

**Company**

Ironshore Pharmaceuticals Inc.

**Drug or Device Name**

JORNAY PM®

**Category**

Pharmaceutical

**Compound/Technical Name**

Methylphenidate hydrochloride

**Trade Name**

JORNAY PM®

**Date of Approval**

08/08/2018

**Therapeutic Categories**

Psychiatry

**Indications**

JORNAY PM is a central nervous system (CNS) stimulant indicated for the treatment of Attention Deficit Hyperactivity Disorder (ADHD) in patients 6 years and older.

**Background**

Attention-deficit/hyperactivity disorder (ADHD) is common, affecting 10% of US children and adolescents, with symptoms often persisting into adulthood. ADHD is associated with impairments in nearly every major domain of life studied to date, including educational success, family conflict, peer relationships, legal problems, occupational and financial difficulties, marital issues, and parenting behavior. ADHD is also associated with many adverse health outcomes, such as increased risk for injuries and accidents, sexually transmitted diseases, diabetes, obesity, and substance use. Due to these and other health concerns, the persistence of childhood ADHD into adulthood, if untreated, has been estimated to reduce life expectancy by 13 years. The economic burden of ADHD in the United States is an estimated \$122.8 billion, mostly driven by unemployment, productivity loss, and health care services. Because ADHD affects all aspects of an individual's life, there is a need for treatment that spans the entire day, from waking until bedtime. Although stimulant treatments, including amphetamines and methylphenidates, are effective for ADHD, surveys have shown that treatment duration remains an issue for many patients, for both children and adults. Most oral long-acting stimulant formulations are administered in the morning and include an immediate-release stimulant component to bridge the gap between administration and onset of efficacy. However, there is often a delay in the initial onset of action of up to two hours after morning administration. If duration into the afternoon or evening is not sufficient, common practice is to add an additional dose of an immediate-

release stimulant in the afternoon. Pharmacokinetics are critical in the ADHD category, with the FDA acknowledging an established relationship between drug-concentration levels and both efficacy and safety, with little to no time delay. Therefore, they recognize that formulations can be developed with the objective of creating specific pharmacokinetic profiles.

## Development

Based on the unmet need for an all-day treatment, from awakening until bedtime, the first conception of evening-dosed JORNAY PM was a theoretical methylphenidate pharmacokinetic curve sketched on a napkin—a smooth curve with methylphenidate rising to therapeutic levels upon awakening and with drug levels lasting until the evening, without peaks and troughs that could possibly result in inconsistent effects across the day. JORNAY PM utilizes the novel DELEXIS® drug delivery platform, which confers delayed-release properties that prevent overnight drug release, as well as extended-release mechanisms that control drug release throughout the day. Drug release relies on time to wetting of its two functional film coatings; it does not rely on any single factor, such as pH trigger, site of release, or gastrointestinal transit, which minimizes inter- and intra-patient variability with respect to early morning release. Resulting from its delayed release, JORNAY PM begins to be released in the colon, a less absorptive site compared to the upper gastrointestinal tract. Extended absorption in the colon is the reason a single dose of JORNAY PM can provide all-day coverage with a dose-dependent duration of effect. The pharmacokinetic characteristics of JORNAY PM have been extensively studied in seven pharmacokinetic studies, all which confirmed that methylphenidate is reliably released in the early morning with almost no drug (<5%) released overnight. Two registrational clinical trials were performed in children aged 6–12 years with ADHD. These trials were unique because they included novel early morning and evening rating scales as key secondary endpoints in addition to standard endpoints that measure classroom behaviors and general ADHD symptoms. Significant improvements with JORNAY PM were reported in the early morning, throughout the day, and in the evening versus placebo. Consequently, JORNAY PM was the first stimulant medication to have early morning efficacy included in its FDA labeling.

## Innovation

JORNAY PM is unique in that it is gradually absorbed in the colon, compared to all other oral long-acting methylphenidates that are rapidly absorbed from the upper gastrointestinal tract. It is the only stimulant administered in the evening, often a less hectic time of the day. Consequently, JORNAY PM is the only oral long-acting methylphenidate that achieves therapeutic levels upon waking, and therefore does not require an immediate-release methylphenidate component as part of its formulation. Furthermore, gradual colonic absorption enables exposure that can be individualized from the early morning until bedtime, in a dose-dependent manner, so that the duration of ADHD symptom control can be tailored by simply titrating to a single dose that works when the patient wakes and continues to last for as long as needed without immediate-release stimulant supplementation in the afternoon. This means that a patient on an appropriate dose of JORNAY PM wakes up treated, which can prevent issues associated with untreated ADHD such as tardiness, family conflicts, or accidents, and does not have to worry about an afternoon supplemental stimulant dose, which can be associated with increased stigma or treatment inconsistency if the dose is missed. DELEXIS technology can also be applied to other therapeutic areas that require precise control over the onset and duration of drug release or precise site of drug absorption in the gastrointestinal tract. Possible applications include treatment for local diseases (eg, ulcerative colitis, colorectal cancer) or to increase bioavailability of a drug via bypass of enzymatic degradation or first-pass metabolism in the upper gastrointestinal tract (eg, type 2 diabetes). DELEXIS can enable these applications because of its

delivery accuracy and precision, a critical technology advancement when compared to traditional colonic delivery formulations, most of which rely on single and highly variable release triggers.

## Pubmed

1. Barkley RA, Fischer M. Hyperactive Child Syndrome and Estimated Life Expectancy at Young Adult Follow-Up: The Role of ADHD Persistence and Other Potential Predictors. *J Atten Disord*. 2019;23(9):907-923. <https://pubmed.ncbi.nlm.nih.gov/30526189/> 2. Childress A, Mehrotra S, Gobburu J, McLean A, DeSousa NJ, Incledon B. Single-Dose Pharmacokinetics of HLD200, a Delayed-Release and Extended-Release Methylphenidate Formulation, in Healthy Adults and in Adolescents and Children with Attention-Deficit/Hyperactivity Disorder. *J Child Adolesc Psychopharmacol*. 2018;28(1):10-18. <https://pubmed.ncbi.nlm.nih.gov/29039979/> 3. Childress AC, Komolova M, Sallee FR. An Update on the Pharmacokinetic Considerations in the Treatment of ADHD with Long-Acting Methylphenidate and Amphetamine Formulations. *Expert Opin Drug Metab Toxicol*. 2019;15(11):937-974. <https://pubmed.ncbi.nlm.nih.gov/31581854/> 4. Childress AC, Cutler AJ, Marraffino A, et al. A Randomized, Double-Blind, Placebo-Controlled Study of HLD200, a Delayed-Release and Extended-Release Methylphenidate, in Children with Attention-Deficit/Hyperactivity Disorder: An Evaluation of Safety and Efficacy Throughout the Day and Across Settings. *J Child Adolesc Psychopharmacol*. 2020;30(1):2-14. <https://pubmed.ncbi.nlm.nih.gov/31464511/> 5. Gomeni R, Komolova M, Incledon B, Faraone SV. Model-Based Approach for Establishing the Predicted Clinical Response of a Delayed-Release and Extended-Release Methylphenidate for the Treatment of Attention-Deficit/Hyperactivity Disorder. *J Clin Psychopharmacol*. 2020;40(4):350-358. <https://pubmed.ncbi.nlm.nih.gov/32590405/> 6. Incledon B, Incledon C, Gomeni R, et al. Effect of Colonic Absorption on the Pharmacokinetic Properties of Delayed-Release and Extended-Release Methylphenidate: In Vivo, In Vitro, and Modeling Evaluations. *Clin Pharmacol Drug Dev*. Published online ahead of print 2022. <https://pubmed.ncbi.nlm.nih.gov/35316579/> 7. Ironshore Pharmaceuticals & Development, Inc. JORNAY PM Prescribing Information. 2021. <https://www.ironshorepharma.com/labeling.pdf> 8. Liu T, Gobburu JVS, Po MD, et al. Pharmacokinetics of HLD200, a Delayed-Release and Extended-Release Methylphenidate: Evaluation of Dose Proportionality, Food Effect, Multiple-Dose Modeling, and Comparative Bioavailability with Immediate-Release Methylphenidate in Healthy Adults. *J Child Adolesc Psychopharmacol*. 2019;29(3):181-191. <https://pubmed.ncbi.nlm.nih.gov/30810347/> 9. Pliszka SR, Wilens TE, Bostrom S, et al. Efficacy and Safety of HLD200, Delayed-Release and Extended-Release Methylphenidate, in Children with Attention-Deficit/Hyperactivity Disorder. *J Child Adolesc Psychopharmacol*. 2017;27(6):474-482. <https://pubmed.ncbi.nlm.nih.gov/29172680/> 10. Schein J, Adler LA, Childress A, et al. Economic Burden of Attention-Deficit/Hyperactivity Disorder Among Adults in the United States: A Societal Perspective. *J Manag Care Spec Pharm*. 2022;28(2):168-179. <https://pubmed.ncbi.nlm.nih.gov/34806909/> 11. Sibley MH, Eugene Arnold L, Swanson JM, et al. Variable Patterns of Remission From ADHD in the Multimodal Treatment Study of ADHD. *Am J Psychiatry*. 2022;179(2):142-151. <https://pubmed.ncbi.nlm.nih.gov/34384227/> 12. Xu G, Strathearn L, Liu B, Yang B, Bao W. Twenty-Year Trends in Diagnosed Attention-Deficit/Hyperactivity Disorder Among US Children and Adolescents, 1997-2016. *JAMA Netw Open*. 2018;1(4):e181471. <https://pubmed.ncbi.nlm.nih.gov/30646132/> 13. U.S. Food and Drug Administration. Attention Deficit Hyperactivity Disorder: Developing Stimulant Drugs for Treatment Guidance for Industry DRAFT GUIDANCE. 2019 <https://www.fda.gov/media/124334/download>

## Attachments

- 1654288210Ref\_Incledon\_et\_al\_2022.pdf
- 1654288217Ref\_Gomeni\_et\_al\_2020.pdf

- 1654288096Ref\_Zhang\_et\_al\_APSARD\_2020\_Poster.pdf
- 1654288109Ref\_Gomeni\_et\_al\_2020.pdf
- 1654288118Ref\_Childress\_et\_al\_2020.pdf
- 1654288129Ref\_Pliska\_et\_al\_2017.pdf
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