Drugs & Therapy Perspectives (2018) 34:411–419
https://doi.org/10.1007/s40267-018-0539-6

ADIS DRUG Q&A

Amphetamine extended-release oral suspension (Adzenys ER™) and orally disintegrating tablets (Adzenys XR-ODT®) in attention-deficit hyperactivity disorder: a profile of their use

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Published online: 1 August 2018

Abstract
Amphetamine extended-release oral suspension (Adzenys ER™) and extended-release orally disintegrating tablets (Adzenys XR-ODT®) are easy-to-administer, long-acting, and convenient CNS stimulant options for treating attention-deficit hyperactivity disorder (ADHD) in children aged ≥ 6 years, adolescents, and adults. The bioavailability of *d*- and *l*-amphetamine with Adzenys ER™ suspension and XR-ODT® is equivalent to that of a corresponding dose of the reference product [i.e. mixed amphetamine salt extended-release capsules (MAS ER)], which has well-established efficacy, tolerability, and safety profiles. As Adzenys ER™ suspension/XR-ODT® contain both immediate- and extended-release amphetamine particles, plasma concentrations of *d*- and *l*-amphetamine increase rapidly, remain relatively stable for several hours, then slowly decline, allowing for once-daily administration. The use of Adzenys ER™ suspension/XR-ODT® may be of particular benefit in individuals who require a rapid onset and prolonged reduction in ADHD symptoms, as well as those who have difficulty swallowing tablets or capsules whole (neither formulation requires swallowing whole tablets/capsules, and both may be taken without regard to food).

Adis evaluation of Adzenys ER™ suspension/ XR-ODT® in the treatment of ADHD

Bioequivalent to a corresponding dose of MAS ER, which has well-established efficacy, tolerability and safety profiles
Adzenys ER™ suspension/XR-ODT® 3.1, 6.3, 9.4, 12.5, 15.7, and 18.8 mg are equivalent to MAS ER 5, 10, 15, 20, 25, and 30 mg, respectively
Provides rapid and sustained increases in *d*- and *l*-amphetamine plasma concentrations, allowing for once-daily administration
Both orange-flavored formulations are easy and convenient to administer, and may be taken with or without food

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How is attention-deficit hyperactivity disorder treated?

Attention-deficit hyperactivity disorder (ADHD) is a chronic neurobehavioral disorder that begins in childhood and may persist throughout adulthood in some patients [1–6]. Pharmacologic treatment and behavioral therapy, alone or together, are used to treat ADHD symptoms, such as inattention, hyperactivity, and impulsivity [1–6].

The pharmacologic treatment of ADHD generally involves the use of CNS stimulants, with various formulations of amphetamine and methylphenidate (all of which have comparable effectiveness, tolerability, and safety profiles) being commonly used [4–8]. Other, generally less commonly used, options include atomoxetine, extended-release guanfacine, and extended-release clonidine [5, 7, 8]. The mechanism of action of amphetamines in the treatment of ADHD is thought to involve restoring the imbalance in dopamine and norepinephrine (noradrenaline) levels in the areas of the brain involved in cognition and emotion; however, their exact mode of therapeutic action is not yet known [6, 9–11]. By blocking the re-uptake of dopamine and norepinephrine from the synaptic cleft into

the presynaptic neurons, amphetamines increase the levels of these monoamine neurotransmitters in the synaptic cleft, thereby leading to an improvement in the clinical symptoms of ADHD.

To provide once-daily, long-acting options to treat ADHD in school-aged children, adolescents, and adults, Neos Therapeutics (Grand Prairie, TX) have developed the following two extended-release formulations of amphetamine: an orange-flavored oral suspension (Adzenys ER™ suspension) [9] and orange-flavored orally disintegrating tablets (Adzenys XR-ODT®) [10]. Adzenys ER™ oral suspension and XR-ODT® contain a 3:1 ratio of *d*- and *l*-amphetamine loaded onto a nearly equivalent mixture of immediate-release and polymer-coated extended-release resin particles. The immediate-release particles are uncoated and are designed to be absorbed in the stomach, whereas the extended-release particles have a pH-dependent, acid-resistant coating that is designed to dissolve in the alkaline environment of the intestinal tract, thereby prolonging the release and activity of amphetamine. The tradenames of these formulations are used hereafter to avoid confusion with other extended-release formulations of amphetamine.

For whom are Adzenys ER™ suspension/XR-ODT® indicated?

In the USA, Adzenys ER™ oral suspension [9] and XR-ODT® [10] are indicated for the treatment of ADHD in children and adolescents aged 6−17 years, and adults (Table 1). The dosage should be individualized based on the response and needs of the patient (Table 1). Doses of 3.1, 6.3, 9.4, 12.5, 15.7 and 18.8 mg of Adzenys ER™ suspension/XR-ODT® are equivalent to 5, 10, 15, 20, 25, and 30 mg of mixed amphetamine salts (MAS) extended-release capsules (MAS ER).

What evidence supports the US approval of Adzenys ER™ suspension/XR-ODT®?

As Adzenys ER™ suspension [12] and XR-ODT® [13] have been shown to bioequivalent to the reference product MAS ER (Adderall XR®) in healthy adults, clinical trials of Adzenys ER™ suspension and XR-ODT® were not required prior to approval by the US FDA [9, 10]. Instead, their approval was based on the clinical evidence for the efficacy and tolerability of MAS ER in the treatment of ADHD in randomized, double-blind trials in treatment-naïve or treatment-experienced children [14, 15], adolescents [16], and adults [17].

The following sections summarize the results of single-dose bioequivalence and other pharmacokinetic studies of Adzenys ER™ suspension [12, 18, 19] and XR-ODT® [13, 20, 21], and of the clinical trials [14–17] supporting the use of these amphetamine formulations.

Evidence of bioequivalence to mixed amphetamine salts extended-release capsules (MAS ER)

The bioequivalence of a single 18.8-mg dose of Adzenys ER™ suspension [12] and XR-ODT® [13] to an equivalent single 30-mg dose of MAS ER was established in two single-dose, randomized, open-label crossover studies in healthy adults (completer $n = 42$ [12] and 39 [13]).

- *Adzenys ER™ suspension* [12] Exposure to *d*- and *l*-amphetamine following administration of 18.8 mg of Adzenys ER™ suspension was bioequivalent to that of 30 mg of MAS ER. The 90% confidence intervals (CIs) for the Adzenys XR-ODT®: MAS ER least-squares geometric mean (LSM) ratios for maximum plasma concentration (C_{max}), area under the concentration–time curve (AUC) from time zero to 5 h ($AUC_{0–5}$), AUC from 5 h to last quantifiable concentration ($AUC_{5–last}$), and AUC from time zero to infinity ($AUC_{0–\infty}$) were within the standard bioequivalence CIs of 80–125% for both *d*- and *l*- amphetamine.
- *Adzenys XR-ODT®* [13] Administration of 18.8 mg of Adzenys XR-ODT® resulted in exposure to *d*- and *l*-amphetamine that was bioequivalent to that of 30 mg of MAS ER. The 90% CIs for Adzenys XR-ODT®: MAS ER LSM ratios for C_{max}, $AUC_{0–last}$, $AUC_{0–\infty}$, and $AUC_{5–last}$ were within the standard 90% bioequivalence CIs of 80–125% for both *d*- and *l*- amphetamine.

Pharmacokinetic profiles

Randomized, open-label studies of the pharmacokinetics of Adzenys ER™ suspension [18, 19] and XR-ODT® [13, 20] have been conducted in children aged 6–12 years with ADHD [18, 20] and healthy adults aged 20–70 years [13, 19] (Table 2). Unless otherwise noted, participants received a single 18.8 mg dose of Adzenys ER™ suspension [18, 19] or XR-ODT® [13, 20] under fasting conditions.

The overall pharmacokinetic profiles of Adzenys ER™ suspension and XR-ODT® allow once-daily administration with or without food, with bodyweight appearing to be the

Table 1 Dosage and administration of Adzenys ER™ oral suspension [9] and Adzenys XR-ODT® [10] in the treatment of ADHD in the USA

What is the approved indication of Adzenys ER™ suspension/XR-ODT®?	
CNS stimulant indicated for the treatment of ADHD in patients aged ≥ 6 years	
How are Adzenys ER™ suspension/XR-ODT® available?	
Adzenys ER™ suspension	Orange-flavored suspension containing 1.25 mg amphetamine per mL
Adzenys XR-ODT®	Orange-flavored tablets containing 3.1, 6.3, 9.4, 12.5, 15.7 or 18.8 mg amphetamine
How should patients/caregivers store and discard Adzenys ER™ suspension/XR-ODT®?	
Storage	Suspension: store in a tight container with a child-resistant closure
	Tablets: remove blister packages from the carton, and store in the ridged, plastic travel case provided
	Both: store at 20–25 °C (68–77 °F); excursions to 15–30 °C (59–86 °F) are permitted
	Both: store in a safe (preferably locked) place to prevent misuse and abuse
Disposal of remaining, unused, or expired suspension/tablets	Follow local laws/regulations for the disposal of CNS stimulants
	Take to authorized collection sites (e.g. retail, clinic, or hospital pharmacies, and law enforcement location)
	If no authorized collector is available, mix tablets/suspension with an undesirable, nontoxic substance (e.g. dirt, cat litter, used coffee grounds) to make it less appealing to children and pets; place the mixture in a container (e.g. sealed plastic bag); discard in the household trash
What is the recommended dosage of Adzenys ER™ suspension/XR-ODT®?	
Starting dosage	Children and adolescents aged 6–17 years: 6.3 mg (5 mL suspension) once daily in the morning
	Adults: 12.5 mg (10 mL suspension) once daily in the morning
Dose titration	Children and adolescents aged 6–17 years: ↑ weekly in increments of 3.1 or 6.3 mg per day, based on the needs/responses of the individual
Maximum dosage	Children aged 6–12 years: 18.8 mg (15 mL suspension)
	Adolescents aged 13–17 years and adults: 12.5 mg (10 mL suspension)
How should patients be switched from other amphetamine products to Adzenys ER™ suspension/XR-ODT®?	
Do not substitute Adzenys ER™ suspension or XR-ODT® for other amphetamine products on a mg-per-mg basis (base compositions and pharmacokinetic profiles differ between products)	
Switch from Adderall XR®	Switch to an equivalent dose of once-daily Adzenys ER™ suspension or XR-ODT® (5, 10, 15, 20, 25 and 30 mg/day of Adderall XR® are equivalent to 3.1, 6.3, 9.4, 12.5, 15.7 and 18.8 mg/day of Adzenys ER™ suspension or XR-ODT®)
Switch from other amphetamine products	Switch to Adzenys ER™ suspension or XR-ODT® using the recommended starting dosage and titration schedule
How should Adzenys ER™ suspension be administered?	
Shake bottle before administration	
Measure the prescribed dose using an oral dosing device or other suitable measuring device, which should be provided by the pharmacist	
Dispense directly into the mouth using the dosing/measuring device; wash the device after each use	
Do not mix with food or other liquids before consuming	
Take with or without food	
How should Adzenys XR-ODT® be administered?	
Immediately prior to administration, remove the tablet from the blister pack by peeling back the foil (do not push the tablet through the foil)	
Remove the tablet with dry hands as soon as the blister is opened, and place the whole tablet on the patient's tongue	
Allow the tablet to disintegrate on the tongue without chewing or crushing	
No liquid is needed to take the tablet; the tablet will disintegrate in saliva so it can be swallowed	
Take with or without food	

ADHD attention-deficit hyperactivity disorder, *ER/XR* extended-release, *ODT* orally disintegrating tablet, ↑ increase

primary determinant of apparent age-related differences in some parameters [9, 10]. The threefold higher exposure to *d*-amphetamine than to *l*-amphetamine (Table 2) is in keeping with the 3: 1 ratio of *d*-amphetamine and *l*-amphetamine in these formulations [13, 18–20].

In children

Following administration of Adzenys ER™ suspension or XR-ODT® in children aged 6–12 years, plasma concentrations of *d*- and of *l*-amphetamine increased rapidly, followed

by broad AUC peak, then by a slow decline (Table 2), in keeping with extended-release profile of these formulations [18, 20].

For both Adzenys ER™ suspension and XR-ODT®, the 95% CIs for geometric mean weight-normalized clearance (CL/F/kg) and weight-normalized volume of distribution (Vd/F/kg) for *d*- and *l*-amphetamine usually fell within the target range of 60–140% for each age group (i.e. 6–7, 8–9, and 10–12 years) [18, 20]. The only exception was CL/F/kg in children aged 6–7 years in the study of Adzenys ER™ suspension [18].

Overall, the pharmacokinetic profile of *d*- and *l*-amphetamine was more variable in children aged 6–7 years than in the older age groups (Table 2) [18, 20]. In addition, mean values for the CL/F/kg of *d*- and *l*-amphetamine increased as age increased from 6–7 to 10 – 12 years, whereas corresponding values for mean Vd/F/kg decreased as age increased [18, 20].

Mean elimination half-life ($t_{½}$) values for *d*- and *l*-amphetamine also decreased as children aged (Table 2). The decrease in exposure with increasing age in these studies may have been caused by the use of a fixed-dose across all body weights from 20 to 56 kg, leading to lower doses/kg in older/heavier children, and the slight increase in clearance of amphetamine with increased age [18, 20]. Overall, when doses are weight normalized, systemic exposure to amphetamine was 30% lower in children than in adults [9, 10].

In adults

The overall pharmacokinetic profile of Adzenys ER™ suspension and XR-ODT® over time in adults is comparable to that in children and adolescents (i.e. a rapid increase in plasma concentrations of *d*- and *l*-amphetamine, followed by a relatively broad AUC peak and a slow decline) [9, 10]. Following administration of Adzenys ER™ suspension and XR-ODT® in adults, C_{max} of *d*- and *l*-amphetamine were achieved in ≈ 5 h, with a mean $t_{½}$ of ≈ 12 – 14 h (Table 2) [19].

Potential for food and drug interactions

Adzenys ER™ suspension and XR-ODT® may be taken with or without food [9, 10].

Relative to when a single 18.8 mg dose of Adzenys ER™ suspension or XR-ODT® was administered to adults in the fasted state, administration 30 min after a high-fat meal was associated with decreases in mean C_{max} values for *d*-amphetamine of 11% (Adzenys ER™ suspension) [19] and 19% (Adzenys XR-ODT®) [13]. Median t_{max} values for *d*- and *l*-amphetamine were ≈ 0.5–1 h (Adzenys ER™ suspension) or ≈ 0.2–2.5 h (Adzenys XR-ODT®) shorter in the fed state than in the fasted state [13, 19]. However, these pharmacokinetic differences were not considered to be clinically relevant [9, 10, 13, 19].

Table 2 Pharmacokinetic profiles of single 18.8 mg doses of Adzenys ER™ oral suspension and Adzenys XR-ODT® under fasting conditions in children with ADHD aged 6–12 years and healthy adults aged 20–70 years

Parameter	Adzenys ER™ oral suspension [18, 19]		Adzenys XR-ODT® [13, 20]	
	d-Amphetamine	*l*-Amphetamine	*d*-Amphetamine	*l*-Amphetamine
Children with ADHD (*n* = 28 in both studies [18, 20])				
Mean C_{max} ± SD (ng/mL)				
6–7 years old	76.8 ± 15.2	26.6 ± 4.7	102.0 ± 18.3	30.9 ± 5.6
8–9 years old	68.0 ± 8.1	23.9 ± 2.4	89.4 ± 14.6	27.7 ± 3.6
10–12 years old	60.0 ± 7.1	20.2 ± 2.2	75.4 ± 18.7	24.2 ± 5.2
Mean t_{max} (h)				
6–7 years old	5.7 ± 1.7	5.9 ± 1.9	3.8 ± 0.8	4.7 ± 1.8
8–9 years old	5.0 ± 1.8	6.3 ± 2.7	5.6 ± 1.8	5.6 ± 1.9
10–12 years old	5.3 ± 1.2	5.5 ± 1.1	6.5 ± 2.3	6.7 ± 2.3
Mean $t_{½}$ ± SD (h)				
6–7 years old	16.7 ± 10.7	24.6 ± 25.9	9.4 ± 1.9	10.9 ± 2.6
8–9 years old	12.6 ± 2.5	13.1 ± 3.1	9.0 ± 1.2	10.3 ± 1.7
10–12 years old	9.6 ± 1.0	10.6 ± 1.0	10.0 ± 2.0	11.7 ± 2.2
Healthy adults (*n* = 29 [19] and 39 [13])				
Mean C_{max} ± SD (ng/mL)	51.9 ± 9.0	16.4 ± 3.0	44.9 ± 8.9	14.5 ± 3.0
Median t_{max} (h) [range]	5.0 [3.0–7.0]	5.0 [3.0–7.5]	5.0 [3.0–12.0]	5.25 [3.0–12.0]
Mean $t_{½}$ ± SD (h)	11.8 ± 1.8	14.5 ± 2.8	11.3 ± 2.0	12.9 ± 2.7

ADHD attention-deficit hyperactivity disorder, C_{max} maximum plasma concentration, *ER/XR* extended-release, *SD* standard deviation, t_{max} time to C_{max}, $t_{1/2}$ elimination half-life, *ODT* orally disintegrating tablet

Certain classes of drugs [i.e. gastrointestinal acidifying and alkalizing agents, monoamine oxidase inhibitors (MAOIs), serotonergic drugs, and tricyclic antidepressants (TCAs)] have the potential to interact with Adzenys ER™ suspension/XR-ODT®, and may result in clinically important outcomes (Table 3) [9, 10]. The concomitant use of Adzenys ER™ suspension/XR-ODT® is contraindicated with MAOIs, is not advised with GI alkalinizing agents or requires precautionary measures with serotonergic drugs and TCAs [9, 10].

As the consumption of alcohol may result in a more rapid release of amphetamine from Adzenys ER™ suspension/XR-ODT®, patients taking Adzenys ER™ suspension/XR-ODT® should be advised to avoid alcohol [9, 10]. The release of amphetamine did not increase in the presence of 5, 10 or 20% alcohol, but substantially increased in the presence of 40% alcohol in an in vitro alcohol-induced dose dumping study [9, 10]. However, in a study in which 32 healthy adults received a single 18.8 mg dose of Adzenys XR-ODT® followed by consumption of 240 mL of 4, 20 or 40% alcohol within 30 min, exposure to *d*- and *l*-amphetamine did not differ to a significant extent relative to intake of the same volume of deionized water [21].

Efficacy evidence supporting the US approval of Adzenys ER™/XR-ODT®

The 3- [15] - and 4-week [16, 17] multicenter trials used as evidence to support the US approval of Adzenys ER™ suspension/XR-ODT® enrolled patients who met DSM-IV criteria for ADHD. These trials started with a washout period, followed by randomization to the treatment groups. In groups receiving MAS ER, patients receiving the lowest-dose of MAS-ER in the trial for the first week, followed by forced titration to achieve the final dosage of MAS ER to which the patient had been randomized (i.e. the daily dose of MAS ER was increased by increments of 10 mg at the beginning of each week until the final assigned dosage was reached).

In children

The clinical efficacy of Adzenys ER™ suspension and XR-ODT® in children aged 6–12 years with ADHD was established based on the results of the following trials of oral MAS ER 10, 20, and 30 mg capsules administered once daily in the morning [14, 15].

- *Classroom analog study* [14] Following a 1- week run-in period with MAS ER 20 mg/day to assess individual tolerability, 51 children with ADHD were randomized in a crossover design to each of the 5 treatment weeks [i.e. once-daily placebo, MAS 10 mg (active control), or MAS ER 10, 20, or 30 mg]. Children were assessed at intervals of ≈ 1.5 h, over 12 h, on seven consecutive Saturdays. In the intent-to-treat (ITT) population ($n = 49$), MAS ER 10, 20, and 30 mg/day provided better efficacy than placebo and was at least as effective as MAS 10 mg/day, as assessed by Swanson, Alger, M-Flynn and Pelham attention and deportment scores, and Permanent Product Measure of Performance scores, which assess academic performance. The improvement in ADHD symptoms and the duration of response were dependent on the dose of MAS ER.
- *Multicenter 3-week trial* [10, 15] Children ($n = 584$) were randomized to receive once-daily placebo, or once-daily MAS ER force-titrated to 10, 20, or 30 mg [15]. In the ITT population ($n = 563$), ADHD Rating Scale-IV (ADHD-RS-IV) scores based on attention and hyperactivity levels as assessed by teachers improved from baseline to a significantly greater extent with MAS ER 10, 20, and 30 mg than with placebo (all $p < 0.001$) [10]. These significant improvements in ADHD-RS-IV scores were shown in both the morning and afternoon assessments, and during all 3 weeks [10]. All three MAS ER dosages were also significantly ($p < 0.05$), more effective than placebo as assessed by improvements from baseline in Connors Global Index Scale for parents, the physician-assessed Clinical Global Impressions Scale for improvement (CGI-I), and the Parent's Global Assessment for improvement [15]. For all endpoints, the 30-mg/day dosage provided the greatest improvements from baseline [15].

In an open-label extension of the placebo-controlled trials [14, 15], improvements in behavioral symptoms with MAS ER were consistently maintained during treatment for up to 2 years [22]. MAS ER was also effective in improving ADHD behavior in the community-practice setting in an open-label study in 2968 school-aged children with ADHD [23].

In adolescents

Evidence of the clinical efficacy of Adzenys ER™ suspension and Adzenys XR-ODT® in adolescents with ADHD was provided by the results of a 4-week multicenter trial of once-daily MAS ER in patients aged 13–17 years [16]. Adolescent patients ($n = 287$) were randomized to receive once-daily placebo or forced titration to once-daily MAS ER 10, 20, 30 and 40 mg [16].

In the ITT population ($n = 278$), ADHD Rating Scale-IV (ADHD-RS-IV) scores improved from baseline to a significantly ($p < 0.001$) greater extent in all four MAS ER treatment groups than in the placebo groups at the end of each

Table 3 Warnings and precautions associated with the use of Adzenys ER™ oral suspension [9] and Adzenys XR-ODT® [10] in the treatment of ADHD. Consult local prescribing information for further details

What should be done to reduce the potential for abuse and dependence with Adzenys ER™ suspension/XR-ODT®?	
Prior to prescribing	Assess the risk of abuse
During therapy	Monitor for signs of abuse and dependence
	Maintain careful prescription records, educate patients about abuse and the proper storage/disposal of stimulants, and periodically re-evaluate the need for treatment
How should Adzenys ER™ suspension/XR-ODT® be used in specific populations?	
Women who are pregnant	Use only if the potential benefit justifies the potential risk to the fetus (insufficient data to determine a drug-associated risk of major congenital malformation or miscarriage)
Women who are breast-feeding	Use is not recommended (infant may potentially experience serious adverse reactions)
What are some of the other warnings and precautions that pertain to the use of Adzenys ER™ suspension/XR-ODT®?	
Serious cardiovascular reactions	Prior to use: assess for evidence of cardiac disease
	Avoid use if there are known structural cardiac abnormalities, cardiomyopathy, serious heart rhythm abnormalities, coronary artery disease, or other serious heart problems
	Further evaluate patients who develop exertional chest pain, unexplained syncope, or arrhythmias
↑ in blood pressure (mean ↑ 2–4 mm Hg) or heart rate (mean ↑ 3–6 beats/min)	Prior to use: consider risks/benefits of treatment in patients in whom an ↑ in blood pressure would be problematic
	Monitor all patients for hypertension and tachycardia
Psychiatric adverse reactions	Patients with a pre-existing psychotic disorder: psychotic symptoms may be exacerbated
	Patients with bipolar disorder: may induce mixed or manic episodes; prior to use, screen patients for risk factors for developing manic episodes
	Patients without a prior history of psychotic or manic symptoms: if psychotic or manic symptoms occur, consider discontinuing Adzenys ER™/XR-ODT®
Priapism	Advise patients to seek immediate medical attention if abnormally sustained, or frequent and painful, erections occur
Peripheral vasculopathy	Monitor patients for digital changes; further clinical evaluation (e.g. referral to a rheumatologist) may be appropriate for certain patients
Long-term growth suppression	Closely monitor growth (height and weight)
	If necessary, interrupt treatment in patients who are not growing as expected
What potentially clinically relevant drug interactions may occur during the use of Adzenys ER™ suspension/XR-ODT®?	
GI acidifying agents (e.g. ascorbic acid, guanethidine, reserpine, etc.)	↓ blood levels and efficacy of amphetamine; ↑ dose of Adzenys ER™/XR-ODT® based on clinical response
GI alkalinizing agents (e.g. sodium bicarbonate)	↑ blood levels and potentiate acidity of amphetamine; avoid co-administration
MAOIs (e.g. selegiline, phenelzine, isocarboxazid, tranylcypromine, etc.)	↑ risk of headaches and other signs of hypertensive crisis; use of Adzenys ER™/XR-ODT® is contraindicated during or within 14 days of treatment with an MAOI
Serotonergic drugs (e.g. SSRIs, SNRIs, triptans, TCAs, fentanyl, lithium, tramadol, tryptophan, etc.)	↑ risk of serotonin syndrome; initiate treatment with lower doses, monitor patients for serotonin syndrome symptoms (particularly during Adzenys ER™/XR-ODT® initiation or dosage ↑)
	Serotonin syndrome occurs: discontinue Adzenys ER™/XR-ODT® and the concomitant serotonergic drug; initiate supportive symptomatic treatment
TCAs (desipramine, protriptyline, etc.)	May ↑ activity of TCA or sympathomimetic agents leading to striking and sustained ↑ in *d*-amphetamine levels in the brain, and potentiation of cardiovascular effects; monitor frequently or use alternative therapy based on clinical response

ADHD attention-deficit hyperactivity disorder, *ER/XR* extended-release, *GI* gastrointestinal, *MAOI* monoamine oxidase inhibitor, *SNRI* serotonin-norepinephrine reuptake inhibitors, *SSRI* selective serotonin reuptake inhibitors, *TCA* tricyclic antidepressant, *ODT* orally disintegrating tablet, ↑ increase, ↓ decrease

week [16]. All MAS ER groups showed significant improvements from baseline for both the ADHD-RS-IV inattentive and hyperactive-impulsive subscale scores ($p < 0.001$ vs placebo). MAS ER 10, 20, 30 and 40 mg/day were also significantly ($p < 0.01$) more effective than placebo with regard to CGI-I scores at endpoint [16]. Of note, evidence was not adequate to conclude that MAS ER dosages > 20 mg/day conferred additional benefit in this patient population [10].

In adults

In adults, the efficacy of Adzenys ER™ suspension/XR-ODT® was established based on a 4-week trial of randomized, forced-titrated treatment with once-daily MAS ER 20, 40, or 60 mg versus placebo in 255 patients with ADHD aged ≥ 18 years [17].

Improvements from baseline in ADHS-RS scores were significantly ($p \leq 0.001$) better with MAS ER 20, 40, and 60 mg/day than with placebo at week 4 [17]. A 2-h duration

of treatment was indicated by the significant ($p < 0.05$) improvements from baseline in Conners' Adult ADHD Rating Scale Short-Version Self-Report Scores at 4- and 12-h after administrations. ADHD symptoms improved within the first week of treatment [17]. As in the trial in adolescents [16], available evidence is not sufficient to conclude that MAS ER dosages > 20 mg/day conferred additional benefit in adults [10].

In an extension of this trial, improvements in ADHD symptoms were sustained when MAS ER treatment was continued for up to 24 weeks [24].

Tolerability evidence supporting the US approval of Adzenys ER™/XR-ODT®

The tolerability profiles of Adzenys ER™ suspension/XR-ODT® are based on the tolerability of MAS ER in the treatment of ADHD in the randomized, double-blind trials in treatment-naïve or -experienced children [15], adolescents [16], and adults [17]. The overall tolerability profile of MAS-ER, and hence of Adzenys ER™ suspension/XR-ODT®, are comparable to those of other long-acting formulations of amphetamine, with most adverse reactions being mild or moderate in intensity. In common with other CNS stimulants, there is a potential for misuse, abuse, and dependence with Adzenys ER™ suspension/XR-ODT®, and precautions should be followed to ameliorate their risk (Table 3).

Table 4 provides a summary of adverse reactions that were reported in ≥ 5% of MAS ER recipients and at an incidence ≥ 2% higher than in placebo recipients in the randomized trials of MAS ER that were used as the basis of the US FDA approval of Adzenys ER™ suspension/XR-ODT®. As expected in clinical trials, rates of adverse reactions, as well as the type of adverse reaction, varied between these trials. Across all age groups, the most commonly reported adverse reactions were the loss of appetite and weight, insomnia, and various digestive order symptoms (i.e., nausea, abdominal pain, dyspepsia, vomiting) [Table 4].

The adverse reactions leading to the discontinuation of MAS ER treatment also varied between the MAS ER trials. In the trial in children, 2.4 and 2.9% of MAS ER and placebo recipients discontinued treatment because of an adverse reaction; corresponding rates in the trial in adolescents were 2.1 and 0%, and in the trial in adults were 12.0 and 1.6%. The most common drug-related adverse reaction leading to the discontinuation of MAS ER at a rate at least twice that with placebo was insomnia (1.3% of adolescents and 5.2% of adults) [insomnia was not reported in children]. No other drug-related adverse reactions led to treatment discontinuation in ≥ 1% of adolescents. In adults, 2.1% of patients discontinued treatment because of anxiety, 1.6% each discontinued due to nervousness, dry mouth, anorexia, tachycardia, and headache, and 1% discontinued due to asthenia.

Longer-term treatment with MAS ER was also well tolerated in the open-label extension studies in school-aged children [22] and adults [24], as well as in school-aged children in the community-practice setting [23].

Tachycardia was reported in adults [17], but not in children [15] or adolescents [16] (Table 4). According to an assessment of the short- and long-term cardiovascular effects of MAS ER in children in the placebo-controlled trial and its extension, MAS ER ≤ 30 mg/day had minimal CV effects in otherwise healthy children with ADHD [25]. Precautions should be followed to minimize the risk of adverse CV-related outcomes, as well as the risk of psychiatric and other adverse outcomes, in at-risk patients (Table 3).

What conclusions can be made regarding Adzenys ER™ suspension/XR-ODT®?

Adzenys ER™ suspension and XR-ODT® are easy-to-administer, long-acting, and convenient options for treating ADHD in children aged ≥ 6 years, adolescents, and adults. They may be especially useful in patients in whom a rapid onset and prolonged reduction in ADHD symptoms is required, and those who have difficulty swallowing whole tablets or capsules. The bioavailability of these amphetamine formulations is equivalent to that of the MAS ER formulation, for which efficacy, tolerability, and safety are well-established.

As the effectiveness, tolerability, and safety profiles of various formulations of amphetamine and methylphenidate are comparable, a number of other factors should be considered when selecting the most appropriate CNS stimulant to treat the individual child, adolescent, or adult with ADHD [5–7]. The use of a formulation that more closely matches the preferences of the individual may improve treatment adherence, thereby potentially improving treatment outcomes [8].

Factors to consider when selecting a CNS stimulant include the preferred length of ADHD coverage and the number of times per day the formulation needs to be administered [5–7]. The pharmacokinetic profiles of Adzenys ER™ suspension and XR-ODT®, which allow for once-daily administration with or without food, may be potentially advantageous for certain patients with ADHD (e.g. those requiring a rapid onset and prolonged reduction in ADHD symptoms throughout and beyond the school/working day). Adzenys ER™ suspension/XR-ODT® include both immediate- and extended-release *d*- and *l*-amphetamine particles, resulting in a rapid increase in plasma concentrations, followed by relatively stable concentrations for several hours, then a slow decrease in

Table 4 Tolerability of once-daily MAS ER vs placebo in the randomized trials [15–17] providing evidence for the use of Adzenys ER™ suspension [9] and Adzenys XR-ODT® [10] in the treatment of ADHD in children, adolescents, and adults

Preferred term for adverse reaction (alphabetic order by body system)	Incidence of the most commonly reported adverse reactions (% of patients)					
	3-week trial in children aged 6–12 years [15]		4-week trial in adolescents aged 13–17 years [16]		4-week trial in adults aged ≥ 18 years [17]	
	MAS ER 10–30 ($n=374$)	Placebo ($n=210$)	MAS ER 10–40 ($n=233$)	Placebo ($n=54$)	MAS ER 20–60 ($n=191$)	Placebo ($n=64$)
General						
Abdominal pain	14	10	11	2		
Fever	5	2				
Headache					26	13
Digestive system						
Diarrhea					6	0
Dry mouth					35	5
Loss of appetite	22	2	36[a]	2	33	3
Nausea	5	3			8	3
Vomiting	7	4				
Nervous system						
Agitation					8	5
Anxiety					8	5
Dizziness					7	0
Emotional liability	9	2				
Insomnia	17	2	12[a]	4	27	13
Nervousness	6	2				
Other						
Tachycardia					6	3
Urinary tract infection					5	0
Weight loss	4	0	9[a]	0	10	0

ADHD attention-deficit hyperactivity disorder, *ER/XR* extended-release, *MAS* mixed amphetamine salts, *ODT* orally disintegrating tablets

[a]Incidence was related to the dosage of MAS ER

concentrations (Table 2). Due to this prolonged activity, additional amphetamine doses do not need to be taken at school or work (thereby maintaining the privacy of the patient), and coverage is provided for post-school and –work activities. Long-acting formulations of CNS stimulants that are administered once daily may result in better adherence to treatment relative to immediate-release formulations that require administration more often [3, 8, 26, 27].

The ability of the patient to swallow tablets or capsules and the ease of administration are other factors that should be considered when selecting the most appropriate formulation for the individual [5–7]. Some patients, especially children, may have difficulty swallowing tablets or capsules whole. Adzenys ER™ suspension and XR-ODT® are both relatively easy to administer; the orange-flavored suspension does not require reconstitution prior to administration, and the orange-flavored XR-ODT® dissolves rapidly on the tongue, followed by swallowing of the disintegrated particles with saliva without the need for water (Table 1). Adzenys ER™ suspension/XR-ODT® may be taken with or without food.

Other factors to consider when choosing a CNS stimulant are the potential risks of drug dependence, abuse, and diversion [5–7]. Due to their slower onset and sustained rate of drug delivery, extended-release formulations of CNS stimulants may reduce the risk of abuse relative to immediate-release formulations, which rapidly reach C_{max}. For example, in a US study in patients in an ADHD treatment center, abuse of prescription stimulants was reported by 14.3% of patients; in these patients, the rate of abuse of immediate-release stimulants was much higher than that of extended-release formulations (79.8 vs 17.2%) [28]. The once-daily administration of Adzenys ER™/XR-ODT® avoids the need for taking or storing controlled substances at school or work, thereby limiting the likelihood of diversion or theft in these settings. Appropriate precautions should be followed to minimize the risks of dependence, misuse, and abuse (Table 3).

Acknowledgements The manuscript was reviewed by: *A.C. Childress*, Center for Psychiatry and Behavioral Medicine, Las Vegas, NV, USA; *R.H. Howland,* University of Pittsburgh School of Medicine, and Western Psychiatric Institute and Clinic, Pittsburgh, PA, USA; *A.S. Poulton*, Sydney Medical School Nepean, The University of Sydney, and Department of Paediatrics, Nepean Hospital, Penrith, NSW, Australia; *B.J. Warren,* College of Nursing, The Ohio State University, Columbus, OH, USA. During the peer review process, the manufacturer of Adzenys ER™/XR-ODT® was also offered an opportunity to review this article. Changes resulting from comments received were made on the basis of scientific and editorial merit.

Funding The preparation of this review was not supported by any external funding.

Compliance with ethical standards

Conflict of interest K.A. Lyseng-Williamson is an employee of Adis/Springer, is responsible for the article content and declares no conflicts of interest.

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