (5.1), and Drug Abuse and Dependence (9.2, 9.3)]*

Known hypersensitivity to methylphenidate or other ingredients of AZSTARYS *[see Contraindications (4)]*

Hypertensive Crisis with Concomitant Use of Monoamine Oxidase Inhibitors *[see Contraindications (4)]*

Risks to Patients with Serious Cardiac Disease *[see Warnings and Precautions (5.2)]*

Increased Blood Pressure and Heart Rate *[see Warnings and Precautions (5.3)]*

Psychiatric Adverse Reactions *[see Warnings and Precautions (5.4)]*

Priapism *[see Warnings and Precautions (5.5)]*

Peripheral Vasculopathy, including Raynaud's Phenomenon *[see Warnings and Precautions (5.6)]*

Long-Term Suppression of Growth in Pediatric Patients *[see Warnings and Precautions (5.7)]*

Acute Angle Closure Glaucoma *[see Warnings and Precautions (5.8)]*

Increased Intraocular Pressure and Glaucoma *[see Warnings and Precautions (5.9)]*

Motor and Verbal Tics, and Worsening of Tourette's Syndrome *[see Warnings and Precautions (5.10)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

Adverse Reactions in Studies with Other Methylphenidate Products in Pediatric Patients and Adults with ADHD

Commonly reported (≥ 5% of the methylphenidate group and at least twice the rate of the placebo group) adverse reactions from placebo-controlled trials of methylphenidate products include: decreased appetite, decreased weight, nausea, abdominal pain, dyspepsia, vomiting, insomnia, anxiety, affect lability, irritability, dizziness, increased blood pressure, and tachycardia.

Adverse Reactions in Studies with AZSTARYS in Pediatric Patients (6 to 12 years) with ADHD

Short-Term Study

A short-term study conducted in 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 (n=155), followed by a 1-week, double-blind, controlled phase in which patients were randomized to continue AZSTARYS (n=74) or switch to placebo (n=76). Because of the study design, the reported adverse reaction rates cannot be used to predict the rates that may be expected in clinical practice.

Long-Term Study

A long-term, open-label safety study was conducted in pediatric patients 6 to 12 years of age with ADHD who either completed the short-term study or were *de novo* patients. This

followed by a 12-month treatment phase for all patients during which 238 patients received open-label AZSTARYS and had evaluable safety data. A total of 154 patients were treated for 12 months. Because of the open-label, uncontrolled design of this study, the reported adverse reaction rates cannot be assessed in terms of a causal relationship to AZSTARYS treatment.

To adjust for normal growth, z-scores were derived (measured in standard deviations [SD]); z- scores normalize for the natural growth

Investigations: alkaline phosphatase increased, bilirubin increased, hepatic enzyme increased, platelet count decreased, white blood cell count abnormal

Musculoskeletal, Connective Tissue and Bone Disorders: arthralgia, myalgia, muscle twitching, rhabdomyolysis, muscle cramps

Nervous System: convulsion, grand mal convulsion, dyskinesia, serotonin syndrome in combination with serotonergic drugs, nervousness, headache, tremor, drowsiness, vertigo, motor and verbal tics

Psychiatric Disorders: disorientation, libido changes, hallucination, hallucination auditory, hallucination visual, logorrhea, mania, restlessness, agitation

Skin and Subcutaneous Tissue Disorders: alopecia, erythema, hyperhidrosis

Urogenital System: priapism

Vascular Disorders: Raynaud's phenomenon

7 DRUG INTERACTIONS

7.1 Clinically Important Interactions with AZSTARYS

Table 1 presents clinically important drug interactions with AZSTARYS.

Table 1: Clinically Important Drug Interactions with AZSTARYS

Monoamine Oxidase Inhibitors (MAOIs)	
Clinical Impact:	Concomitant use of MAOIs and CNS stimulants, including AZSTARYS, can cause hypertensive crisis. Potential outcomes include death, stroke, myocardial infarction, aortic dissection, ophthalmological complications, eclampsia, pulmonary edema, and renal failure *[see Contraindications (4)]*.
Intervention:	Do not administer AZSTARYS concomitantly with MAOIs or within 14 days after discontinuing MAOI treatment *[see Contraindications (4)]*.
Antihypertensive Drugs	
Clinical Impact	AZSTARYS

Risperidone

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.

Data

Animal Data

In embryo-fetal development studies conducted in rats and rabbits, dexmethylphenidate hydrochloride was administered orally at doses of up to 20 and 100 mg/kg/day, respectively, during the period of organogenesis. No evidence of malformations was found in either the rat or rabbit study; however, delayed fetal skeletal ossification was observed at the highest dose level in rats. When dexmethylphenidate hydrochloride was administered to rats throughout pregnancy and lactation at doses of up to 20 mg/kg/day, post-weaning body weight gain was decreased in male offspring at the highest dose, but no other effects on postnatal development were observed. At the highest doses tested, plasma levels [area under the curves (AUCs)] of dexmethylphenidate in pregnant rats and rabbits were approximately 3 and 1 times, respectively, those in adults dosed with 40 mg/day dexmethylphenidate hydrochloride.

Racemic methylphenidate hydrochloride has been shown to cause malformations (increased incidence of fetal spina bifida) in rabbits when given in doses of 200 mg/kg/day throughout organogenesis.

No evidence of developmental effects were found in an embryo-fetal development study with oral administration of serdexmethylphenidate in rabbits during organogenesis at doses of up to 374 mg/kg/day. At the highest dose tested, the plasma level [area under the curve (AUC)] of serdexmethylphenidate in pregnant rabbits was approximately 49 times that in adults dosed with 52 mg/day serdexmethylphenidate.

8.2 Lactation

Risk Summary

There are no available data on the presence of serdexmethylphenidate in human milk, effects on the breastfed infant, or effects on milk production. Dexmethylphenidate is the d-threo enantiomer of racemic methylphenidate. Limited published literature, based on milk sampling from seven mothers reports that methylphenidate is present in human milk, which resulted in infant doses of 0.16% to 0.7% of the maternal weight-adjusted dosage and a milk/plasma ratio ranging between 1.1 and 2.7. There are no reports of adverse effects on the breastfed infant and no effects on milk production. Long-term neurodevelopmental effects on infants from stimulant exposure are unknown. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for AZSTARYS and any potential adverse effects on the breastfed infant from AZSTARYS or from the underlying maternal condition.

Clinical Considerations

Monitor breastfeeding infants for adverse reactions, such as agitation, anorexia, and reduced weight gain.

8.4 Pediatric Use

The safety and effectiveness of AZSTARYS have been established in pediatric patients ages 6 to 17 years

Serdexmethylphenidate was administered orally to juvenile rabbits at doses up to 280 mg/kg/day (approximately 50 times the MRHD of 52 mg/day serdexmethylphenidate given to children on a mg/m^2 basis), respectively, for 6 months, starting at postnatal Day 28 and continuing through sexual maturity (postnatal Day 196). No adverse findings were observed at the highest dose of serdexmethylphenidate.

8.5 Geriatric Use

Clinical trials of AZSTARYS did not include any patients aged 65 years and over.

9 DRUG ABUSE AND DEPENDENCE

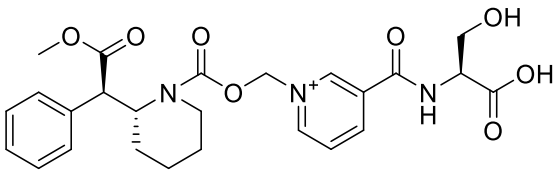
9.1 Controlled Substance

AZSTARYS contains dexmethylphenidate hydrochloride, a Schedule II controlled substance, and serdexmethylphenidate, a Schedule IV controlled substance.

9.2 Abuse

AZSTARYS has a high potential for abuse and misuse which can lead to the development of a substance use disorder, including addiction *[see Warnings and Precautions (5.1)]*. AZSTARYS

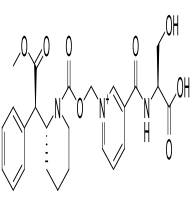
The chemical name of serdexmethylphenidate chloride is 3-(((*1S*)-1-carboxy-2-hydroxyethyl)carbamoyl)-1-((((*2R*)-2-(2-(*1R*)-methoxy-2-oxo-1-phenylethyl)piperidine-1-carbonyl)oxy)methyl)pyridinium chloride. Its molecular formula is $C_{25}H_{30}N_3O_8^+ \bullet Cl^-$, and its structural formula is:



Dexmethylphenidate is 357 n 10.112 792

Serdexmethylphenidate chloride is a white to off-white crystalline powder. Its solutions are acid to litmus. It is freely soluble in water, soluble in methanol, and slightly soluble in alcohol and acetone. Its molecular weight is 535.98 g/mol.

Dexmethylphenidate is the *d-threo* enantiomer of racemic *d*,*l*-methylphenidate hydrochloride. The chemical name of dexmethylphenidate hydrochloride is methyl (*R*)-2-phenyl-2-((*R*)-piperidin-2-yl)acetate hydrochloride. Its molecular formula is $C_{14}H_{19}NO_2$



12.2 Pharmacodynamics

Dexmethylphenidate

Race

There is insufficient experience with the use of AZSTARYS to detect ethnic variations in pharmacokinetics.

Age

The shapes of the plasma concentration time profiles for dexmethylphenidate were similar in pediatric patients (6 to 17 years of age) with ADHD and healthy adults. After the same dose administration of AZSTARYS, dexmethylphenidate exposure in pediatric patients (13 to 17 years of age) and adults was about half of that in pediatric patients 6 to 12 years of age. Plasma concentrations of dexmethylphenidate when adjusted for dose and body weight were similar across all age groups.

Renal Impairment

There is no experience with the use of AZSTARYS 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.

Hepatic Impairment

There is no experience with the use of AZSTARYS in patients with hepatic impairment.

Drug Interaction Studies

Clinical Studies

CYP2D6 substrate: No clinically significant differences in desipramine (CYP2D6 substrate) were observed when co-administered with methylphenidate.

In Vitro Studies

Alcohol: No clinically significant differences in the rate or amount of release of either serdexmethylphenidate or methylphenidate were observed with alcohol concentrations of 5% and 40%.

Cytochrome P450 (CYP) enzymes: Serdexmethylphenidate and methylphenidate do not appear to be substrates, inducers or inhibitors of CYP1A2, 2C8, 2C9, 2C19, 2D6, 2E1 or 3A.

Transporters:

Carcinogenesis

Lifetime studies to evaluate the carcinogenic potential of serdexmethylphenidate have not been conducted.

Lifetime carcinogenicity studies have not been carried out with dexmethylphenidate hydrochloride.

In a lifetime carcinogenicity study carried out in B6C3F1 mice, racemic methylphenidate caused an increase in hepatocellular adenomas, and in males only, an increase in hepatoblastomas was seen at a daily dose of approximately 60 mg/kg/day. This dose is approximately 4 times the MRHD of 40 mg of dexmethylphenidate hydrochloride on a mg/m^2 basis. Hepatoblastoma is a relatively rare rodent malignant tumor type. There was no increase in total malignant hepatic tumors. The mouse strain used is sensitive to the development of hepatic tumors, and the significance of these results to humans is unknown.

Racemic methylphenidate hydrochloride did not cause any increase in tumors in a lifetime carcinogenicity study carried out in F344 rats; the highest dose used was approximately 45 mg/kg/day, which is approximately 5 times the MRHD of 40 mg of dexmethylphenidate hydrochloride on a mg/m^2 basis.

In a 24-week carcinogenicity study with racemic methylphenidate in the transgenic mouse strain p53+/-, which is sensitive to genotoxic carcinogens, there was no evidence of carcinogenicity. Male and female mice were fed diets containing the same concentrations as in the lifetime carcinogenicity study; the high-dose group was exposed to 60 to 74 mg/kg/day of racemic methylphenidate hydrochloride.

Mutagenesis

Serdexmethylphenidate was not mutagenic in the in vitro Ames reverse mutation assay, in the in vitro mammalian cell micronucleus assay using human peripheral blood lymphocytes, in the in vivo rat bone barrow micronucleus assay, or in the in vivo rat alkaline comet assay.

Dexmethylphenidate was not mutagenic in the in vitro Ames reverse mutation assay, in the in vitro mouse lymphoma cell forward mutation assay, or in the in vivo mouse bone marrow micronucleus test. In an in vitro assay using cultured Chinese Hamster Ovary (CHO) cells treated with racemic methylphenidate, sister chromatid exchanges and chromosome aberrations were increased, indicative of a weak clastogenic response.

Impairment of Fertility

Racemic methylphenidate hydrochloride did not impair fertility in male or female mice that were fed diets containing the drug in an 18-week continuous breeding study. The study was conducted

14 CLINICAL STUDIES

Pediatric Patients 6 to 12 years of age with ADHD

The efficacy of AZSTARYS for the treatment of ADHD in pediatric patients 6 to 12 years of age was evaluated in a randomized, double-blind, placebo-controlled, parallel group, analog classroom study (Study 1; NCT# 03292952). That study was conducted in 150 pediatric patients 6 to 12 years of age who 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).

Following washout of previous ADHD medication, subjects entered an open-label dose-optimization period (3 weeks) with an initial dosage of 39.2 mg/7.8 mg once daily in the morning. The dose could be titrated on a weekly basis to either 26.1 mg/5.2 mg, 39.2 mg/7.8 mg, or 52.3 mg

Table 2

Adults and Pediatric Patients 13 to 17 years of age with ADHD

The efficacy of 52.3 mg/10.4 mg 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 [see Clinical Pharmacology (12.3)].

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Bottles of 100 ..... NDC 65038-0561-99

Storage

Store at 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C to 30°C (59°F to 86°F). [See USP Controlled Room Temperature]. Protect from moisture.

Dispense in tight container (USP).

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- Instruct patients about the risk of peripheral vasculopathy, including Raynaud's phenomenon, and associated signs and symptoms: fingers or toes may feel numb, cool, painful, and/or may change color from pale, to blue, to red.
- Instruct patients to report to their physician any new numbness, pain, skin color change, or sensitivity to temperature in fingers or toes.
- Instruct patients to call their physician immediately with any signs of unexplained