CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

209311Orig1s000

OTHER ACTION LETTERS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 209311

COMPLETE RESPONSE

Ironshore Pharmaceuticals & Development, Inc.
C/O Baker Botts L.L.P.
Attention: Margaret Sampson
98 San Jancinto Boulevard, Suite 1500
Austin, TX 78701

Dear Ms. Sampson:

Please refer to your New Drug Application (NDA) dated September 30, 2016, received September 30, 2016, and your amendments, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Jornay PM (methylphenidate hydrochloride) Modified Release Capsules, 20 mg, 40 mg, 60 mg, 80 mg, and 100 mg.

We have completed our review of this application, as amended, and have determined that we cannot approve this application in its present form. We have described our reasons for this action below and, where possible, our recommendations to address these issues.

CLINICAL

Although your pharmacokinetic data in adults suggest that evening doses of HLD 200 would result in delayed release and, thus, not impact sleep, the safety findings from the Phase 3 studies did not confirm these predictions. In Study 108, approximately 33% of patients treated with HLD 200 experienced insomnia (compared to approximately 9% of patients in the placebo group). Although Ritalin (the reference listed drug) labeling does not include data describing the rate of adverse reactions, a number of other approved methylphenidate product labels do. The labeled rates of insomnia in methylphenidate clinical trials range from 2 to 13% (vs. 0 to approximately 5% on placebo). We recognize the limitations of cross-trial comparisons; nevertheless, treatment with HLD 200 resulted in more than double the rate of insomnia compared to the highest observed rate with any other approved methylphenidate product. In addition, it appears that the risk for insomnia is greater for younger children (43% in children ages 6 to 9; 30% in children ages 10 to 12), and that adjusting the timing of the evening dose does not appear to mitigate this risk (33% if HLD 200 is administered at 8 pm; 36% if HLD 200 is administered after 8 pm).

To obtain marketing authorization for this patient population, you would need to conduct an additional study to find a lower dose that is safe and effective. A double-blind, placebo-controlled, fixed-dose study in children ages 6 to 12 years could potentially identify a dose at which this product is effective yet the adverse reactions are acceptable. You may wish to consider an additional study in adolescents ages 13 to 17 years; if a favorable benefit-risk profile

cannot be achieved in children, we could consider labeling that limits use to adolescents if the benefit-risk profile is acceptable in that population.

PRESCRIBING INFORMATION

We reserve comment on the proposed labeling until the application is otherwise adequate. We encourage you to review the labeling review resources on the *PLR Requirements for Prescribing Information* and *Pregnancy and Lactation Labeling Final Rule* websites, including regulations and related guidance documents and the Selected Requirements for Prescribing Information (SRPI) − a checklist of important format items from labeling regulations and guidances.

If you revise labeling, use the SRPI checklist to ensure that the prescribing information conforms with format items in regulations and guidances. Your response must include updated content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm

PROPRIETARY NAME

Please refer to correspondence dated, July 19, 2017, which addresses the proposed proprietary name, Jornay PM. This name was found acceptable pending approval of the application in the current review cycle. Please resubmit the proposed proprietary name when you respond to the application deficiencies.

SAFETY UPDATE

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(*b*). The safety update should include data from all nonclinical and clinical studies/trials of the drug under consideration regardless of indication, dosage form, or dose level.

1. Describe in detail any significant changes or findings in the safety profile.

2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:

    - Present new safety data from the studies/clinical trials for the proposed indication using the same format as in the original submission.
    - Present tabulations of the new safety data combined with the original application data.
    - Include tables that compare frequencies of adverse events in the original application with the retabulated frequencies described in the bullet above.
    - For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.

3. Present a retabulation of the reasons for premature trial discontinuation by incorporating the drop-outs from the newly completed trials. Describe any new trends or patterns identified.

4. Provide case report forms and narrative summaries for each patient who died during a clinical trial or who did not complete a trial because of an adverse event. In addition, provide narrative summaries for serious adverse events.

5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original application data.

6. Provide updated exposure information for the clinical studies/trials (e.g., number of subjects, person time).

7. Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.

8. Provide English translations of current approved foreign labeling not previously submitted.

OTHER

Within one year after the date of this letter, you are required to resubmit or take other actions available under 21 CFR 314.110. If you do not take one of these actions, we may consider your lack of response a request to withdraw the application under 21 CFR 314.65. You may also request an extension of time in which to resubmit the application.

A resubmission must fully address all the deficiencies listed in this letter and should be clearly marked with "**RESUBMISSION**" in large font, bolded type at the beginning of the cover letter of the submission. The cover letter should clearly state that you consider this resubmission a complete response to the deficiencies outlined in this letter. A partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

You may request a meeting or teleconference with us to discuss what steps you need to take before the application may be approved. If you wish to have such a meeting, submit your meeting request as described in the draft FDA Guidance for Industry, "Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products," March 2015 at http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm437431.pdf.

The drug product may not be legally marketed until you have been notified in writing that this application is approved.

If you have any questions, contact Martin Yoon, Regulatory Project Manager, at (240) 402-3911 or martin.yoon@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Mitchell V. Mathis, MD
Director
Division of Psychiatry Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MITCHELL V Mathis
07/28/2017