

Methylphenidate extended-release oral suspension for the treatment of attention-deficit/hyperactivity disorder: a practical guide for pharmacists

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Abstract: Attention-deficit/hyperactivity disorder (ADHD) is a neurodevelopmental condition that affects children, adolescents, and adults worldwide. The purpose of this review was to inform pharmacists of the numerous options to treat ADHD, with a focus on one of the more recently approved formulations, methylphenidate extended-release oral suspension (MEROS). Symptoms of ADHD can negatively impact an individual's health and quality of life and impair function in multiple settings. Psychostimulants such as methylphenidate- and amphetamine-based agents are first-line pharmacologic treatments for ADHD. However, there are multiple formulations, including immediate release (administered two to three times/day), solid extended release (ER), or transdermal patch. MEROS is a once daily, long-acting liquid preparation that has demonstrated favorable safety and efficacy in patients with ADHD. MEROS may improve treatment adherence in patients who cannot tolerate or have difficulties administering pill or transdermal patch formulations.

Keywords: drug formulation, administration, adherence

Introduction

Attention-deficit/hyperactivity disorder (ADHD) is a chronic neurodevelopmental disorder characterized by symptoms of inattention, impulsivity, and hyperactivity.^{1,2} The onset of ADHD most commonly occurs in childhood,³ but for a number of individuals, symptoms continue into adolescence and adulthood.⁴ ADHD can substantially impair an individual's ability to function in school, work, home, and other social environments, resulting in significant academic, social, and family problems.⁵⁻⁷ Individuals may experience higher rates of unintentional injuries, emergency department visits, suspension, expulsion, and dropping out of school and are at a greater risk of developing other psychiatric disorders and drug dependence.^{4-6,8-10} ADHD is also associated with a considerable socioeconomic burden, primarily resulting from reduced productivity, income loss, and increased health care costs.¹¹ Despite the socioeconomic burden associated with ADHD, many adults and children with ADHD remain undiagnosed and untreated.^{12,13} Given the numerous pharmacologic agents and formulations available, the purpose of this review was to inform pharmacists of these available pharmacologic options and formulations, with a focus on one of the more recently approved formulations, methylphenidate extended-release oral suspension (MEROS).

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Treatment of ADHD

Clinical practice guidelines published by the American Academy of Child and Adolescent Psychiatry (AACAP)² and the American Academy of Pediatrics (AAP)¹⁴ recommend pharmacologic and behavioral interventions for individuals with ADHD. Pharmacotherapies recommended by these guidelines include amphetamine- and methylphenidate-based psychostimulants, as well as nonstimulants (US Food and Drug Administration [FDA]-approved stimulant and nonstimulant medications; Table 1).^{2,14} Psychostimulants have been the standard of care for ADHD for several decades.¹⁵ Nonstimulants (eg, serotonin–norepinephrine reuptake inhibitors, α_2 adrenergic receptor agonists, tricyclic antidepressants, bupropion) are sometimes prescribed for individuals whose symptoms do not improve adequately with stimulants, who experience intolerable side effects, and/or have certain comorbidities.^{3,16,17} Currently, only three nonstimulants have FDA approval for the treatment of ADHD (Table 1).^{18–21}

Psychostimulants increase dopamine levels in the brain, thereby improving concentration and reducing hyperactive and impulsive behaviors. The primary pharmacologic action of methylphenidate-based treatments is the inhibition of plasma membrane dopamine and noradrenaline transporters. Amphetamine-based compounds are thought to inhibit dopamine and norepinephrine transporters, reverse dopamine uptake by dopamine transporters, and promote release of dopamine via interactions with vesicular monoamine transporter 2.²² Regardless of mechanism of action, both methylphenidate- and amphetamine-based stimulants have demonstrated favorable safety and efficacy for the treatment of children, adolescents, and adults with ADHD.^{21,23}

For a number of years, stimulants were only available as immediate-release (IR) formulations, which are characterized by a short duration of action, necessitating multiple daily administrations (eg, two to three times a day).² This requirement can be particularly problematic for children who attend school, resulting in complications related to privacy, stigmatization by classmates, and risk of nonadherence to treatment.^{2,24} As a result, prescriptions for extended-release (ER) formulations now exceed those for IR formulations for children with ADHD.^{24–26} Some major advantages of ER formulations for school-age children are better pharmacokinetic profile (eg, lower peak concentrations) and the ability to provide all-day coverage, which avoids the necessity to administer additional doses during school or aftercare programs.²

Despite the availability of these ER formulations, many require children to swallow an intact tablet/capsule or wear a transdermal patch. However, some children have diffi-

culty swallowing tablets or cannot tolerate the transdermal patch.^{27–30} The instructions for some capsule formulations of some ER formulations allow for opening the capsule and dispersing the contents into food (eg, yogurt, apple sauce) or liquid (eg, water, orange juice) for administering to patients who are unable to swallow tablets.^{31–33} There is concern among clinicians, however, that such modifications to treatment administration could result in inaccurate dosing (eg, food microwaved, contents not completely eaten).³⁴ Furthermore, ER delivery mechanisms can be compromised if the medication is chewed rather than swallowed, resulting in dose dumping.³⁵ Therefore, a liquid ER formulation of methylphenidate or amphetamine may be beneficial for the treatment of ADHD, as it will allow for an easier dosing regimen compared with IR formulations and circumvent challenges posed by ER tablet or capsule formulations.³⁵

Although stimulant and nonstimulant medications have demonstrated efficacy for the treatment of ADHD, meta-analyses of double-blind, placebo-controlled trials have demonstrated a superior effect size for stimulants in both children and adults.^{36,37} Owing to the availability of a range of different classes and formulations of ADHD pharmacotherapies, it is important that pharmacists play a key role in medication monitoring and patient counseling. Key points for pharmacists to consider when dispensing ADHD medications are summarized in Table 2.^{38–41}

MEROS

MEROS is a long-acting liquid preparation (Quillivant XR; NextWave Pharmaceuticals, Inc, a subsidiary of Pfizer Inc, New York, NY, USA) approved by the FDA in 2012 for the treatment of ADHD in patients aged 6 years or older.^{42,43} MEROS was designed with the goal of combining the desired pharmacokinetic characteristics of both IR and ER formulations of methylphenidate: rapid initial absorption leading to a rapid clinical effect followed by an extended period of release allowing for the clinical effect to last throughout the day.³⁵ MEROS is composed of cationic polymer matrix particles that bind D,L-threo-methylphenidate racemic mixture via an ion exchange mechanism. The particles are covered with a coating of various thicknesses to confer ER properties. The resulting preparation is a blend of uncoated and coated particles that is ~20% IR and ~80% ER methylphenidate.⁴⁴ MEROS is supplied as a powder that should be reconstituted by the pharmacist prior to dispensing to produce an oral suspension that does not require refrigeration. Reconstituted MEROS should be stored at 25°C (range 15–30°C) and is stable for up to 4 months.⁴² Full instructions for use of MEROS are presented in Figure 1.

Table 1 FDA-approved pharmacotherapies for the treatment of ADHD

Stimulant	Brand name	Generic name	Age range for approved use	Formulation	Dose range (mg/day)	Weekly dosage adjustments (mg/day)
Amphetamine based	Adderall ⁵⁴	Amphetamine and dextroamphetamine	Children ≥ 3 years of age	Tablet (IR)	3–5 years: 2.5–40 ≥ 6 years: 5–40	3–5 years: 2.5 ≥ 6 years: 5
	Adderall XR ⁵⁵	Amphetamine and dextroamphetamine	Children aged 6–17 years, adults	Capsule (50% IR:50% ER)	6–12 years: 5–30 Adolescents: 10–30 Adults: 20	6–12 years: 5 or 10 Adolescents: 20 Adults: 20
	Adzenys XR ODT ⁵⁶	Amphetamine	Children aged 6–17 years, adults	Orally disintegrating tablet (XR)	6–12 years: 6.3–18.8 13–17 years: 6.3–12.5 Adults: 12.5	6–17 years: 3.1 or 6.3
	Dexedrine ⁵⁷	Dextroamphetamine	Children ≥ 6 years of age	Spansule (SR)	≥ 6 years: 5–40	≥ 6 years: 5
	Dyanavel XR ⁵⁸	Amphetamine	Children ≥ 6 years of age	Oral suspension (XR)	≥ 6 years: 2.5–20	≥ 6 years: 2.5–10
	Evekeo ⁵⁹	Amphetamine	Children ≥ 3 years of age	Tablet	3–5 years: 2.5–40 ≥ 6 years: 5–40	3–5 years: 2.5 ≥ 6 years: 5
	ProCentra ⁶⁰	Dextroamphetamine	Children aged 3–16 years	Oral solution	3–5 years: 2.5–40 ≥ 6 years: 5–40	3–5 years: 2.5 ≥ 6 years: 5
	Vyvanse ³³	Lisdexamfetamine	Children aged 6–17 years, adults	Capsule	≥ 6 years: 30–70	10–20
	Aptensio XR ⁶¹	Methylphenidate	Children aged 6–17 years	Capsule (ER)	≥ 6 years: 10–60	≥ 6 years: 10
	Concerta ⁶²	Methylphenidate	Children aged 6–17, adults up to age 65 years	Tablet (22% IR:78% ER)	6–12 years: 18–54 ≥ 13 years: 18–72	18
Methylphenidate based	Daytrana ⁶³	Methylphenidate	Children aged 6–17 years	Patch	≥ 6 years: 10–30	≥ 6 years: 5
	Focalin ³¹	Dexmethylphenidate	Children aged 6–17 years	Tablet (IR)	≥ 6 years: 5–20	2.5–5
	Focalin XR ⁶⁴	Dexmethylphenidate	Children aged 6–17 years, adults	Capsule (50% IR:50% ER)	≥ 6 years: 5–30 Adults: 10–40	≥ 6 years: 5 Adults: 10
	Metadate ER ⁶⁵	Methylphenidate	Children ≥ 6 years of age, adults	Tablet (ER)	≥ 6 years: 10–60	≥ 6 years: 5–10
	Metadate CD ²²	Methylphenidate	Children aged 6–15 years	Capsule (30% IR:70% ER)	≥ 6 years: 20–60	≥ 6 years: 10–20
	Methylin ⁶⁶	Methylphenidate	Children ≥ 6 years of age, adults	Chewable tablet or oral solution	≥ 6 years: 10–60	≥ 6 years: 5–10
	Methylin ER ⁶⁷	Methylphenidate	Children ≥ 6 years of age, adults	Tablet (ER)	≥ 6 years: 10–60	≥ 6 years: 5–10
	QuilliChew ER ⁶⁸	Methylphenidate	Children ≥ 6 years of age	Chewable tablet (ER)	≥ 6 years: 20–60	≥ 6 years: 10, 15, or 20
	Quillivant XR ⁴²	Methylphenidate	Children aged 6–17 years	Liquid (20% IR:80% ER)	≥ 6 years: 20–60	≥ 6 years: 10–20
	Ritalin ⁶⁹	Methylphenidate	Children ≥ 6 years of age, adults	Tablet (IR)	≥ 6 years: 10–60 Adults: 10–60	≥ 6 years: 5–10
Ritalin SR ⁶⁹	Methylphenidate	Children ≥ 6 years of age, adults	Tablet (SR)	≥ 6 years: 10–60 Adults: 10–60	≥ 6 years: 5–10	
Ritalin LA ⁷⁰	Methylphenidate	Children aged 6–12 years	Capsule (50% IR:50% ER)	≥ 6 years: 10–60	≥ 6 years: 10	

(Continued)

Table 1 (Continued)

Nonstimulants	Brand name	Generic name	Formulation	Dose range (mg/day)	Weekly dosage adjustments (mg/day)
Norepinephrine uptake inhibitor	Strattera ¹⁸	Atomoxetine	Capsule	<70 kg: 0.5–1.4 ^a ≥70 kg: 40–100	–
Alpha adrenergic agents	Intuniv ¹⁹	Guanfacine	Tablet (ER)	≥6 years: 1–7	1 ^b
	Kapvay ²⁰	Clonidine	Tablet (ER)	≥6 years: 0.1–0.4	0.1

Notes: ^amg/kg/day and ^bmg/week. Copyright © 2013. Adapted with permission from the American College of Clinical Pharmacy. Originally published in Caballero J. Attention-deficit/hyperactivity disorder. In: Benavides S, Nahata MC, editors. *Pediatric Pharmacotherapy*. Lenexa, KS: American College of Clinical Pharmacy; 2013:435–448.⁵³

Abbreviations: FDA, US Food and Drug Administration; ADHD, attention-deficit/hyperactivity disorder; IR, immediate release; ER, extended release; SR, sustained release; XR, extended release.

Bioequivalence of MEROS versus IR methylphenidate oral solution was demonstrated in a pharmacokinetic study in healthy adults such that the relative bioavailability of MEROS 60 mg versus IR methylphenidate 60 mg oral solution (given as two 30 mg doses 6 hours apart) was 95%.³⁵ In a randomized, dose-optimized, laboratory, school efficacy and safety study conducted over 6–8 weeks in 45 subjects aged 6–12 years, MEROS significantly improved symptoms of ADHD at the primary efficacy end point of 4 hours post dose versus placebo (Swanson, Kotkin, Agler, M-Flynn, and Pelham [SKAMP] rating scale⁴⁵ – combined score was 7.12 [95% CI: 4.85, 9.39] for MEROS versus 19.58 [17.31, 21.86] for placebo; $P < 0.0001$). These improvements were observed 45 minutes post dose and continued for up to 12 hours.⁴⁴ MEROS treatment also improved numerous secondary efficacy outcomes including Permanent Product Measure of Performance⁴⁶ (PERMP; a skill-adjusted, written math test designed to assess attention and the ability to complete written seat work), ADHD Rating Scale IV⁴⁷ (ADHD-RS), Clinical Global Impression – Severity⁴⁸ (CGI-S), and Clinical Global Impression – Improvement⁴⁸ (CGI-I) scale scores.⁴⁹ At each time point tested for the PERMP, the number of problems attempted and the number answered correctly were significantly higher during treatment with MEROS compared with placebo ($P < 0.0001$ to $P = 0.0155$, number attempted; $P < 0.0001$ to $P = 0.0016$, number correct).⁴⁹ As with the SKAMP – combined score, the treatment differences for MEROS versus placebo on PERMP reached statistical significance at 45 minutes post dose ($P < 0.0001$, both number attempted and number correct) and remained statistically significant until the last post-dose assessment at 12 hours ($P = 0.0019$, number attempted; $P = 0.0008$, number correct).^{44,49} Mean ADHD-RS total scores improved from 39.3 (± 7.6) at baseline to 12.6 (± 6.3) at the end of the open-label phase. The percentage of responders (defined as $\geq 50\%$ improvement in ADHD-RS) was 87.2%. As measured by the CGI-S at baseline, 63.3% of participants were considered moderately ill and 25% were considered markedly ill; however, at the end of the open-label phase, most participants were considered borderline ill (51.3%) or not ill at all (20.5%), and no participants were considered either markedly or severely ill. Furthermore, at the end of the open-label phase, all participants were considered either much improved (41%) or very much improved (59%) as measured by CGI-I.⁴⁹

Safety

The safety and tolerability profile of MEROS is comparable with that of other methylphenidate formulations.^{44,49} In the

Table 2 Medication monitoring and patient counseling**What the pharmacist needs to know**

- Titration of stimulant medication is often necessary at the initiation of therapy – the pharmacist should expect prescriptions with incremental dosing increases in the first several months of treatment
- Special ordering may be required as stimulant medications are Schedule CII drugs
- The FDA requires distribution of a Patient Medication Guide sheet specific for the drug being dispensed
- Counsel individuals with ADHD (or parents/caregivers) to emphasize the importance of taking the proper dose at the appropriate time, warn or inquire about potential adverse effects, and caution patients about the risks of taking pseudoephedrine-containing OTC cold/allergy medication concomitantly with stimulants
- Provide education to patients (or parents/caregivers) when administration of the medication dispensed is a change from the original dosage form
- Review black box warning for stimulant medications dispensed
- Monitor for signs of abuse, misuse, and diversion of stimulant medications

Notes: Data from these studies.^{38–41}

Abbreviations: FDA, US Food and Drug Administration; ADHD, attention-deficit/hyperactivity disorder; OTC, over the counter.

randomized, double-blind, placebo-controlled, crossover trial of MEROS in 45 children aged 6–12 years, the most common treatment-emergent adverse events (TEAEs) during the open-label phase were decreased appetite (55.6%), upper abdominal pain (42.2%), affect lability (26.7%), initial insomnia (22.2%), insomnia (17.8%), and headache (17.8%). In the double-blind phase, TEAEs generally had a lower incidence than in the open-label phase, with only affect lability reported in $\geq 5\%$ of subjects receiving MEROS (MEROS: 8.9%; placebo: 2.2%).^{44,49} No severe TEAEs were reported during the double-blind phase, and three subjects reported three severe TEAEs each (ie, affect lability, aggression, initial insomnia) during the open-label phase.^{44,49} Two subjects withdrew from the study during the open-label phase because of these TEAEs (ie, affect lability, aggression).⁴⁹ There were no deaths or serious adverse events and no occurrences of suicidal ideation or behavior during the study.^{44,49}

Reconstitution and administration

There are several key points for pharmacists to consider when dispensing MEROS.⁴² First, reconstitution of the powder with water followed by vigorous shaking of the bottle for at least 10 seconds is critical to ensure the powder is fully suspended. It is important that the individual with ADHD, parent, or caregiver should be informed of the importance of vigorously shaking the bottle for at least 10 seconds prior to measuring each dose. Second, the bottle adapter, which is supplied in each box of MEROS, must be fully and securely inserted into the neck of the bottle, and the tip of the oral dosing dispenser (also supplied in every box of MEROS) must be inserted into the upright bottle adapter before the bottle is turned upside down and the required volume is drawn into the oral dosing dispenser. Finally, the dose should be administered directly into the patient's mouth.

Conclusion

ADHD is a chronic disorder with debilitating symptoms that is often present in childhood and adolescence but can persist into adulthood. Despite the increasing prevalence of ADHD, a number of individuals remain undiagnosed and untreated,^{12,13,50} which is possibly due to the considerable stigma associated with the disorder.^{50,51} For patients diagnosed and receiving treatment, many are restricted to receiving medications that are inconvenient and/or not appropriate for their age or stage of development.^{2,24,29} IR formulations were the mainstay of ADHD therapy for many years but are inconvenient due to their short duration and multiple dosing schedules. For many patients with ADHD, ER formulations represent a more convenient option due to a once daily dosing regimen.² However, a number of challenges associated with administration of ER formulations remain (eg, children's inability to swallow tablets, dermal reactions to topical patches).^{27–30} In addition, unreliable dosing and kinetics may occur when ER products are crushed or opened and contents are administered with food or drink.⁵²

MEROS is a once-daily, long-acting, liquid preparation of methylphenidate that may be an option for patients who cannot tolerate or have difficulties with administering pill or transdermal patch formulations.³⁵ MEROS has been shown in clinical studies to improve symptoms and exhibit a safety and tolerability profile similar to other stimulant ADHD medications.^{44,49} However, it is important that pharmacists ensure that MEROS is properly dispensed and patients or their family members are provided with thorough instructions regarding its use.

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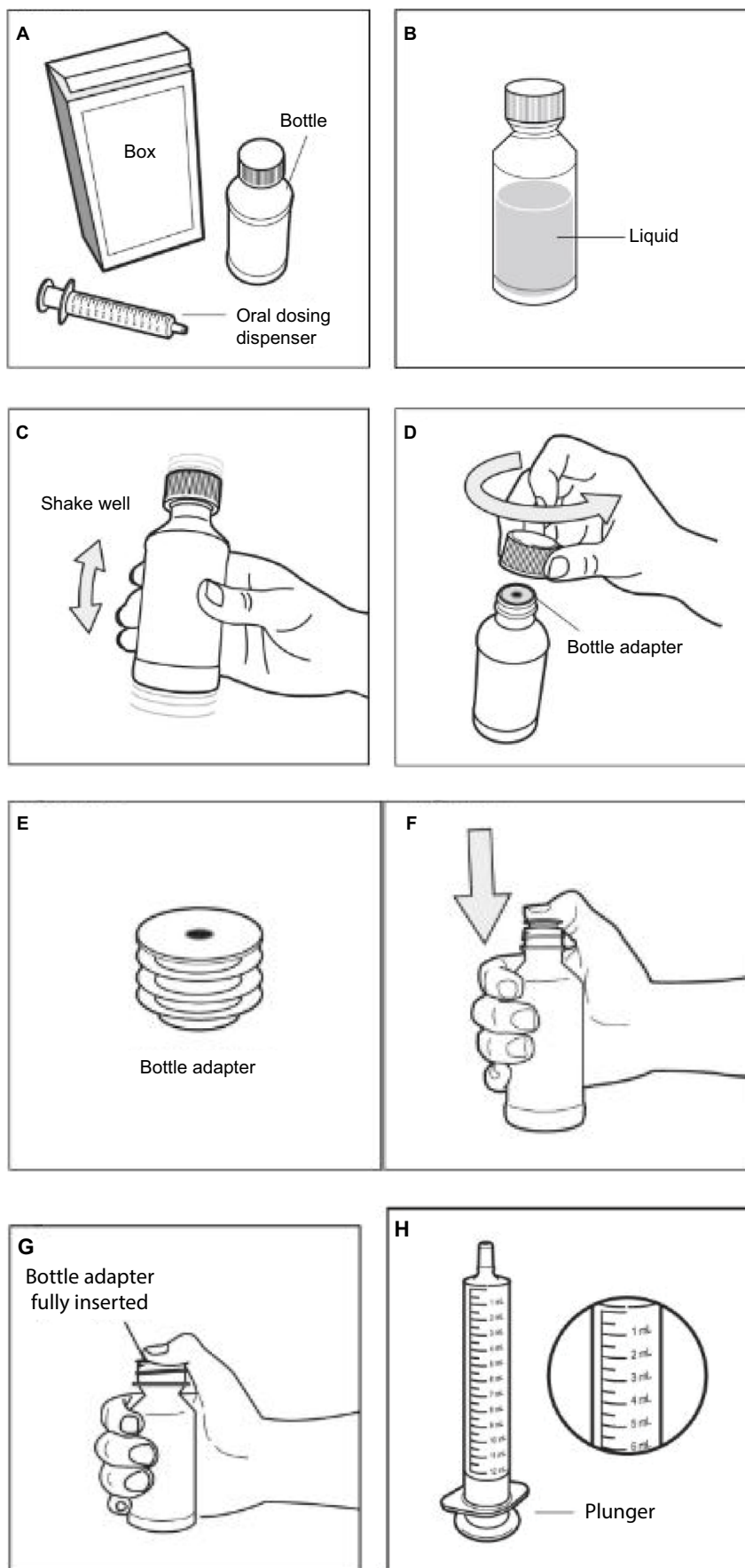


Figure 1 (Continued)

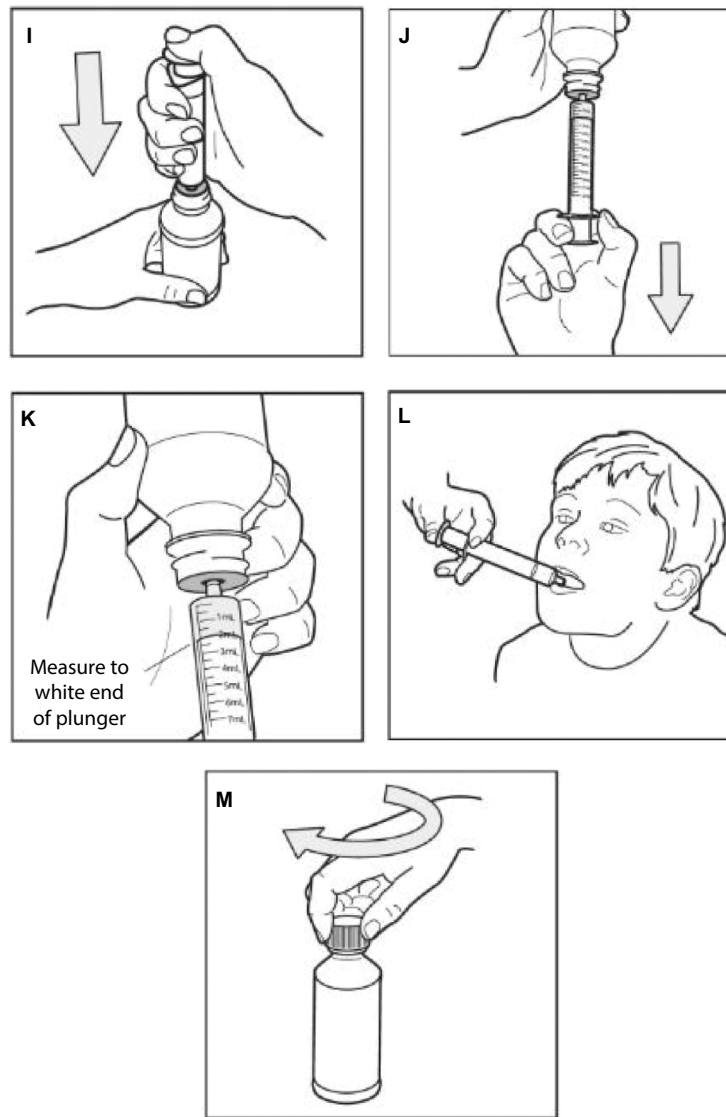


Figure 1 MEROS (Quillivant XR) instructions for use.⁴²

Notes: Step 1. Remove the MEROS bottle and oral dosing dispenser from the box (A). If the oral dosing dispenser is missing or not provided, please contact your pharmacist for a replacement. Step 2. Check and make sure that the MEROS bottle contains liquid medicine (B). If MEROS is still in powder form, do not use it. Return it to your pharmacist. Step 3. Shake the bottle well (up and down) for at least 10 seconds before each use (C). Step 4. Uncap the bottle and check that the bottle adapter has been fully inserted into the bottle (D). If bottle adapter (E) has not been inserted by the pharmacist into the bottle, insert adapter into the bottle as shown (F and G). Once the bottle adapter has been fully inserted into the bottle (G), it should not be removed. If the bottle adapter has not been inserted and is missing from the box, contact your pharmacist. The bottle adapter must be fully inserted and should be flush against the mouth of the bottle and must remain in place to allow the child-resistant cap to engage. Step 5. Check the MEROS dose in milliliters as prescribed by your doctor. Locate this number on the oral dosing dispenser (H). Step 6. Insert tip of the oral dosing dispenser into the upright bottle and push the plunger all the way down (I). Step 7. With the oral dosing dispenser in place, turn the bottle upside down. Pull the plunger to the number of milliliters you need (the amount of liquid medicine in Step 5 [J]). Measure the number of milliliters of medicine from the white end of the plunger (K). Step 8. Remove the oral dosing dispenser from the bottle adapter. Step 9. Slowly squirt MEROS directly into your or your child's mouth (L). Step 10. Cap the bottle tightly. Store the bottle upright at 59°F–86°F (15°C–30°C; M).

Abbreviation: MEROS, methylphenidate extended-release oral suspension; XR, extended release.

Disclosure

JC declares that he has no conflict of interest. EHD and FW are employees of Pfizer Inc. HWB was a paid consultant to Pfizer in connection with the development of the manuscript. The authors report no other conflicts of interest in this work.

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