

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

212102Orig1s000

ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS



NDA 212102

REFUSAL TO FILE

Zogenix, Inc.
Attention: AJ Acker
Vice President, Global Regulatory Affairs
5858 Horton Street, Suite 455
Emeryville, CA 94608

Dear Mr. Acker:

Please refer to your New Drug Application (NDA) dated February 5, 2019, received February 5, 2019, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA), for Fintepla (fenfluramine) oral solution 2.5 mg per ml.

After a preliminary review, we find your application is not sufficiently complete to permit a substantive review. Therefore, we are refusing to file this application under 21 CFR 314.101(d) for the following reasons:

- You have not submitted nonclinical studies to assess the potential for chronic administration of fenfluramine to result in novel or more severe toxicity compared to shorter duration studies. Therefore, you will need to conduct toxicity studies of 6 and 9 months' duration in rodent and nonrodent, respectively (see ICH M3(R2), January 2010; ICH M3(R2), February 2013). A focused histopathological evaluation of cardiac valves should be incorporated into these studies.
- You have confirmed that the SAS datasets submitted on February 5, 2019, for Study 1 were incorrect as they were not the final version used in the statistical analyses performed for the Clinical Study Report. You resubmitted raw and derived data for Study 1 on March 15, 2019. The application must be complete at the time of submission to allow adequate time for review, and this holds especially true for critical parts of the application such as the datasets in question. Extensive review of an application occurs upon submission and the erroneous datasets you included in your application prevented us from completing important steps of our review process that are necessary to support the filing of your application. Additionally, it is not clear why the derived efficacy endpoint measurements differ considerably between your penultimate and final version of datasets for the majority of the subjects in Study 1. Prior to your resubmission, you will need to conduct an extensive data quality assessment to ensure the accuracy of the trial results.

While not issues related to our refusal to file this application, you should address the following issues if the application is resubmitted.

You included only analysis (ADAM) datasets for the ISS dataset. In order for us to perform a full review of your application, we require tabulation (SDTM) and analysis (ADAM) datasets for the ISS, as well as the individual studies. Please provide SDTM and ADAM datasets for the ISS in your resubmission.

You submitted a proposed risk management plan (RMP) with restrictive elements to your NDA. If risk management beyond labeling is necessary, you should instead submit a proposed Risk Evaluation and Mitigation Strategy (REMS) to your application. In your proposed RMP, details of how requirements will be completed are missing (e.g., how the pharmacy verifies completion of monitoring, how patients will be prompted to complete any proposed required monitoring, etc.). A proposed REMS should include full details of each requirement for all stakeholders, including relevant appended materials. A REMS document template and instructions for use can be found in the draft guidance for industry *Format and Content of a REMS Document*, available at: <https://www.fda.gov/AboutFDA/Transparency/Basics/ucm325201.htm>. A complete review of the proposed REMS, including whether a REMS is necessary to ensure the benefits of the drug outweigh its risks, will occur in conjunction with the full clinical review of your NDA.

Your NDA submission should be amended to provide abuse-related information and cross-linkage in appropriate sections of the NDA, as follows:

- a. Section 1.11.4 should contain your proposal and rationale for placing or not placing the drug substance or product into any schedule of the Controlled Substance Act (CSA).
- b. Section 2.7.4 should contain a subsection devoted to details of your abuse potential assessment, including a description of data, interpretation, and discussion of all abuse potential data provided in the NDA under other modules, including any drug accountability discrepancies and an analysis of abuse-related adverse events. Section 2.7.4 should also contain a comprehensive table of contents that provides links to all studies (nonclinical and clinical) and references in the NDA submission related to the assessment of abuse potential.

Please note that this filing review represents a preliminary review of the application and is not indicative of deficiencies that would be identified if we performed a complete review.

Within 30 days of the date of this letter, you may request in writing a Type A meeting about our refusal to file the application. A meeting package should be submitted with this Type A meeting request. To file this application over FDA's protest, you must avail yourself of this meeting.

If, after the meeting, you still do not agree with our conclusions, you may request that the application be filed over protest. In that case, the filing date will be 60 days after the date you requested the meeting. The application will be considered a new original application for user fee purposes, and you must remit the appropriate fee. If you choose to file over protest, FDA will generally not review any amendments to the application and will generally not issue information requests during the review cycle. Resubmission goals will not apply to any resubmission of this application.

PROPOSED PROPRIETARY NAME

If you intend to have a proprietary name for the above-referenced product, submit a new request for review of a proposed proprietary name when you resubmit the application. For questions regarding proprietary name review requests, please contact the OSE Project Management Staff by telephone at (301) 796-3414 or by email at OSECONSULTS@cder.fda.gov.

If you have any questions, contact Susan Daugherty, Regulatory Project Manager, by telephone at (301) 796-0878 or by email at susan.daugherty@fda.hhs.gov.

Sincerely yours,

{See appended electronic signature page}

Billy Dunn, MD
Director
Division of Neurology Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/

WILLIAM H Dunn
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