4164-01-P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. FDA-2016-N-3120]

Kremers Urban Pharmaceuticals, Inc.; Grant of Hearing Request Regarding a Proposal to Withdraw Approval of an Abbreviated New Drug Application for Extended-Release Methylphenidate Tablets

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA or the Agency) is announcing a formal evidentiary public hearing on the proposal to withdraw approval of the abbreviated new drug application (ANDA) 091695, submitted by Kremers Urban Pharmaceuticals, Inc. (Kremers) for methylphenidate hydrochloride extended-release tablets. On October 18, 2016, the Director of FDA's Center for Drug Evaluation and Research (CDER) published a notice of opportunity for hearing on a proposal to withdraw approval of ANDA 091695. Kremers submitted a timely request for hearing on that proposal. This notice of hearing provides factual and legal information concerning CDER's proposal to withdraw approval of ANDA 091695 and identifies the factual issues that will be the subject of the evidentiary hearing.

DATES: A prehearing conference will be held on [INSERT DATE 45 DAYS AFTER DATE OF PUBLICATION IN THE *FEDERAL REGISTER*], beginning at 10:00 a.m. Eastern Daylight Time. Any person wishing to participate in this hearing shall submit a written notice of participation by [INSERT DATE 30 DAYS AFTER DATE OF PUBLICATION IN THE *FEDERAL REGISTER*]. Disclosure of data and information as required by 21 CFR 12.85(b) must be made by [INSERT DATE 60 DAYS AFTER DATE OF PUBLICATION IN THE *FEDERAL REGISTER*].

ADDRESSES: You may submit a written notice of participation and data and information

required under 21 CFR 12.85 by either of the following methods:

Electronic Submissions

Submit electronically in the following way:

- Federal eRulemaking Portal: https://www.regulations.gov. Follow the instructions for submitting information. Information submitted electronically, including attachments, to https://www.regulations.gov will be posted to the docket unchanged. Because your information will be made public, you are solely responsible for ensuring that your information does not include any confidential information that you or a third party may not wish to be posted, such as medical information, your or anyone else's Social Security number, or confidential business information, such as a manufacturing process. Please note that if you include your name, contact information, or other information that identifies you in the body of your information, that information will be posted on https://www.regulations.gov.
- If you want to submit any information with confidential information that you do not wish to be made available to the public, submit the information as a written/paper submission and in the manner detailed (see "Written/Paper Submission" and "Instructions").

Written/Paper Submissions

Submit written/paper submissions as follows:

- Mail/Hand delivery/Courier (for written/paper submissions): Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852.
- For written/paper submissions sent to the Dockets Management Staff, FDA will post your submission, as well as any attachments, except for the information submitted, marked and identified, as confidential, if submitted as detailed in "Instructions."

Instructions: All submissions received must include the Docket No. FDA-2016-N-3120 for "Kremers Urban Pharmaceuticals, Inc.; Grant of Hearing Request Regarding a Proposal to

Withdraw Approval of an Abbreviated New Drug Application for Extended-Release Methylphenidate Tablets." Received submissions will be placed in the docket and, except for those submitted as "Confidential Submissions," publicly viewable at https://www.regulations.gov or at the Dockets Management Staff between 9 a.m. and 4 p.m., Monday through Friday, 240-402-7500.

- Confidential Submissions—To make a submission with confidential information that you do not wish to be made publicly available, send your submissions only as a written/paper submission. You should submit two copies total. One copy will include the information you claim to be confidential with a heading or cover note that states "THIS DOCUMENT CONTAINS CONFIDENTIAL INFORMATION." The Agency will review this copy, including the claimed confidential information, in its consideration of any decisions on this matter. The second copy, which will have the claimed confidential information redacted/blacked out, will be available for public viewing and posted on https://www.regulations.gov. Submit both copies to the Dockets Management Staff. If you do not wish your name and contact information to be made publicly available, you can provide this information on the cover sheet and not in the body of your submissions and you must identify this information as "confidential." Any information marked as "confidential" will not be disclosed except in accordance with 21 CFR 10.20 and other applicable disclosure law. For more information about FDA's posting of information to public dockets, see 80 FR 56469, September 18, 2015, or access the information at: https://www.govinfo.gov/content/pkg/FR-2015-09-18/pdf/2015-23389.pdf.

Docket: For access to the docket to read background documents or the electronic and written/paper comments received, go to https://www.regulations.gov and insert the docket number, found in brackets in the heading of this document, into the "Search" box and follow the prompts and/or go to the Dockets Management Staff, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852, 240-402-7500.

DAB E-File: Beginning on the date of this notice, parties to the hearing and participants should make submissions related to this hearing to Departmental Appeals Board electronic filing system (DAB E-File) at: https://dab.efile.hhs.gov/, except insofar as they are submitting initial notices of participation or disclosing data and information pursuant to 21 CFR 12.85. Submissions to DAB E-File by parties and participants must conform to the Case Development Order (Ref. 1) and other orders issued by the presiding officer. Although certain regulations in 21 CFR part 12 require submissions for hearing matters to be filed with the Dockets Management Staff, FDA will deem a submission made by a party or participant to DAB E-File that conforms to the presiding officer's orders and this notice to satisfy any such applicable requirement and will make the submission available in the docket (see "Docket"). Non-parties and non-participants should continue to make submissions through Dockets Management Staff, as detailed in "Electronic Submissions" and "Written/Paper Submissions." The record will continue to be accessible at https://www.regulations.gov or through the Dockets Management Staff, between 9 a.m. and 4 p.m., Monday through Friday.

FOR FURTHER INFORMATION CONTACT: Karen Fikes, Office of Scientific Integrity, Food and Drug Administration, 10903 New Hampshire Avenue, Bldg. 1, Rm. 4218, Silver Spring, MD 20993, 301-796-9603.

SUPPLEMENTARY INFORMATION:

I. Background

CONCERTA (methylphenidate hydrochloride) extended-release tablets, 18 mg, 27 mg, 36 mg, 54 mg, are the subject of the new drug application 021121, held by Janssen Pharmaceuticals, Inc., which FDA approved on August 1, 2000. CONCERTA is a central nervous system stimulant intended for the treatment of attention deficit hyperactivity disorder in children 6 years of age and older, adolescents, and adults up to the age of 65. CONCERTA is a multiphasic modified-release product that is formulated to release a bolus of methylphenidate, resulting in an initial rapid rise in plasma concentration of the drug comparable to the effect of an

immediate-release methylphenidate formulation, followed by sustained delivery later in the day, thereby allowing for once-daily dosing. According to its approved labeling, CONCERTA is expected to have a 12-hour duration of effectiveness. The relative bioavailability of CONCERTA in adults is comparable to immediate-release methylphenidate administered three times daily, but the CONCERTA formulation minimizes the fluctuations between peak and trough concentrations associated with immediate-release methylphenidate administered three times daily.

FDA approved ANDA 091695, held by Kremers, for a generic version of CONCERTA under the requirements of section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 355(j)) and FDA's implementing regulations.[1] FDA approved ANDA 091695 on July 9, 2013, for the 18 mg and 27 mg strengths and on September 23, 2013, for the 36 mg and 54 mg strengths.

At the time of approval, FDA determined that ANDA 091695 included data sufficient to demonstrate the bioequivalence of the Kremers product to CONCERTA. The bioequivalence testing and data submitted in the ANDA were consistent with the recommendations provided in a draft guidance for industry on "Methylphenidate Hydrochloride," issued on September 14, 2012 (77 FR 56851). The draft guidance provided information and recommendations for establishing bioequivalence to CONCERTA that reflected FDA's understanding, at that time, of how to evaluate the pharmacokinetic properties of such methylphenidate hydrochloride extended-release tablets to support a demonstration of bioequivalence. The demonstration of bioequivalence was necessary to the approval of Kremers' product. Unlike the sponsor of CONCERTA, Kremers was not required to submit clinical studies to demonstrate the safety and effectiveness of its product. Instead, FDA approved Kremers' ANDA based on a finding that the product was bioequivalent to

[1] Kremers is now owned by Lannett Company, Inc. (Lannett). The original applicant for ANDA 091695 was Kudco Ireland, Ltd. (Kudco). This notice of hearing refers to Kremers, Lannett, and Kudco collectively as Kremers.

CONCERTA and met the other requirements for ANDA approval in section 505(j) of the FD&C Act and FDA's implementing regulations.

After approval of ANDA 091695, FDA received adverse event reports describing an insufficient therapeutic effect of Kremers' product, particularly during the latter part of the 12-hour period after dosing. Due to those adverse event reports, CDER initiated a "tracked safety issue" to investigate the reports of insufficient therapeutic effect together with other data and information related to the Kremers product. After reevaluating the question of what evidence is needed to demonstrate bioequivalence to CONCERTA, FDA concluded that, to ensure therapeutic effect throughout the 12-hour therapeutic time course, an absence of a significant difference in drug exposure between a proposed generic product and CONCERTA must be shown during the entire therapeutic time course, including the latter part of the 12-hour period after drug administration. On November 6, 2014 (79 FR 65978), FDA issued a revised draft guidance for industry on "Bioequivalence Recommendations for CONCERTA (Methylphenidate Hydrochloride) Extended-Release Tablets" with recommendations for establishing bioequivalence to CONCERTA that reflected CDER's new understanding that there would need to be a comparison of the extent of methylphenidate exposure produced by a generic drug versus CONCERTA during the specific time period that corresponds to the latter part of the expected 12-hour duration of effectiveness.

CDER reanalyzed Kremers' original bioequivalence data submitted to support approval under the new recommendations in the revised draft guidance and concluded that the data failed to show an absence of a significant difference in the extent of drug exposure between the 54-mg strength of the Kremers product (on which the in vivo bioequivalence testing was conducted) and CONCERTA during the 7- to 12-hour time period after administration under fasting conditions and during the 8- to 12-hour time period after administration under fed conditions. CDER also analyzed new data submitted by Kremers in

June 2015 under the recommendations in the revised draft guidance and found that Kremers' product failed to meet the recommendations for bioequivalence because the data did not show an absence of a significant difference in the extent of drug exposure between the Kremers product and CONCERTA during the 8- to 12-hour time period after administration under fed conditions.

On October 18, 2016, CDER published a notice of opportunity for hearing (NOOH) on its proposal to withdraw approval of ANDA 091695 held by Kremers for methylphenidate hydrochloride extended-release tablets (81 FR 71741). Kremers submitted a timely request for hearing on November 10, 2016, and its summary of data, information, and analyses in support of its request for hearing on December 4, 2017. Kremers submitted a supplement to its submission on May 2, 2018.

II. Presiding Officer

The Office of the Commissioner hereby appoints Administrative Law Judge Kourtney LeBlanc, at the Department of Health and Human Services' Departmental Appeals Board, to serve as presiding officer under 21 CFR 12.60 and to conduct the hearing in accordance with authority prescribed in 21 CFR 12.70.

III. Statutory Grounds for the Hearing

In the NOOH, published October 18, 2016, CDER proposed to withdraw approval of ANDA 091695 under section 505(e)(3) of the FD&C Act (21 U.S.C. 355(e)(3)) and 21 C.F.R. 314.150(a)(2)(iii). Section 505(e)(3) of the FD&C Act requires FDA to withdraw an approval if it finds "on the basis of new information before [FDA] with respect to such drug, evaluated together with the evidence available to [FDA] when the application was approved, that there is a lack of substantial evidence that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling thereof." The NOOH explained that, absent information showing bioequivalence between the Kremers product and CONCERTA, there is no basis to

conclude that the finding of safety and effectiveness for CONCERTA can support approval of the Kremers product.

Kremers has the burden of proof in this proceeding. See 21 CFR 12.87(d) (putting the burden of proof on the hearing participant contesting withdrawal of approval of a drug application).

IV. Factual Issues for the Hearing

The central factual issue for this hearing is whether the Kremers methylphenidate product has been shown to be bioequivalent to CONCERTA. On February 24, 2026, pursuant to 21 CFR 12.85(a)(4), CDER submitted to the Dockets Management Staff, *inter alia*, a narrative position statement that identifies two specific sub-issues for the hearing:

1. Given that CONCERTA is approved for a 12-hour duration of effectiveness, to establish bioequivalence to CONCERTA, is it necessary to show that there is an absence of a significant difference in drug exposure between the Kremers methylphenidate product and CONCERTA during the entire therapeutic time course, including the latter part of the 12-hour period after drug administration?
2. If so, has it been shown that there is an absence of a significant difference in drug exposure between the Kremers methylphenidate product and CONCERTA during the entire therapeutic time course, including the latter part of the 12-hour period?

The Office of the Commissioner is granting a hearing on the question raised by the second of the two sub-issues identified by CDER. But the first sub-issue identified by CDER appears to be a legal question turning on the meaning of "bioequivalent" in section 505(j)(2)(A)(iv) of the FD&C Act (21 U.S.C. 355(j)(2)(A)(iv)) (*see also* 21 CFR part 320). Under 21 CFR 12.24(b)(1), however, "[a] hearing will not be granted on issues of policy or law." As a result, the Office of the Commissioner is granting a hearing on the first sub-issue only to the

extent that it raises a factual or scientific question not captured by the second sub-issue.[2] The presiding officer may also further revise these factual issues for the hearing under 21 CFR 12.35(b).

V. Parties to the Hearing

The parties to the hearing will be FDA's CDER and Kremers. Other interested persons shall be permitted to participate as nonparty participants as provided by 21 CFR 12.45 and 12.89.

VI. Disclosure of Information by CDER, Kremers, and Other Hearing Participants

In accordance with 21 CFR 12.85(a), CDER has filed with the Dockets Management Staff a narrative statement setting forth its position on the issues of the hearing and a summary of the types of evidence to be introduced in support of its position in the hearing, together with copies of data and information contained in the Center's files that relate to the issues to be resolved at the hearing. Hearing participants other than CDER, including Kremers, shall disclose data and information and submit their narrative statements pursuant to 21 CFR 12.85(b) to the Dockets Management Staff (see "Addresses") on or before [INSERT DATE 60 DAYS AFTER DATE OF PUBLICATION IN THE *FEDERAL REGISTER*], or within another period of time set by the presiding officer. Interested persons may also examine the data on the drug subject to this hearing notice (with the exception of any data identified as confidential pursuant to the provisions of 21 CFR 10.20(j)) via https://www.regulations.gov or at the Dockets Management Staff, between 9 a.m. and 4 p.m., Monday through Friday (see "Addresses").

VII. Prehearing Conference

The prehearing conference will be held on [INSERT DATE 45 DAYS AFTER DATE OF PUBLICATION IN THE *FEDERAL REGISTER*], beginning at 10:00 a.m. Eastern Daylight Time, by videoconference with instructions to be provided. The hearing will be held on a date to

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[2] Insofar as Kremers or another participant wishes to challenge the legal underpinnings of CDER's proposal to withdraw approval of the Kremers methylphenidate product, they may do so via an appropriate appeal to the Office of the Commissioner under 21 CFR part 12 (*see, e.g.,* 21 CFR 12.120) if the presiding officer makes a decision resting on those underpinnings. The record of the hearing will inform the Office of the Commissioner's decision on any such appeal.

be set at the prehearing conference. Written notices of participation shall be filed with the Dockets Management Staff no later than [INSERT DATE 30 DAYS AFTER DATE OF PUBLICATION IN THE *FEDERAL REGISTER*]. All participants are required both to attend the prehearing conference and to be prepared to comply with the provisions of 21 CFR 12.92.

VIII. Conclusion

In accordance with the foregoing, under section 505 the FD&C Act (21 U.S.C. 355) and under authority delegated to me, I order that a formal evidentiary public hearing be held on the issues set out in this notice. The hearing will be open to the public by visiting the HHS Live Streaming page at www.hhs.gov/live. A direct link for the hearing will be visible on the HHS Live Streaming page once a hearing date has been set by the presiding officer after the prehearing conference. Interested persons are encouraged to monitor the docket for any updated links for public access.

IX. Reference

1. U.S. Department of Health and Human Services, Departmental Appeals Board, Civil Remedies Division, Kremers Urban Pharmaceuticals, Inc. Proposal to Withdraw Approval of an Abbreviated New Drug Application for Extended Release Methylphenidate Tablets, Case Development Order [Civil Remedies Division Procedures, March 28, 2016], [INSERT DATE OF PUBLICATION IN THE *FEDERAL REGISTER*].

George Warren,

Director of the Office of Scientific Integrity.

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