



## Methylphenidate Extended-Release Capsules with Multilayer Beads: A New Once Daily Product for ADHD

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It is estimated that 5 to 7% of children and adolescents worldwide meet the criteria for attention deficit hyperactivity disorder (ADHD), with symptoms persisting into adulthood for more than 50%.<sup>1</sup> Current treatment guidelines focus on a multimodal treatment approach, with behavioral and educational interventions and pharmacologic therapy when appropriate. Prior to the approval of Concerta<sup>®</sup> in 2000, management of ADHD in older children and adolescents often required the administration of a stimulant multiple times during the day. The introduction of a preparation that provided symptom control for 12 hours from a single dose ushered in a new era in treatment.<sup>2</sup>

Since the approval of Concerta<sup>®</sup>, an extended-release tablet formulated using osmotic-release oral system (OROS) technology, several other once-daily products have entered the market in the United States. Two capsule formulations containing extended-release beads, Metadate CD<sup>®</sup> and Ritalin LA<sup>®</sup>, were approved in 2001 and 2002, respectively, and an extended-release oral liquid, Quillivant XR<sup>®</sup>, was approved in 2012. On April 17, 2015, the Food and Drug Administration (FDA) approved Aptensio XR<sup>™</sup>, an extended-release methylphenidate capsule containing multilayered beads (MPH-MLR) that provides up to 12 hours of ADHD symptom control for patients 6 years of age and older.<sup>3-8</sup>

### Formulation

The MPH-MLR capsule contains *d,l* methyl  $\alpha$ -phenyl-2-piperidineacetate hydrochloride. The beads contained in the MPH-MLR capsule consist of an immediate-release layer that contains approximately 40% of the dose and a controlled-release layer that contains the remaining 60% of the dose. Unlike Metadate CD<sup>®</sup> and Ritalin LA<sup>®</sup>, which contain beads with differing levels of coating resulting in either an

immediate or delayed dissolution, the beads in MPH-MLR are uniform, with each bead contributing to both the immediate and extended response.<sup>8</sup>

### Pharmacokinetics and Pharmacodynamics

Upon oral administration of MPH-MLR, plasma methylphenidate concentrations rise rapidly, with an initial peak at 2 hours followed by a gradual decline over the next 4 to 6 hours. A second increase in methylphenidate concentrations begins at 6 hours, with a second peak at approximately 7 to 8 hours. The relative bioavailability of the product is 100%.<sup>8-10</sup>

The pharmacokinetic profile of MPH-MLR was evaluated in a randomized, open-label cross-over study conducted in 26 healthy adults.<sup>9</sup> All subjects received each of the three treatment arms: an 80 mg capsule whole, an opened 80 mg capsule sprinkled onto applesauce, and methylphenidate 25 mg immediate-release (IR) given three times daily. Under fasting conditions, the capsule provided a maximum concentration ( $C_{max}$ ) of  $23.5 \pm 11.4$  ng/mL at 2 hours, with an area under the concentration time curve (AUC) of  $258.1 \pm 94.2$  ng•hr/mL and a half-life of  $5.1 \pm 1.6$  hours. The results when the beads were sprinkled on applesauce were similar to those with the capsule, with a  $C_{max}$  of  $21.8 \pm 9.5$  ng/mL, an AUC of  $258.0 \pm 84.4$  ng•hr/mL and a half-life of  $5.4 \pm 2.5$  hours. For comparison, IR methylphenidate produced a  $C_{max}$  of  $29.1 \pm 14.9$  ng/mL, an AUC of  $281.7 \pm 171.6$  ng•hr/mL and a half-life of  $3.4 \pm 0.7$  hrs.

Administration of MPH-MLR with a high fat meal produced an increase in the  $C_{max}$  of 28% and an 18% increase in AUC, but resulted in a decrease in the second peak concentration, suggesting a shift towards a slightly greater percentage of the dose was released earlier. The

variation produced with administration of MPH-MLR with food was not considered clinically significant. Methylphenidate is metabolized via deesterification to  $\alpha$ -phenyl-piperidine acetic acid. The effects of hepatic or renal insufficiency on the elimination of MPH-MLR have not been studied.

A pediatric pharmacokinetic study of MPH-MLR conducted in 2007 provided similar results to those obtained in adults.<sup>11</sup> The crossover study was conducted in 14 children (13 males, 1 female) with ADHD, ranging in age from 6 to 12 years (mean  $9.6 \pm 2.5$  years). Patients were randomized to receive either MPH-MLR or IR methylphenidate given twice daily with a 14-day washout before receiving the other treatment. Doses ranged from 20 to 80 mg/day, with a mean dose of 38.6 mg/day. Pharmacokinetic parameters were comparable between the two products, with the exception of a 60% higher  $C_{max}$  with the immediate-release product compared to MPH-MLR ( $20.41 \pm 8.5$  ng/mL versus  $12.12 \pm 5.76$  ng/mL) which was expected. The results for AUC were similar:  $155.11 + 71.16$  ng•hr/mL for MPH-MLR and  $144.95 \pm 53.89$  ng•hr/mL for IR methylphenidate. The half-life for MPH-MLR was  $5.07 \pm 1.47$  hrs, compared to  $2.86 \pm 0.41$  hrs for IR methylphenidate.

Data obtained in these studies, as well as the initial pediatric clinical trial have been used to create a pharmacokinetic/pharmacodynamic model to predict dose response.<sup>12</sup> The one-compartment, first-order elimination population pharmacokinetic model was used for simulations of response to doses between 10 and 80 mg. The model demonstrated a positive correlation between maximum concentration and improvement in symptoms. An unexpected relationship was found between increasing body weight and reduced symptom control. Traditionally methylphenidate has not been dosed by weight, but this model suggests that weight may need to be factored into dosing considerations for older children and adolescents in order to maximize patient response.

#### Clinical Trials

Two pediatric studies comparing MPH-MLR to IR methylphenidate were conducted early in the initial development of the drug.<sup>13,14</sup> In 2007, Weiss and colleagues conducted a randomized, double-blind, crossover study of MPH-MLR and twice daily IR methylphenidate in 90 children with ADHD.<sup>13</sup> The patients, 6-17 years of age, completed a 1-week baseline assessment followed by the two medications given for 5 weeks. Patient response was evaluated by

Clinical Global Impressions (CGI) and Conners' Parent and Teacher Rating Scales (CPRS and CTRS). Mean doses were 32 mg/day for MPH-MLR and 32.5 mg/day for IR methylphenidate, with a mean weight-based dose of  $0.8 \pm 0.3$  mg/kg/day in both groups. The majority of patients in both groups were rated as being much improved or very much improved on the CGI (73.2% for MPH-MLR and 81% for IR methylphenidate). Normalized scores were reported in 77.4% and 81.1% of patients in the MPH-MLR and IR methylphenidate groups, respectively, and 78.9% and 90.4% for the CTRS.

The investigators conducted a second double-blind, crossover, placebo-controlled study comparing the effects of MPH-MLR, IR methylphenidate and placebo in children undergoing repeated behavioral and cognitive testing.<sup>14</sup> Seventeen children (15 boys and two girls, mean age  $11.3 \pm 2.2$  years) were given each drug for 1 week prior to testing. Both formulations of methylphenidate significantly reduced Stop Signal Reaction Time compared to placebo ( $p = 0.001$  and  $p = 0.0005$ , for MPH-MLR and IR methylphenidate, respectively) as well as the Errors of Omission on the Continuous Performance Task ( $p = 0.0039$  and  $p = 0.0001$ ) and IOWA-Conners Inattention/Overactivity Index ( $p = 0.0001$  for both). Both groups also demonstrated an increase in the CGI Efficacy Index ( $p = 0.0001$  and  $p = 0.0017$ ), further demonstrating the comparable efficacy and duration of MPH-MLR to standard treatment with IR methylphenidate.

Two more recent randomized, double-blind placebo-controlled studies were used to gain FDA approval for MPH-MLR.<sup>15,16</sup> In 2014, Wigal and colleagues conducted a study of MPH-MLR in 20 children with ADHD from 6 to 12 years of age (mean age  $8.7 \pm 1.9$  years).<sup>15</sup> Following a 2-to 4-week open-label dose optimization period, patients were randomized to either MPH-MLR or placebo given once daily for one week. After testing, the patient was crossed over to the alternative treatment arm for one week. The primary endpoint was the least-squares mean post-treatment SKAMP-Total score. The resulting mean score was significantly lower in the treatment group (1.32 compared to 2.18 for the placebo group,  $p = 0.0001$ ). Scores taken each hour from 1 to 12 hours post-dose were also significantly lower in the patients getting MPH-MLR ( $p \leq 0.0261$ ), demonstrating 12-hour duration of effect.

Clinician assessment using the ADHD Rating Scale IV (ADHD-RS-IV) also showed a

significant benefit from treatment, with a lower least squares mean ADHD-RS-IV total of 10.27 in the MPH-MLR group compared to 17.64 in the placebo group ( $p = 0.0019$ ). Subscores for inattention were 4.20 and 8.42 in the MPH-MLR group and placebo groups, respectively ( $p = 0.0003$ ) and 6.08 and 9.22 for hyperactivity/impulsivity ( $p = 0.0391$ ). There were no serious adverse effects in either group.

The authors published a second study in the April 2015 issue of *CNS Drugs*.<sup>16</sup> This multicenter parallel, double-blind, placebo-controlled phase 3 study included 221 children and adolescents (ages 6-18 years) with ADHD. Patients were randomized to MPH-MLR (10, 15, 20, or 40 mg) or placebo following a 4-week screening phase. Treatment was given in a blinded fashion for one week followed by an 11-week open-label dose optimization period, with follow-up at 30 days. The primary outcome was change from baseline in the ADHD-RS-IV, with secondary endpoints of changes in ADHD-RS-IV subscores and CGI Improvement Scale scores.

There were significant reductions in ADHD-RS-IV total scores at the end of the double-blind phase (day 7) for the 20 mg and 40 mg MPH-MLR doses (-12.0 and -12.6 versus -5.0 for placebo,  $p = 0.0145$  and  $0.0011$ , respectively). The reduction in ADHD-RS-IV hyperactivity subscore was also significant for the 40 mg dose (-5.9 versus -2.4,  $p = 0.0061$ ) and the reduction in the inattention score was significant at both the 20 mg and 40 mg doses (-7.2 and -7.3 versus -2.7,  $p = 0.0118$  and  $0.0026$ ). The authors suggest that the lack of benefit seen with the 10 mg and 15 mg doses may have reflected the relatively small number of patients remaining on those doses at the end of the optimization phase (3.5% of patients). ADHD-RS-IV and CGI Improvement scores continued to show the benefit of MPH-MLR with improvement from baseline to the end of the study, with an average decrease in ADHD-RS-IV of 22.5 from baseline.

#### Warnings and Precautions

As with all stimulant medications, a thorough patient and family history should be obtained prior to initiation of MPH-MLR to evaluate for the presence of heart disease, arrhythmias, or sudden death. Serious cardiovascular adverse effects have been reported in adults taking methylphenidate or other stimulants. Myocardial infarction and sudden death have also been reported in children. Use of stimulant medications is not recommended in patients with structural heart defects, arrhythmias, coronary artery disease, or cardiomyopathy.

Patients and families should be aware of the risk for abuse or dependence with the use of stimulants. These drugs may produce an exacerbation of pre-existing psychiatric conditions or produce new psychotic or manic symptoms. The estimated incidence of this adverse effect, based on a pooled analysis of multiple clinical trials, is 0.1%. If symptoms occur, the stimulant should be discontinued.<sup>8</sup>

Methylphenidate should not be administered to patients with a known hypersensitivity to it or to related therapies such as dexmethylphenidate. Angioedema and anaphylaxis reactions to methylphenidate have been reported, but appear to be rare.<sup>8</sup>

#### Adverse Effects

Initial information on the safety of MPH-MLR in children and adolescents comes from the two placebo-controlled clinical trials conducted prior to approval. A total of 243 children between 6 and 17 years of age were included.<sup>8,15,16</sup> The most commonly reported adverse effects were similar to those reported in other pediatric methylphenidate trials and to trials of MPH-MLR in adults: headache (10.9% in the treated patients versus 8.5% in the placebo group), insomnia (9.8% versus 2.1%), dizziness (2.2% versus 2.1%), abdominal pain (8.2% versus 0%), nausea (3.8% versus 2.1%), vomiting (3.8% versus 0%), and decreased appetite (4.9% versus 0%).

Four patients in the 2015 study by Wigal and colleagues experienced moderate to severe adverse effects during the open-label phase: two patients had viral infections not thought to be related to treatment, but aggression in one patient and mood swings in another were considered to be related to MPH-MLR. Two patients withdrew from the study during the initial double-blind phase for conditions not considered to be related to the study.

Although not observed in the clinical studies with MPH-MLR, methylphenidate and other stimulants may increase blood pressure (mean increase 2-4 mm Hg) and heart rate (mean increase 3-6 bpm). While the change is clinically insignificant in most patients, some may have a larger increase. Patients should be assessed at baseline, upon initiation and periodically during treatment. Use of stimulants in children less than 13 years of age has also been associated with a transient slowing of growth after initiation of treatment.<sup>8</sup>

#### Drug Interactions

Administration of methylphenidate and monoamine oxidase inhibitors (MAOI) may lead to a hypertensive crisis.<sup>8</sup> Concomitant use or administration of methylphenidate within 14 days of MAOI use is contraindicated.

#### Availability and Dosing Recommendations

Aptensio XR™ is available in 10 mg, 15 mg, 20 mg, 30 mg, 40 mg, 50 mg, and 60 mg capsules. The recommended initial dose for patients 6 years of age and older is 10 mg once daily in the morning. The dose may be increased weekly by 10 mg increments based on patient response. The maximum recommended dose is 60 mg. The capsules may be taken with or without food, but should be taken in the same manner each day to minimize variation in absorption. For patients unable to swallow the capsule, the capsule may be opened and the beads sprinkled onto a spoonful of applesauce. The applesauce should be swallowed immediately without chewing or biting down on the beads.<sup>8</sup> The efficacy of the beads when sprinkled on other foods has not yet been studied.

#### Summary

Methylphenidate extended-release capsules with multilayer beads offer a new alternative for once daily treatment of ADHD. It combines the benefits of several methylphenidate products already on the market. Like other extended release capsules, it can be opened and sprinkled onto food, an advantage for patients unable to swallow an intact capsule or tablet. Unlike these capsules, however, MPH-MLR provides symptom control for 12 hours, similar to Concerta®. Additional studies are needed to compare the efficacy of this new product with other once-daily preparations to define its role in the treatment of ADHD.

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