Effect of Food Intake on the Pharmacokinetics of a Novel Methylphenidate Extended-Release Oral Suspension for Attention Deficit Hyperactivity Disorder

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Abstract
We conducted an open-label, single-dose, randomized, crossover study in healthy adults to assess the impact of food on the bioavailability of 60 mg methylphenidate extended-release oral suspension (MEROS; Quillivant XR™)—a long-acting stimulant for the treatment of attention deficit hyperactivity disorder—by comparing the pharmacokinetic parameters under fed and fasting conditions. When MEROS 60 mg was administered under fed conditions compared with fasting conditions, the exposure of methylphenidate (d enantiomer) was higher, with a mean area under the plasma concentration-vs-time curve (AUC)₀–ₚ of 160.2 ng*h/mL vs 140.4 ng*h/mL, and a mean AUC₀–inf of 163.2 ng*h/mL vs 143.7 ng*h/mL, respectively. The ratios of the ln-transformed geometric means for methylphenidate for AUC₀–ₚ and AUC₀–inf were 119.5% (90%CI, 115.7% to 123.5%) and 119.0% (90%CI, 115.2% to 122.8%), respectively, within the standard 80% to 125% bioequivalence acceptance range indicating no food effect on the overall exposure (rate and extent). There was a small increase in the peak plasma concentration (127.6% [90%CI, 119.9% to 135.8%]). However, this effect was small and not likely to be clinically significant. Overall, MEROS 60 mg was safe in both the fed and fasting condition when administered to healthy volunteers in this study.

Keywords
attention deficit hyperactivity disorder, drug food interaction, methylphenidate, pharmacokinetics, oral administration

Attention deficit hyperactivity disorder (ADHD) is a common neurobehavioral disorder affecting children and adolescents, with a lifetime prevalence of approximately 11.0% in those 4 to 17 years of age. Stimulant medications, including methylphenidates and amphetamines, are currently the most commonly used medications used to treat ADHD and are endorsed by professional medical associations and supported by clinical practice guidelines.

The pharmacologic options for ADHD have expanded significantly in the last 15 years with the development of effective long-acting forms of stimulants and nonstimulants. Long-acting medications for ADHD can be used as initial treatment and have helped simplify treatment regimens. Methylphenidate extended-release oral suspension (MEROS) was approved for the treatment of ADHD in patients ages 6 years and older in 2012 and is the only long-acting liquid formulation available for methylphenidate.

MEROS is supplied as a powder that is reconstituted with water by the pharmacist prior to dispensing. On reconstitution, MEROS forms an extended-release oral suspension of methylphenidate, available in a 25 mg per 5 mL (5 mg/mL) concentration and intended for once-daily oral administration. According to the

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label, for patients ages 6 years and above, the recommended starting dose is 20 mg given orally once daily in the morning. Dosage may be increased weekly in increments of 10 to 20 mg. Daily dosage above 60 mg is not recommended. The formulation contains approximately 20% immediate-release and 80% extended-release methylphenidate. MEROS has demonstrated onset of action in 45 minutes and duration of action through 12 hours postdosing. The relative bioavailability of 60 mg of MEROS compared with 60 mg of immediate-release methylphenidate hydrochloride (HCl) oral solution (given as 2 30-mg doses 6 hours apart) is 95%. This article describes the assessment of the impact of food on the bioavailability of MEROS 60 mg in healthy adult subjects by comparing the pharmacokinetic (PK) parameters under fed and fasting conditions. The safety of MEROS 60 mg administered under fed and fasting conditions was also examined.

Methods
Study Design
This was an open-label, single-dose, randomized, 3-period, 3-treatment crossover study in healthy male and female adults under fasting and fed conditions. The main objectives of this study were to assess the relative bioavailability of a single 60-mg dose of MEROS (Quillivant XR™, Pfizer Inc, New York, New York; concentration equivalent to 5 mg/mL methylphenidate HCl) compared with 60 mg immediate-release methylphenidate HCl oral solution, doses 30 mg twice daily, and to assess the impact of food on the relative bioavailability of MEROS by comparing the PK parameters under fasting and fed conditions. The rate and extent of absorption (relative bioavailability) of MEROS relative to immediate-release methylphenidate HCl oral solution have been reported in detail elsewhere. The effects of food on the bioavailability of MEROS, based on pharmacokinetic data collected during 2 of the 3 treatment periods (60 mg MEROS in fasting and fed conditions), are reported here.

The study was conducted in accordance with the guidelines set forth by the International Conference on Harmonisation Guidelines for Good Clinical Practice, the Code of Federal Regulations for Good Clinical Practice, and the Declaration of Helsinki regarding the treatment of human subjects in a study. The study protocol and the Consent Form were approved by an institutional review board (St. Charles Community Institutional Review Board, St. Charles, Missouri) prior to the conduct of any study procedures. Screening assessments to determine study eligibility occurred within 28 days prior to the first dose of study drug in the first treatment period (period 1). Subjects were admitted to the clinic at least 10.5 hours prior to day 1 dosing and were required to stay for PK sampling for 24 hours after day 1 dosing and to return to the clinic for a blood collection at 36 hours postdose. Following a 7-day washout period, subjects returned to the clinical center to be dosed with the alternative treatment as per the randomization schedule (period 2). Study medication was administered by an oral dosing syringe and followed by administration of 8 fl oz of room-temperature water.

Enrolled subjects received either 1 single 60-mg oral dose of MEROS administered at hour 0, 30 minutes after initiation of an FDA standardized high-fat–high-calorie test meal preceded by an overnight fast of at least 10 hours (test treatment) or 1 single 60-mg oral dose of MEROS administered at hour 0 after an overnight fast of at least 10 hours (reference treatment). The test meal consisted of 2 eggs cooked in butter, 2 strips of bacon, 2 slices of toast with butter, 4 oz of hash brown potatoes, and 8 fl oz of whole milk. All subjects were required to remain upright during the first 10 hours postdosing. No fluid was to be allowed from 1 hour predose to 1 hour postdose except that included with the dose and the high-fat–high-calorie test meal. Throughout the study, standardized meals and beverages were served. Meals were the same in content and quantity during each confinement period. The following meals were served: a small fat-free snack, a standardized meal, dinner, and a snack were served at 4, 7, 11, and 14 hours postdose, respectively. When fluids were not restricted, standardized beverages were allowed ad lib.

Blood samples for PK analysis (6 mL) were collected into K2EDTA vacutainers at the following specified time points in each treatment period: predose and 0.5, 1, 1.33, 1.67, 2, 2.5, 3, 4, 5, 6, 6.5, 7, 7.33, 7.67, 8, 8.5, 9, 10, 12, 14, 16, 24, and 36 hours postdose. Sampling for predose through 9 hours postdose was carried out via intravenous catheter with sodium heparin lock; the remaining sampling was carried out by direct venipuncture.

Safety assessments included vital signs (screening, predose, and 1, 2, 4, 6, 8, 12, and 24 hours postdose, and end of study or early discontinuation), electrocardiogram (screening, predose, 4, 12, 24 hours postdose, and end of study/early discontinuation), clinical laboratory tests (screening and end of study/early discontinuation), suicide assessment (Columbia-Suicide Severity Rating Scale; screening and 6 hours postdose), and recording of adverse events (AEs) throughout the study.

Study Participants
The study inclusion/exclusion criteria are described in detail in another publication.
Eligible subjects were healthy male and female individuals aged ≥18 years at the time of the first dosing, with a body mass index of 18 to 32 kg/m², who provided written informed consent and were able to complete the screening process within 28 days prior to first dosing. Subjects were deemed healthy if there were no clinically relevant abnormalities documented by the medical history, full physical examination (including but not limited to an evaluation of the cardiovascular, gastrointestinal, respiratory, and central nervous systems), vital sign assessments, electrocardiogram, clinical laboratory assessments, and the Columbia-Suicide Severity Rating Scale.

Excluded from the study were subjects with any evidence or history of a clinically significant disorder involving the cardiovascular, respiratory, renal, gastrointestinal, immunologic, hematologic, endocrine, or neurologic system(s) or psychiatric disease, including those who had received treatment for asthma within the past 5 years; those with positive hepatitis B surface antigen, hepatitis C antibody, or HIV antibody serology results; those with a history of glaucoma, structural cardiac abnormalities, seizures, hypertension, Tourette syndrome or tics; or with a history of treatment for depression, anxiety, tension, or agitation.

In addition, subjects with a clinically significant illness during the 4 weeks prior to the first dosing, or those who reported receiving an investigational drug within 30 days prior to the first dosing, were pregnant, lactating or breastfeeding, smoking or using tobacco and/or nicotine products, or with a history of treatment for alcoholism, substance abuse, or drug abuse within the past 2 years were not allowed in the study. Reported difficulty fasting or consuming standardized meals, or reported intolerance to fatty foods or inability to consume a high-fat diet was also exclusionary.

Prescription and nonprescription medications, other than hormonal contraceptives and hormone replacement therapy, were not allowed for a period of 14 days and 7 days, respectively, prior to period 1 dosing and through the end of the study; cytochrome P450 enzyme inducers were restricted for 28 days prior to period 1 dosing and through the end of the study; monoamine oxidase inhibitors were not allowed for a period of 14 days prior to period 1 dosing through 14 days after the final dose of the study medication.

**Bioanalytical Methods**

After collection, samples were stored in an ice bath or Kryorack™ until processed. Plasma was separated from whole blood by centrifugation at approximately 3000 revolutions per minute for 10 minutes at 4°C, transferred into duplicate 8-mL polypropylene tubes, and stored frozen at −20°C (range ±10°C) within 1.5 hours of collection until assayed. Plasma samples were analyzed for d- and l-methylphenidate concentrations; however, the d and l enantiomers of methylphenidate differ in terms of their activities and PK properties, with much higher pharmacological activity and exposure observed for the d enantiomer3–9; hence, results reported here are based on data for the d enantiomer of methylphenidate.

A validated, high-performance liquid chromatographic-tandem mass spectrometric method was used to determine plasma d-methylphenidate concentrations. d-Methylphenidate was quantitated using a liquid-liquid extraction procedure with l-amphetamine (Cerillian, Round Rock, Texas) as the internal standard. Each 100-μL aliquot of quality-control sample (d-three methylphenidate; Chemtos, Austin, Texas) and 100 μL plasma study sample was mixed with 500 μL of internal working standard solution (5.00 ng/mL) and 100 μL of 10% ammonium hydroxide solution and vortexed; 5.00 mL of n-heptane was added. Following centrifugation, the organic layer was transferred to a culture tube and evaporated at 40°C. The residue was reconstituted in 700 μL of reconstitution solution, and an aliquot was injected onto the liquid chromatographic-tandem mass spectrometric system. The liquid chromatography system used a 150 × 4.6 mm (5-μm particle size) SUPELCO Chirobiotic V column (Sigma-Aldrich Corp, St. Louis, Missouri) with an isocratic flow of 83:17 (v:v) mobile phase A:mobile phase B, at a flow rate of 1.6 mL/min. Mobile phase A consisted of 0.25% ammonium trifluoroacetate solution in methanol, and mobile phase B consisted of 0.25% ammonium trifluoroacetate solution in deionized water. Positive ions were detected in the multiple-reaction monitoring mode with precursor→product ion pairs of 234.0→84.0 m/z for d-methylphenidate and 136.0→119.0 m/z for l-amphetamine.

All samples were run in a single day. The lower limit of quantitation for d-methylphenidate in plasma samples was 0.10 ng/mL (calibration range 0.100 to 20.0 ng/mL). Nine concentrations were used for the standard calibration curves; percentage bias was within ±3.8%, and r² was greater than 0.997.

**Pharmacokinetic Evaluation**

The PK parameters were estimated for methylphenidate using a noncompartmental approach in SAS® software (SAS Inc, Cary, North Carolina).

The PK parameters were area under the plasma concentration-vs-time curve (AUC) from time 0 to the time of the last quantifiable concentration (AUC₀→t), AUC from time 0 extrapolated to infinite time (AUC₀→∞) calculated as the sum of the AUC₀→t plus the ratio of the last measurable plasma concentration to the terminal rate constant, maximum plasma
Table 1. Summary of Baseline Demographics

| | MEROS 60 mg, Fed Conditions | MEROS 60 mg, Fasting Conditions |
|---|---|---|
| **N** | 27 | 28 |
| **Age, years** | | |
| Mean (±SD) | 37.1 (±13.6) | 36.5 (±13.6) |
| Range | 19–68 | 19–68 |
| **Age groups, n (%)** | | |
| 18-39 years | 17 (63.0) | 18 (64.3) |
| 40-64 years | 9 (33.3) | 9 (32.1) |
| 65-75 years | 1 (3.7) | 1 (3.6) |
| **Male sex, n (%)** | | |
| | 23 (85.2) | 23 (82.1) |
| **BMI, kg/m²** | | |
| Mean (±SD) | 25.1 (±3.3) | 25.0 (±3.3) |
| Range | 18.4–30.5 | 18.4–30.5 |
| **Ethnicity/race, n (%)** | | |
| Hispanic/Latino | | |
| Black | 1 (3.7) | 1 (3.6) |
| White | 1 (3.7) | 1 (3.6) |
| Non-Hispanic/non-Latino | | |
| Black | 8 (29.6) | 9 (32.1) |
| White | 17 (63.0) | 17 (60.7) |

MEROS, methylphenidate extended-release oral suspension; BMI, body mass index; SD, standard deviation.

concentration (C_{max}), time to maximum plasma concentration (T_{max}), apparent first-order terminal rate constant (calculated from a semi-log plot of the plasma concentration-vs-time curve), and apparent first-order terminal half-life (t_{1/2}; calculated as 0.693/terminal rate constant).

**Statistical Analyses**

Based on a fixed type-I error of 5% and an estimated intrasubject coefficient of variation of 20% obtained from a pilot study, a sample size of 20 was required to provide at least 80% power to detect a difference between test and reference treatments, assuming a test/reference ratio of 95% to 105%. A total of 30 subjects were enrolled to account for potential dropouts.

Standard noncompartmental methods were used to calculate PK parameters for methylphenidate (d-enantiomer) plasma concentrations. Analyses of variance (ANOVA) using SAS software were performed on the ln-transformed PK parameters, AUC_t, AUC_{inf}, and C_{max} and on the untransformed PK parameters T_{max}, K_{el}, and t_{1/2}, with sequence, treatment, and period as fixed effects and subject within sequence as a random effect. Ratios of means and corresponding 90%CIs were calculated using the treatment least-squares means for ln-transformed, AUC_t, AUC_{inf}, and C_{max}; CIs were expressed as a percentage relative to the least-squares means of the reference treatment. Exposure equivalence was concluded if the 90%CIs for the ratio of adjusted geometric means for AUC_{inf}, and C_{max} for d-methylphenidate were completely within the boundaries of 80% to 125%. Descriptive statistics were used to summarize all PK parameters. For the statistical analysis, subject sample values below the lower limit of quantitation were reported as 0.

**Results**

**Study Population**

The study was conducted at a single site in the United States (Cetero Research–St. Charles, St. Charles, Missouri) from March 15 to March 31, 2010.

Thirty subjects were enrolled and randomized to receive study treatment. All 30 subjects (25 male, 5 female) received a 60-mg dose of MEROS and were included in the safety analyses. Two subjects withdrew consent for personal reasons, and the remaining 28 subjects completed the study. Completed subjects included 23 male and 5 female subjects with a mean age of 36.8 years (range 19 to 68 years), 65.5% of whom were white (for a summary of demographic data for subjects included in the PK analyses, see Table 1). One subject did not finish the high-fat–high-calorie test meal prior to dosing and was excluded from the PK analysis; hence, 28 subjects were included in the PK analysis under fasting conditions, and 27 subjects were included in the PK analysis under fed conditions.

**Pharmacokinetics**

The mean plasma methylphenidate concentration-time profile following single-dose administration of MEROS 60 mg under the fed and fasted states is shown in Figure 1. Following attainment of C_{max}, mean
methylphenidate plasma concentrations declined in parallel, irrespective of food intake (Figure 1).

The exposure (AUC) of methylphenidate was higher when MEROS 60 mg was administered under fed conditions compared with fasting conditions, with mean $AUC_{0-1}$ of 160.2 ng·h/mL vs 140.4 ng·h/mL, and mean $AUC_{0-\infty}$ of 163.2 ng·h/mL vs 143.7 ng·h/mL, respectively (Table 2). The rate of exposure ($C_{\text{max}}$) of methylphenidate was also higher when MEROS 60 mg was administered under fed conditions compared with fasting conditions ($C_{\text{max}}$ of 17.0 ng/mL vs 13.6 ng/mL, respectively), and absorption of methylphenidate was more rapid under fed conditions, with median $T_{\text{max}}$ occurring at 4.0 hours and 5.0 hours, respectively (Table 2). When compared with fasting conditions, under fed conditions the average $C_{\text{max}}$ and $AUC_{0-1}$ of methylphenidate increased by 25% and 14%, respectively. Food intake did not affect the mean $t_{1/2}$ values (fed condition 5.24 hours; fasting conditions 5.65 hours) (Table 2). Variability (coefficient of variation [CV]) estimates under fed and fasting conditions for $AUC_{0-1}$ (CV = 49.1% and 50.6%, respectively), $AUC_{0-\infty}$ (CV = 49.2% and 50.7%, respectively), and $C_{\text{max}}$ (CV = 45.5% and 42.6%, respectively) were similar (Table 2).

When MEROS 60 mg was administered under fed conditions compared with fasting conditions, the 90% CIs for the $AUC_{0-1}$ and $AUC_{0-\infty}$ geometric mean ratios fell within the standard 80% to 125% bioequivalence criteria. The ratios of the ln-transformed geometric means and 90% CIs for methylphenidate for $AUC_{0-1}$ and $AUC_{0-\infty}$ were 119.5% (90% CI, 115.7% to 123.5%) and 119.0% (90% CI, 115.2% to 122.8%), respectively, indicating no effect on the overall exposure to MEROS after administration with food. The ratio of ln-transformed geometric means (90% CI) for $C_{\text{max}}$ was 127.6% (119.9% to 135.8%), which falls outside of the standard 80% to 125% bioequivalence criteria, indicating a slight increased rate of absorption of MEROS after administration in the fed condition (Table 3).

### Safety

Overall, 12 of 30 subjects receiving MEROS 60 mg under fed or fasting conditions reported a total of 25 treatment-emergent AEs; all AEs were mild in intensity. Ten subjects reported 15 AEs after receiving MEROS under fed conditions compared with 6 subjects (10 AEs) after receiving MEROS under fasting conditions; 4 subjects reported AEs on both fed and fasted treatment. Headache (fed: $n = 5/29$ [17.2%]; fasting: $n = 3/28$ [10.7%]) was the most commonly reported AE and was generally considered to be possibly related to the treatment. AEs are listed by fed and fasting conditions in Table 4.

There were no deaths, serious AEs, or discontinuations due to AEs reported, nor were there any clinically significant abnormalities in laboratory test data, vital signs, or electrocardiograms, and no subject had suicidal ideation or behavior.

### Table 2. Summary of Pharmacokinetic Parameters of Methylphenidate Following a Single Dose of MEROS 60 mg Under Fed and Fasting Conditions

|                    | MEROS 60 mg, Fed Conditions | Meros 60 mg, Fasting Conditions |
|--------------------|-----------------------------|--------------------------------|
|                    | $N = 27$                    | $N = 28$                       |
| $AUC_{0-1}$ (ng·h/mL) | 160.2 (78.6)                | 140.4 (71.1)                   |
| $AUC_{0-\infty}$ (ng·h/mL) | 163.2 (80.3)               | 143.7 (72.8)                   |
| $AUC_{0-1} / AUC_{0-\infty}$ | 0.98 (0.01)                | 0.98 (0.02)                    |
| $C_{\text{max}}$ (ng/mL)  | 17.0 (7.7)                  | 13.6 (5.8)                     |
| $T_{\text{max}}$ (h)     | 4.0 (1.3–7.3)               | 5.0 (1.7–6.0)                  |
| $t_{1/2}$ (h)           | 5.24 (1.1)                  | 5.65 (0.85)                    |

Data shown are arithmetic mean (standard deviation), with the exception of values for $T_{\text{max}}$, which are shown as median (range).

MEROS indicates methylphenidate extended-release oral suspension; AUC, area under the plasma concentration-vs-time curve, from time 0 to the time of the last quantifiable concentration ($AUC_{0-1}$), or AUC from time 0 extrapolated to infinite time ($AUC_{0-\infty}$); $C_{\text{max}}$, maximum plasma concentration; $T_{\text{max}}$, time of maximum plasma concentration; $K_{\text{dil}}$, apparent first-order terminal rate constant; $t_{1/2}$, apparent first-order terminal half-life.
Table 3. Ratio of the Adjusted Geometric Means and Associated 90% CIs for Methylphenidate (d enantiomer) Pharmacokinetic Parameters Following Single Oral Doses of MEROS 60 mg Under Fed and Fasting Conditions

| Parameter            | MEROS 60 mg, Fed Conditions | MEROS 60 mg, Fasting Conditions | Ratio (%) | 90% CI      |
|----------------------|----------------------------|--------------------------------|-----------|------------|
| AUC<sub>0–t</sub> (ng·h/mL) | 144.4                      | 120.8                          | 119.5     | 115.7–123.5 |
| AUC<sub>0–inf</sub> (ng·h/mL) | 147.3                      | 123.8                          | 119.0     | 115.2–122.8 |
| C<sub>max</sub> (ng/mL)    | 15.5                       | 12.2                           | 127.6     | 119.9–135.8 |

Data shown are the ln-transformed geometric means.
MEROS indicates methylphenidate extended-release oral suspension; AUC, area under the plasma concentration-vs-time curve, from time 0 to the time of the last quantifiable concentration (AUC<sub>0–t</sub>), or AUC from time 0 extrapolated to infinite time (AUC<sub>0–inf</sub>); C<sub>max</sub>, maximum plasma concentration.

*Ratio of the ln-transformed adjusted geometric mean for MEROS 60 mg under fed vs fasting conditions.

Table 4. Summary of Adverse Events Reported Following Single Dose of MEROS 60 mg Under Fed and Fasting Conditions

| Adverse Event, n (%) | MEROS 60 mg, Fed Conditions | N = 29 | MEROS 60 mg, Fasting Conditions | N = 28 |
|----------------------|----------------------------|--------|-------------------------------|--------|
| Headache             | 5 (17.2)                   | 3 (10.7)|                               |        |
| Dizziness            | 2 (6.9)                    | 2 (7.1) |                               |        |
| Palpitations         | 2 (6.9)                    | 1 (3.6) |                               |        |
| Nervousness          | 1 (3.4)                    | 1 (3.6) |                               |        |
| Blurred vision       | 1 (3.4)                    | 1 (3.6) |                               |        |
| Abdominal pain       | 1 (3.4)                    | 0       |                               |        |
| Dry mouth            | 1 (3.4)                    | 0       |                               |        |
| Hot flush            | 1 (3.4)                    | 0       |                               |        |
| Nausea               | 0                          | 1 (3.6) |                               |        |
| Chest discomfort     | 0                          | 1 (3.6) |                               |        |

MEROS indicates methylphenidate extended-release oral suspension.

Discussion

It is important to establish if there are any food effects of once-daily extended-release methylphenidate formulations in children with ADHD because the timing of the dose administration is typically after breakfast. This study in healthy adult subjects demonstrated that food intake has a small impact on the bioavailability of MEROS 60 mg, slightly increasing both the rate and extent of absorption.

Consistent with the extended-release nature of MEROS, the rate of exposure (C<sub>max</sub>) of MEROS was lower than that of the immediate-release methylphenidate HCl oral solution when administered under fasting conditions. The presence of food reduced the time to peak concentration of MEROS by approximately 1 hour when compared with under fasting conditions. Following the intake of a high-fat–high-calorie meal prior to administration of MEROS 60 mg, the average C<sub>max</sub> of MEROS increased by 25%, and the extent of exposure of MEROS (AUC<sub>0–inf</sub>) increased by 14% compared with administration of MEROS under fasting conditions. These changes are not likely to be clinically significant.

The food effect exhibited by MEROS is different than those for other methylphenidate products. For immediate-release methylphenidate formulations, food intake prolongs the time to peak concentration by approximately 1 hour. A similar effect has been observed with once-daily solid dosage forms of extended-release formulations of methylphenidate (such as tablets and capsules) when administered with food. The relative bioavailability of long-acting OROS<sup>®</sup>, an osmotic controlled-release tablet formulation of methylphenidate HCl, is similar to that of immediate-release methylphenidate under fed and fasting conditions. Studies have shown that peak plasma concentrations and AUC for OROS<sup>®</sup> were approximately 10% to 30% higher, and time to peak concentration was delayed by approximately 1 hour, by the presence of food. Various tablet or capsule formulations of extended-release methylphenidate HCl also exhibit delayed PK profiles similar to that of OROS<sup>®</sup> when administered with food.

The formulation of MEROS is unique, with a matrix formulation that, unlike other formulations, is more resilient to degradation by stomach acid, making the drug release rate less likely to be altered by food intake and gastric transit time. MEROS is supplied as a powder that is reconstituted with water by the pharmacist prior to dispensing and is composed...
of cationic drug-polymer complexes, consisting of a d,l-threomethylphenidate racemic mixture bound to matrix particles via an ion-exchange mechanism. Eighty percent of these drug complexes are coated with an extended-release coating polymer, which allows for release of methylphenidate throughout the day; the remaining 20% are left uncoated and act as immediate-release methylphenidate. The IR component provides the requisite fast absorption rate needed to achieve a 45-minute onset of efficacy, and food should not impact that outcome.

The suspension formulation of MEROS provides a treatment option for children with ADHD who struggle with solid dosage forms—ie, those who are unwilling or unable to swallow tablets/capsules or to use sprinkles or transdermal patches. Based on C\text{max}, bioequivalence was not observed for MEROS 60 mg administered under fed and fasting conditions. However, the difference in C\text{max} between fed and fasted conditions was small (geometric mean ratio 127.6\% [90\%CI, 119.9\% to 135.8\%]). In an open-label, randomized crossover study, the C\text{max} for MEROS 60 mg administered in a fasted state was substantially lower (geometric mean ratio 69.13\% [90\%CI, 63.72\% to 75.00\%]) compared with an equivalent dose of an immediate-release MPH oral solution (30 mg twice daily); thus, the increased C\text{max} observed when MEROS was administered after a high-fat, high-calorie meal was lower than that observed with an equivalent dose of the reference treatment, fasted. Further, the 90\%CIs for the AUC\text{0–1} and AUC\text{0–inf} geometric mean ratios fell within the standard 80\% to 125\% bioequivalence acceptance range, indicating no food effect on the overall (rate and extent) exposure in these healthy adult subjects. These results suggest that MEROS can be administered with or without food for the treatment of ADHD. The shorter T\text{max} observed in the fed condition suggests that taking MEROS with food may shorten the time it takes for the medicine to start working.

Conclusions

This study in healthy adult subjects demonstrated no food effect on the overall (rate and extent) exposure of MEROS; there was a small increase in the peak plasma concentration (but not exposure). The effect was small and likely without clinical implications. Overall, MEROS administered as a single oral dose of 60 mg (12 mL oral suspension equivalent to 25 mg methylphenidate HCl per 5 mL [5 mg/mL]) demonstrated a favorable safety profile in healthy adult subjects under fasting and fed conditions. The AEs reported during the study were anticipated and are common among the AEs reported following administration of methylphenidate.

Disclosures

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