NDA 021164

NDA APPROVAL

Fabre-Kramer Pharmaceuticals, Inc.
Attention: Stephen J. Kramer, MD
Chief Executive Officer
5847 San Felipe, Suite 2000
Houston, TX 77057

Dear Dr. Kramer:

Please refer to your new drug application (NDA) dated September 30, 1999, received October 1, 1999, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Exxua (gepirone) extended-release tablets.

We acknowledge receipt of your amendment dated December 23, 2022, which constituted a complete response to our November 2, 2007, action letter.

We acknowledge receipt of your major amendments dated April 28, May 8, 12, and 24, 2023, which extended the goal date by three months.

This NDA provides for the use of Exxua (gepirone) extended-release tablets for the treatment of major depressive disorder.

APPROVAL & LABELING

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at FDA.gov.[1] Content of labeling must be identical to the enclosed labeling (text for the Prescribing Information and Medication Guide) as well as annual reportable changes not included in the enclosed labeling. Information on submitting SPL files using eLIST

[1] http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm

may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As.*[2]

The SPL will be accessible via publicly available labeling repositories.

CARTON AND CONTAINER LABELING

Submit final printed carton and container labeling that are identical to the carton and container labeling submitted on September 19, 2023, as soon as they are available, but no more than 30 days after they are printed. For administrative purposes, designate this submission "**Final Printed Carton and Container Labeling for approved NDA 021164**." Approval of this submission by FDA is not required before the labeling is used.

DATING PERIOD

Based on the stability data submitted to date, the expiry dating period for Exxua (gepirone) extended-release tablets shall be 48 months from the date of manufacture when stored at 20°C to 25°C (68°F to 77°F).

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are waiving the pediatric study requirement for ages 0 to 6 years because necessary studies are impossible or highly impracticable due to the low incidence of MDD in this age group and difficulty accurately diagnosing MDD in younger children.

We note that you have fulfilled the pediatric studies requirement for ages 7 to 17 years for this application.

[2] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o)(3) of the FDCA authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to assess a signal of a serious risk of major birth defects, miscarriage, or other adverse maternal or fetal outcomes.

Furthermore, the active postmarket risk identification and analysis system as available under section 505(k)(3) of the FDCA will not be sufficient to assess these serious risks.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following studies:

4485-1 Collect data from a prospective pregnancy exposure registry, preferably a disease-based multiproduct registry, using a cohort analysis that compares the maternal, fetal, and infant outcomes of women with MDD exposed to Exxua (gepirone) during pregnancy with an unexposed comparator population(s) in a timely manner. Align the study protocol with protocol(s) outside the US to reach the target sample size. The registry will identify and record pregnancy complications, major and minor congenital malformations, spontaneous abortion, stillbirths, elective terminations, preterm births, small-for-gestational-age births, and any other adverse outcomes, including postnatal growth and development. Outcomes described in the protocol will be assessed throughout pregnancy. Infant outcomes, including effects on postnatal growth and development, will be assessed through at least the first year of life.

The timetable you agreed upon, via email, on September 15, 2023, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	09/2025
Study Completion:	03/2035
Final Report Submission:	03/2036

4485-2 Conduct an additional pregnancy study that uses a different design from the pregnancy registry (for example a retrospective cohort study using claims or electronic medical record data or a case control study) to assess major congenital malformations, spontaneous abortions, stillbirths, small for gestational age births and preterm births in women exposed to Exxua

(gepirone) during pregnancy compared to an unexposed control population.

The timetable you agreed upon, via email, on September 15, 2023, states that you will conduct this study according to the following schedule:

Final Protocol Submission: 09/2025
Study Completion: 04/2030
Final Report Submission: 04/2031

Finally, we have determined that only clinical trials (rather than a nonclinical or observational study) will be sufficient to identify an unexpected serious risk of gepirone exposure in breastfed infants and to assess a known serious risk of QTc prolongation effect.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following trials:

4485-3 Perform a lactation study (milk only) in lactating women who have received Exxua (gepirone) to assess concentrations of gepirone in breastmilk using a validated assay and to assess the effects on the breastfed infant.

The timetable you agreed upon, via email, on September 15, 2023, states that you will conduct this trial according to the following schedule:

Final Protocol Submission: 03/2025
Trial Completion: 03/2027
Final Report Submission: 12/2027

4485-4 Conduct a multiple dose thorough QT/QTc study in healthy subjects to assess the effects of gepirone ER and its major metabolites on the QTc interval using 12-lead digital ECG recordings. The study should include a positive control, a placebo control, the highest recommended dose (72.6 mg once daily) and a supratherapeutic dose which covers the high clinical exposure scenario. The primary analysis should be by-time as described in the ICH E14 guideline. The sample size of the study should have at least as much power as one be based on excluding a 10-msec mean increase from placebo in baseline-adjusted QTc interval.

The timetable you agreed upon, via email, on September 15, 2023, states that you will conduct this trial according to the following schedule:

Final Protocol Submission:	05/2025
Trial Completion:	09/2026
Final Report Submission:	02/2027

FDA considers the term *final* to mean that the applicant has submitted a protocol, the FDA review team has sent comments to the applicant, and the protocol has been revised as needed to meet the goal of the study or clinical trial.[3]

Submit clinical protocol(s) to your IND 033626 with a cross-reference letter to this NDA. Submit nonclinical and chemistry, manufacturing, and controls protocols and all final report(s) to your NDA. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate: **Required Postmarketing Protocol Under 505(o), Required Postmarketing Final Report Under 505(o), Required Postmarketing Correspondence Under 505(o).**

Submission of the protocol(s) for required postmarketing observational studies to your IND is for purposes of administrative tracking only. These studies do not constitute clinical investigations pursuant to 21 CFR 312.3(b) and therefore are not subject to the IND requirements under 21 CFR part 312.

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B(a)(1) of the FDCA, as well as 21 CFR 314.81(b)(2)(vii) requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B(a)(1) and 21 CFR 314.81(b)(2)(vii) to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 314.81(b)(2)(vii). We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

[3] See the guidance for Industry *Postmarketing Studies and Clinical Trials—Implementation of Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act (October 2019).* https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

POSTMARKETING COMMITMENTS SUBJECT TO REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitments:

4485-5 Conduct a controlled trial to evaluate the longer-term (i.e., maintenance) efficacy of gepirone ER in the treatment of adults with major depressive disorder (MDD). The population should include significant U.S. representation and include underrepresented racial and ethnic minorities. This trial must include a placebo group and must utilize a double-blind, randomized-withdrawal design following an adequate period of stabilization with open-label treatment of gepirone ER. This trial design must incorporate long-term safety assessments (including pre-, post-, and on-treatment electrocardiograms).

Because the short-term trials used to support efficacy were not fixed-dose, it is important to establish the dose-response for maintenance. Therefore, following open-label stabilization, this trial should randomize subjects to fixed doses of the to-be-marketed doses of gepirone ER (and placebo) during the maintenance phase.

The timetable you agreed upon, via email, on September 15, 2023, states that you will conduct this trial according to the following schedule:

Final Protocol Submission: 06/2025
Study/Trial Completion: 01/2029
Final Report Submission: 01/2030

A final submitted protocol is one that the FDA has reviewed and commented upon, and you have revised as needed to meet the goal of the study or clinical trial.

Submit clinical protocols to your IND 033626 for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all postmarketing final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii) you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies/trials, number of patients/subjects entered into each study/trial. All submissions, including supplements, relating to these postmarketing commitments should be prominently labeled "**Postmarketing Commitment Protocol**," "**Postmarketing Commitment Final Report**," **or** "**Postmarketing Commitment Correspondence**."

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. For information about submitting promotional materials, see the final guidance for industry *Providing Regulatory Submissions in Electronic and Non-Electronic Format—Promotional Labeling and Advertising Materials for Human Prescription Drugs.*[4]

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the Prescribing Information, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. Form FDA 2253 is available at FDA.gov.[5] Information and Instructions for completing the form can be found at FDA.gov.[6]

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

POST APPROVAL FEEDBACK MEETING

New molecular entities qualify for a post approval feedback meeting. Such meetings are used to discuss the quality of the application and to evaluate the communication process during drug development and marketing application review. The purpose is to learn from successful aspects of the review process and to identify areas that could benefit from improvement. If you would like to have such a meeting with us, call the Regulatory Project Manager for this application.

COMPENDIAL STANDARDS

A drug with a name recognized in the official United States Pharmacopeia or official National Formulary (USP-NF) generally must comply with the compendial standards for strength, quality, and purity, unless the difference in strength, quality, or purity is plainly stated on its label (see FD&C Act § 501(b), 21 USC 351(b)). FDA typically cannot share application-specific information contained in submitted regulatory filings with third parties, which includes USP-NF. To help ensure that a drug continues to comply with compendial standards, application holders may work directly with USP-NF to revise

[4] For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/media/128163/download.
[5] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf
[6] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf

official USP monographs. More information on the USP-NF is available on USP's website[7].

If you have any questions, contact Sarah Seung, Senior Regulatory Project Manager, at 240-402-3879 or sarah.seung@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Teresa Buracchio, MD
Director (Acting)
Office of Neuroscience
Office of New Drugs
Center for Drug Evaluation and Research

ENCLOSURE(S):

- Content of Labeling
  - Prescribing Information
  - Medication Guide
- Carton and Container Labeling

[7] https://www.uspnf.com/

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

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