NDA 212102

GENERAL ADVICE

Zogenix, Inc.
Attention: AJ Acker
Vice President, Global Regulatory Affairs
5959 Horton Street, Suite 500
Emeryville, CA 94608

Dear Mr. Acker:

Please refer to your new drug application (NDA) dated September 25, 2019, received September 25, 2019, and your amendments, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Fintepla (fenfluramine) oral solution 2.2 mg per mL.

We also refer to our approval letter date June 25, 2020, wherein the drug concentration of fenfluramine was incorrectly stated as *2.5 mg per mL*; it should have stated *2.2 mg per mL*. The table below describes the specific corrections to the approval letter.

Approval Letter Section	Incorrect Language	Correct Language
First page, 1st paragraph	Please refer to your new drug application (NDA) dated September 25, 2019, received September 25, 2019, and your amendments, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Fintepla (fenfluramine) oral solution *2.5 mg per mL*.	Please refer to your new drug application (NDA) dated September 25, 2019, received September 25, 2019, and your amendments, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Fintepla (fenfluramine) oral solution *2.2 mg per mL*.
First page, 4th paragraph	This NDA provides for the use of Fintepla (fenfluramine) oral solution, *2.5 mg per mL*, for the treatment of seizures associated with Dravet syndrome in patients 2 years of age and older.	This NDA provides for the use of Fintepla (fenfluramine) oral solution, *2.2 mg per mL*, for the treatment of seizures associated with Dravet syndrome in patients 2 years of age and older.
Controlled Substance Scheduling, 1st sentence	Fintepla (fenfluramine) oral solution *2.5 mg per mL* is currently controlled in Schedule IV under the Controlled Substances Act (CSA).	Fintepla (fenfluramine) oral solution *2.2 mg per mL* is currently controlled in Schedule IV under the Controlled Substances Act (CSA).

This General Advice letter acknowledges the error described above and incorporates the correction of the error. The effective approval date will remain June 25, 2020, the date of the original approval letter.

If you have any questions, call Stephanie N. Parncutt, M.H.A., Senior Regulatory Health Project Manager, at (301) 796-4098 or email at Stephanie.Parncutt@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Nick Kozauer, M.D.
Acting Director
Division of Neurology 2
Office of Neuroscience
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/

NICHOLAS A KOZAUER
07/10/2020 03:41:52 PM

NDA 212102

NDA APPROVAL

Zogenix, Inc.
Attention: AJ Acker
Vice President, Global Regulatory Affairs
5959 Horton Street, Suite 500
Emeryville, CA 94608

Dear Mr. Acker:

Please refer to your new drug application (NDA) dated September 25, 2019, received September 25, 2019, and your amendments, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Fintepla (fenfluramine) oral solution 2.5 mg per mL.

We acknowledge receipt of your major amendment dated February 22, 2020, which extended the goal date by three months.

We also acknowledge receipt of your amendment dated March 24, 2020, which was not reviewed for this action.

This NDA provides for the use of Fintepla (fenfluramine) oral solution, 2.5 mg per mL, for the treatment of seizures associated with Dravet syndrome in patients 2 years of age and older.

APPROVAL & LABELING

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

CONTROLLED SUBSTANCE SCHEDULING

Fintepla (fenfluramine) oral solution 2.5 mg per mL is currently controlled in Schedule IV under the Controlled Substances Act (CSA). However, we note this designation is currently being reevaluated. FDA will transmit a scheduling recommendation to the Drug Enforcement Administration (DEA), but your drug product remains a Schedule IV controlled substance until the DEA has made a final scheduling decision. We further note that, when a final scheduling decision has been published in the Federal Register, you will need to make appropriate revisions to the Prescribing Information, Medication Guide, Instructions for Use, and carton and container labeling by submitting a supplement to the NDA. This revision would include the statements in the labeling detailing the scheduling of Fintepla (fenfluramine) oral solution 2.5 mg per mL as required under 21 CFR 201.57(a)(2) and (c)(10)(i).

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, Instructions for Use, and Medication Guide) as well as annual reportable changes not included in the enclosed labeling. Information on submitting SPL files using eLIST 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.

We request that the labeling approved today be available on your website within 10 days of receipt of this letter.

CARTON AND CONTAINER LABELING

Submit final printed carton and container labeling that are identical to the carton and container labeling submitted on May 15, 2020, as soon as they are available, but no more than 30 days after they are printed. Please submit these labeling electronically according to the guidance for industry *Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications*. For administrative purposes, designate this submission "**Final Printed Carton and Container Labeling for approved NDA 212102**." Approval of this submission by FDA is not required before the labeling is used.

RARE PEDIATRIC DISEASE PRIORITY REVIEW VOUCHER

We also inform you that your request for a rare pediatric disease priority review voucher has been denied. You did not qualify for the voucher because the application did not meet the following eligibility criteria:

- It is a human drug application as defined in section 735(1) of the FD&C Act and submitted under section 505(b)(1) of the FD&C Act or section 351(a) of the PHS Act:
    - That contains no active ingredient (including any ester or salt of the active ingredient) that has been previously approved in any other application

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

under section 505(b)(1), 505(b)(2), or 505(j) of the FD&C Act or section 351(a) or 351(k) of the PHS Act;

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- You may also review the requirements related to this program by visiting FDA's Rare Pediatric Disease Priority Review Voucher Program web page.[3]

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.

Because this drug product for this indication has an orphan drug designation, you are exempt from this requirement.

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 identify an unexpected serious risk of adverse maternal, fetal, and infant outcomes resulting from the use of Fintepla (fenfluramine) during pregnancy, or to assess known serious risks of valvular heart disease and pulmonary arterial hypertension in patients treated with fenfluramine.

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 risk(s).

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

3887-1 A fertility and early embryonic development study of fenfluramine in rat.

[3] https://www.fda.gov/industry/developing-products-rare-diseases-conditions/rare-pediatric-disease-rpd-designation-and-voucher-programs

The timetable you submitted on June 15, 2020 states that you will conduct this study according to the following schedule:

Study Completion: 11/2019
Final Report Submission: 03/2020 (submitted)

3887-2 An embryofetal development study of fenfluramine in rat.

The timetable you submitted on June 15, 2020, states that you will conduct this study according to the following schedule:

Study Completion: 11/2019
Final Report Submission: 03/2020 (submitted)

3887-3 An embryofetal development study of fenfluramine in rabbit.

The timetable you submitted on June 15, 2020, states that you will conduct this study according to the following schedule:

Study Completion: 11/2019
Final Report Submission: 03/2020 (submitted)

3887-4 A pre- and postnatal development study of fenfluramine in rat.

The timetable you submitted on June 15, 2020, states that you will conduct this study according to the following schedule:

Study Completion: 11/2019
Final Report Submission: 03/2020 (submitted)

3887-5 A 6-month carcinogenicity study of fenfluramine in transgenic mouse.

The timetable you submitted on June 15, 2020, states that you will conduct this study according to the following schedule:

Study Completion: 04/2020
Final Report Submission: 12/2021

3887-6 A 2-year carcinogenicity study of fenfluramine in rat.

The timetable you submitted on June 15, 2020, states that you will conduct this study according to the following schedule:

Study Completion: 06/2021
Final Report Submission: 12/2021

3887-7 A single-arm pregnancy safety study to collect and analyze information for a minimum of 10 years on pregnancy complications and birth outcomes in women exposed to Fintepla (fenfluramine) during pregnancy. Provide a complete protocol that includes details regarding how you plan to encourage patients and providers to report pregnancy exposures, measures to ensure complete data capture regarding pregnancy outcomes and any adverse effects in offspring, and plans for comprehensive data analysis.

The timetable you submitted on June 15, 2020, states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	12/2020
Final Protocol Submission:	08/2021
Annual Interim Report Submissions:	08/2022
	08/2023
	08/2024
	08/2025
	08/2026
	08/2027
	08/2028
	08/2029
	08/2030
	08/2031
Study Completion:	08/2032
Final Report Submission:	08/2033

3887-8 A prospective observational registry study in epilepsy patients taking Fintepla using data from the REMS Registry and additional data beyond what is collected in the REMS registry. The primary objectives are to characterize the risks of the development of symptomatic or asymptomatic valvular heart disease (VHD) and/or pulmonary arterial hypertension (PAH). This includes recruiting an adequate number of patients to assess the incidence of VHD and PAH, to identify risk factors for VHD and PAH, and to evaluate the impact of duration, dose-exposure, and cumulative exposure on the development of VHD and PAH. Evaluation should include the assessment of echocardiographic data; patients in the study should be evaluated with echocardiograms at baseline and every six months for five years, or until the last echocardiogram following interruption of Fintepla treatment.

The timetable you submitted on June 15, 2020, states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	12/2020
Final Protocol Submission:	08/2021
Annual Interim Report Submissions:	08/2022
	08/2023
	08/2024
	08/2025
	08/2026
	08/2027
	08/2028
	08/2029
	08/2030
Study Completion:	08/2031
Final Report Submission:	08/2032

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.[4]

Finally, we have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to identify an unexpected serious risk resulting from altered pharmacokinetics of Fintepla due to hepatic impairment.

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

3887-9 A clinical pharmacokinetic trial to determine an appropriate dose of Fintepla (fenfluramine) to minimize toxicity in patients with varying degrees of hepatic impairment. Design and conduct the trial in accordance with the FDA Guidance for Industry entitled “Pharmacokinetics in Patients with Impaired Hepatic Function: Study Design, Data Analysis, and Impact on Dosing and Labeling.”

The timetable you submitted on June 17, 2020, states that you will conduct this trial according to the following schedule:

Final Protocol Submission:	09/2020
Trial Completion:	09/2021
Final Report Submission:	03/2022

[4] 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.

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.[5]

Submit clinical protocol(s) to your IND 125797 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 or FDA's regulations under 21 CFR parts 50 (Protection of Human Subjects) and 56 (Institutional Review Boards).

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 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 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.

RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS

Section 505-1 of the FDCA authorizes FDA to require the submission of a risk evaluation and mitigation strategy (REMS), if FDA determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks.

[5] 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.

In accordance with section 505-1 of FDCA, we have determined that a REMS is necessary for Fintepla to ensure the benefits of the drug outweigh the risks of valvular heart disease and pulmonary arterial hypertension.

Your proposed REMS must also include the following:

Communication Plan: We have determined that a communication plan targeted to healthcare providers who are likely to prescribe Fintepla will support implementation of the elements of your REMS. The communication plan provides for the dissemination of information about the risks of valvular heart disease and pulmonary arterial hypertension and the requirements of the REMS for healthcare providers.

Elements to Assure Safe Use: Pursuant to 505-1(f)(1), we have also determined that Fintepla can be approved only if elements necessary to assure safe use are required as part of the REMS to mitigate the risks of valvular heart disease and pulmonary arterial hypertension listed in the labeling of the drug.

Your REMS includes the following elements to mitigate these risks:

- Healthcare providers have particular experience or training, or are specially certified
- Pharmacies that dispense the drug are specially certified
- The drug is dispensed to patients with evidence or other documentation of safe-use conditions
- Each patient using the drug is subject to certain monitoring
- Each patient using the drug is enrolled in a registry

Implementation System: The REMS must include an implementation system to monitor, evaluate, and work to improve the implementation of the elements to assure safe use (outlined above) that require pharmacies that dispense the drug be specially certified and that the drug be dispensed to patients with documentation of safe use conditions.

Your proposed REMS, submitted on September 25, 2019, amended and appended to this letter, is approved.

The REMS consists of a communication plan, elements to assure safe use, an implementation system, and a timetable for submission of assessments of the REMS.

Your REMS must be fully operational before you introduce FINTEPLA into interstate commerce.

The REMS assessment plan must include, but is not limited to, the following:

Program Outreach and Communication

1. REMS communication plan activities (6-month, 1-year, and 2-year assessments only)
    a. Sources for the distribution lists for healthcare providers
    b. Number of healthcare providers targeted
    c. The number of REMS materials packets sent by date and method of distribution
    d. The number of mailings successfully delivered, and the number returned as undeliverable
    e. The number of emails successfully delivered, opened, and unopened

Program Implementation and Operations

2. REMS Program Implementation (6-month and 1-year assessments only)
    a. Date of first commercial distribution of Fintepla
    b. Date when the REMS website became live and fully operational
    c. Date when the REMS Call center was established and fully operational
    d. Date healthcare providers could become certified
    e. Date when pharmacies could become certified
    f. Date when patients could become enrolled

3. REMS Certification and Enrollment Statistics (provide for each reporting period and cumulatively)
    a. Healthcare provider certification
        i. The number of newly certified and active (i.e. who have prescribed Fintepla at least once during the reporting period) healthcare providers stratified by provider type (e.g., Doctor of Medicine, Doctor of Osteopathic Medicine, Advanced Nurse Practitioner, Physician Assistant, Other), specialty, and geographic region (as defined by US Census)
        ii. A summary of the methods of healthcare provider certification (e.g., fax, online)
        iii. The number of healthcare providers who were unable to become certified, accompanied by a summary of the reasons they were unable to be certified

iv. The number of healthcare providers who became decertified, accompanied by a summary of reasons for decertification

b. Pharmacy certification
    i. The number of newly certified, active (i.e., have dispensed Fintepla at least once during the reporting period), and recertified pharmacies stratified by pharmacy setting (i.e., inpatient, outpatient) and geographic region (as defined by US Census)
    ii. A summary of the methods of pharmacy certification and recertification (e.g., fax, online)
    iii. The number of pharmacies that were unable to become certified, accompanied by a summary of the reasons they were unable to become certified
    iv. The number of pharmacies that became decertified, accompanied by a summary of reasons for decertification
c. Patient enrollment
    i. The number of newly enrolled and active (i.e., have received Fintepla at least once during the reporting period) patients stratified by age, gender, race, ethnicity and geographic region (as defined by US Census)
    ii. A summary of the methods of patient enrollment (e.g., fax, mail)
d. Wholesalers/Distributor enrollment
    i. The number of newly enrolled and active (i.e., have shipped Fintepla at least once during the reporting period) wholesaler/distributors

4. Fintepla Utilization Data (provide for each reporting period and cumulatively)
    a. The number of Fintepla shipments sent to pharmacies, overall and stratified by quantity per shipment
    b. The number of pharmacies sent Fintepla shipments, stratified by pharmacy setting (i.e., outpatient or inpatient) and geographic region (as defined by US Census)
    c. The number of Fintepla prescriptions that were dispensed, overall and stratified by quantity dispensed per prescription and whether the prescription was new or a refill
    d. The number of healthcare providers who wrote Fintepla prescriptions that were dispensed, stratified by specialty, the number of dispensed prescriptions written by each healthcare provider, and the number of patients for whom dispensed prescriptions were written by each healthcare provider

e. The number of unique patients who received Fintepla, stratified by age, gender, race, ethnicity, and geographic region (as defined by US Census)
f. The number of prescriptions not dispensed, accompanied by a listing and summary of reasons for not dispensing the prescription
g. The number of prescription dispensing delays (i.e., prescription not dispensed within 10 business days of receipt), overall and stratified by whether the prescription was new or a refill; accompanied by a summary of the length of the delays and a listing and summary of reasons for delays in prescription dispensing

5. REMS Infrastructure and Performance (provide for each reporting period and cumulatively)
    a. REMS Website
        i. The number of visits and unique visits to the REMS website
        ii. The number of REMS materials downloaded and printed for each material

    b. REMS Call Center
        i. The number of calls received by the REMS call center, stratified by stakeholder type and reason for the call
        ii. The number of REMS materials requested through the REMS call center
        iii. The number of issues/complaints reported to the REMS call center, accompanied by a description of the top five reasons for calls by each stakeholder or 80% of calls by each stakeholder (whichever accounts for the greater number of calls) and the resolution (if applicable)
        iv. A description of each call, including stakeholder type, that may indicate an issue with access, burden, or an adverse event
        v. A summary of corrective actions resulting from issues identified

6. REMS Compliance (provide for each reporting period and cumulatively)
    a. The number and percentage of Fintepla shipments sent to non-certified pharmacies among all shipments
    b. The number and percentage of Fintepla prescriptions dispensed that were written by non-certified healthcare providers among all dispensed prescriptions in the outpatient setting
        i. For all prescriptions dispensed in the outpatient setting that were written by a non-certified healthcare provider, a summary including whether ECHO tests were obtained, whether the healthcare

provider later became certified, and if so, the time elapsed between dispensing and healthcare provider certification

c. The number and percentage of Fintepla prescriptions dispensed that were written by non-certified healthcare providers for patients not under the care of a certified healthcare provider among all dispensed prescriptions in the inpatient setting
    i. For all prescriptions dispensed in the inpatient setting that were written by non-certified healthcare providers for patients not under the care of certified healthcare providers, a summary including whether ECHO tests were obtained, whether the healthcare providers later became certified, and if so, the time elapsed between dispensing and healthcare provider certification
d. The number and percentage of Fintepla prescriptions dispensed to non-enrolled patients among all dispensed prescriptions, stratified by pharmacy setting (i.e., outpatient or inpatient)
e. For all prescriptions dispensed to non-enrolled patients, a summary of whether ECHO tests were obtained, whether the patients later became enrolled, and if so, the time elapsed between dispensing and patient enrollment, stratified by pharmacy setting
f. The number and percentage of Fintepla prescriptions dispensed that were written by non-certified healthcare providers for non-enrolled patients among all dispensed prescriptions, stratified by pharmacy setting (i.e., outpatient or inpatient).
    i. For all prescriptions dispensed that were written by non-certified healthcare provider for non-enrolled patients, a summary of whether ECHO tests were obtained, whether the patients later became enrolled, and if so, the time elapsed between dispensing and patient enrollment, stratified by pharmacy setting
    ii. For each prescription dispensed that was written by a non-certified healthcare provider for a non-enrolled patient, a link to the associated pharmacy noncompliance data and root cause analysis results
g. The number and percentage of prescriptions dispensed that bypassed the REMS authorization process among all dispensed prescriptions, stratified by pharmacy setting (i.e., outpatient or inpatient)
    i. For all prescriptions dispensed that bypassed the REMS authorization process, a summary of whether ECHO tests were obtained, healthcare provider certification status, patient enrollment status, and whether a current Patient Status Form is on file stratified by pharmacy setting
h. The number and percentage of prescriptions dispensed by noncertified pharmacies

i. The number and percentage of shipments that were shipped by wholesalers/distributors not enrolled in the REMS
j. The number of instances of noncompliance accompanied by a description of each instance and the reason for the occurrence (if provided). For each instance of noncompliance, report the following information:
    i. The unique ID(s) of the stakeholder(s) associated with the noncompliance event or deviation to enable tracking over time
    ii. The source of the noncompliance data
    iii. The results of root cause analysis
    iv. The number and percentage of patients who received Fintepla who were not enrolled in the REMS registry among all patients who received Fintepla and among all patients enrolled in the REMS registry, stratified by pharmacy setting (i.e., outpatient or inpatient)
k. A copy of the current audit plan for each stakeholder
l. A detailed description of deviations and major and minor audit findings, including information about the root cause of the noncompliance and a description of the corrective and preventive actions taken to address noncompliance with distribution and dispensing requirements
m. Report of audit findings by stakeholder type (i.e., REMS call center, pharmacy, or wholesaler-distributor):
    i. The number of audits expected and performed
    ii. The number of deficiencies noted, stratified by deficiency type
    iii. The number of critical events. A critical event is defined as a single occurrence of:
        1. Dispensing to a non-enrolled patient in the inpatient or outpatient setting
        2. Dispensing a prescription written by a non-certified prescriber in the outpatient setting
        3. Dispensing after obtaining a “Not Authorized” status
        4. Dispensing after bypassing the authorization process
    iv. For those with deficiencies noted, the number that successfully completed a corrective and preventive action (CAPA) plan within one month of the audit
        1. For those with deficiencies noted that did not complete a CAPA within one month of the audit, a description of the actions taken
    v. The existence of documentation demonstrating the completion of training for all relevant staff

vi. The existence of documentation demonstrating the existence of processes and procedures for complying with the REMS
vii. The existence of documentation demonstrating the verification of the designated authorized representative at each certified pharmacy
    1. If the authorized representative has changed since initial certification, the number of new authorized representatives and recertifications per pharmacy

Safe Use Behaviors

7. Patient Status Forms (provide for each reporting period and cumulatively)
    a. The number and percentage of patients who had a Patient Status Form submitted prior to initial dispensing among all patients who were dispensed a new prescription for Fintepla, stratified by pharmacy setting (i.e., outpatient or inpatient)
    b. The number and percentage of patients who did not have a Patient Status Form submitted prior to initial dispensing among all patients who were dispensed a new prescription for Fintepla, stratified by pharmacy setting (i.e., outpatient or inpatient) and whether the patient had an ECHO test
        i. For all patients who did not have a Patient Status Form submitted prior to initial dispensing and who did not have an ECHO test performed, a summary of the reasons ECHO tests were not performed and the source of reason information (i.e., healthcare provider or patient)
        ii. For each patient who did not have a Patient Status Form submitted prior to initial dispensing and who did not have an ECHO test performed, the source of noncompliance data and a link to the associated pharmacy noncompliance data and root cause analysis results
    c. The time between the submissions of previous and subsequent Patient Status Forms on record
    d. The number and percentages of patients who had a Patient Status Form documenting the prescriber not authorizing further prescriptions due to noncompliance with ECHOs among all patients receiving Fintepla, stratified by the period of time since the last submitted Patient Status Form authorizing treatment
    e. The number and percentage of patients who had a Patient Status Form documenting prescriber not authorizing treatment “Other” and the reason for not authorizing

f. The number and percentage of patients who had a Patient Status Form submitted within 180 days (approximately six months) of their most recent Patient Status Form among all patients who were dispensed Fintepla during the reporting period and did not have a Patient Status Form documenting their discontinuation of Fintepla
g. The number and percentage of patients who did not have a Patient Status Form submitted within 180 days (approximately six months) of their most recent Patient Status Form among all patients who were dispensed Fintepla and did not have a Patient Status Form documenting their discontinuation of Fintepla
h. The type, frequency, and outcome of outreach activities performed to obtain outstanding Patient Status forms
i. The number of "Authorized – Warning" patient statuses sent to pharmacies by the REMS
j. The number of healthcare providers who were contacted by the Fintepla REMS program documenting the "Authorized Warning" and the results of the outreach
k. The number and percentage of patients who had a Patient Status Form submitted within 270 days (approximately nine months) of their most recent Patient Status Form among all patients who were dispensed Fintepla during the reporting period, did not have a Patient Status Form documenting their discontinuation of Fintepla (submitted prior to or within 72 hours of the six month due date), and did not have a Patient Status Form submitted by the 180-day due date.
l. The number of patients who did not have a Patient Status Form submitted within 270 days (approximately nine months) of their most recent Patient Status Form, among all patients who were dispensed Fintepla during the reporting period, did not have a Patient Status Form documenting their discontinuation of Fintepla (submitted prior to or within 72 hours of the six month due date), and did not have a Patient Status Form submitted by the 180-day due date.
    i. For all patients who did not have a Patient Status Form submitted within 270 days of their most recent Patient Status Form and who did not have an ECHO test performed, a summary of the reasons ECHO tests were not performed and the source of reason information (i.e., healthcare provider or patient)
    ii. For each patient who did not have a Patient Status Form submitted within 270 days of their most recent Patient Status Form and who did not have an ECHO test performed, the source of noncompliance data and a link to the associated pharmacy noncompliance data and root cause analysis results

m. The number of patients who were continually dispensed Fintepla for 270 days or more (inpatient dispensing included) who did not have a Patient Status Form submitted within 450 days (approximately 15 months) of their most recent Patient Status Form
    i. For all patients who did not have a Patient Status Form submitted within 450 days of their most recent Patient Status Form and who did not have an ECHO test performed, a summary of the reasons ECHO tests were not performed and the source of reason information (i.e., healthcare provider or patient)
    ii. For each patient who did not have a Patient Status Form submitted within 270 days of his/her most recent Patient Status Form who was dispensed Fintepla and who did not have an ECHO test performed, the source of noncompliance data and a link to the associated pharmacy noncompliance data and root cause analysis results
n. The number and percentage of patients who had a Patient Status Form submitted within three to six months after discontinuation of Fintepla among all patients who had a Patient Status Form documenting their discontinuation of Fintepla and among all patients who did not received a dispensed prescription for Fintepla in the past six months
o. The number and percentage of patients who did not have a Patient Status Form submitted within three to six months after discontinuation of Fintepla among all patients who had a Patient Status Form documenting their discontinuation of Fintepla and among all patients who did not receive a dispensed prescription for Fintepla in the past six months
p. The number of unique patients who experienced a treatment interruption, including the duration of treatment interruption and reason for treatment interruption
q. The number and percentage of unique patients who were not authorized to receive Fintepla due to lack of ECHO testing among all patients who received Fintepla in compliance with the REMS requirements
    i. For all patients who were not authorized to receive Fintepla due to lack of ECHO testing, a summary of the reasons ECHO tests were not performed and the source of reason information (i.e., healthcare provider or patient).
r. Starting with the 2-year assessment, the estimated travel time (reported continuously with measures of central tendency and variability) for patients to:
    i. ECHO site
    ii. Certified prescriber's office

Knowledge

8. Knowledge Assessments (provide for each reporting period and cumulatively)
    a. The number of completed post-training knowledge assessments for prescribers, including the method of completion and the number of attempts to complete.
    b. A summary of the most frequently missed knowledge assessment questions.
    c. A summary of potential comprehension or perception issues identified with the knowledge assessment.
9. Stakeholder Surveys (beginning with the 1-year assessment report and annually thereafter with each assessment report)
    a. Healthcare provider surveys to assess if healthcare providers are educated on the following:
        i. The risk of valvular heart disease and pulmonary arterial hypertension associated with Fintepla
        ii. The need to counsel patients on how to recognize and respond to signs and symptoms of valvular heart disease and pulmonary arterial hypertension
        iii. The need to enroll patients in the REMS
        iv. The need to submit documentation that baseline and periodic cardiac monitoring of patients is being done to identify valvular heart disease and pulmonary arterial hypertension
    b. Patient (caregiver) surveys to assess if patients (caregivers) are educated on the following:
        i. How to recognize and respond to symptoms of valvular heart disease and pulmonary arterial hypertension
        ii. The need to have baseline and periodic cardiac monitoring

Health Outcomes and/or Surrogates of Health Outcomes

10. Health Outcomes (provide for each reporting period and cumulatively)
    a. Number of cases of patients with changes in the ECHO or abnormal ECHO who were not authorized to receive Fintepla based on Patient Status forms among all patients who were active in the REMS during the reporting period and cumulatively. Stratify by whether a Cardiovascular Adverse Event Reporting Form was received as a result of these ECHO changes or not
    b. Number of patients who had a new diagnosis of VHD or PAH who were not authorized to receive Fintepla based on Patients Status forms among all patients who were active in the REMS during the reporting period and

cumulatively. Stratify by whether a Cardiovascular Adverse Event Reporting Form was received as a result of these ECHO changes or not

11. Safety Surveillance (provide for each reporting period and cumulatively)

a. Known, or suspected adverse events related to valvular heart disease or pulmonary hypertension are to be reported regardless of outcome. Root cause analyses of whether periodic monitoring of ECHOs was followed per the Prescribing Information are to be included. Provide an overall analysis and discussion of all cases identified from all sources (i-v) including but not limited to the following for each case: drug discontinued due to cardiac toxicity, pertinent clinical data, ECHOs over time, duration and dose of Fintepla used, treatment required and clinical outcome. Sources of the data (including but not limited to):
    i. Patient Status Form
    ii. Cardiovascular Adverse Event Reporting Form
    iii. Spontaneous adverse event reports
    iv. Literature searches
    v. Social media
        1. Dravet Foundation
        2. Lennox Gastaut Syndrome Foundation

b. Include an overall analysis and discussion on information collected on the Patient Status Form and Cardiovascular Adverse Event Reporting Form which further assess the registry data with respect to safe use. Provide data in tabular format. Provide a unique identifier for patients so that changes over the course of subsequent REMS reports can be tracked

    i. Number of reported unique cases and unique patients with changes in the ECHO or abnormal ECHO

    ii. Of those, stratify to include for both cases and patients:
        1. Type of Cardiac Finding (VHD, PAH, Other New Abnormality) as characterized on the Cardiovascular Adverse Event Reporting Form
        2. Of the reported cases of VHD, stratify to include:
            - Number of cases reporting specific valve involved, sorted by type (mitral, aortic, tricuspid, pulmonic)
            - Classification of regurgitation on ECHO at the time the change occurred (mild, moderate, severe)

- Number of cases reporting Restricted Valve Motion, sorted by valve type
- Number of cases reporting Valve Thickening, sorted by valve type
- Number of cases reporting Patient Symptomatic
- Number of cases reporting Signs on Physical Exam
- Number of cases reporting patient is on Stiripentol
- Patient Age (Mean, Range)
- Patient Age group (group by < 2 years of age, 2-5, 6-11, 12-17, 17 and older)
- Total Dose (Mean, Range)
- Daily Dose (mg/kg/day)
- BMI (group by Underweight, Normal, Overweight, and Obese based on CDC definitions for children)
- Cumulative Time to Event Analysis, stratified by Patient Age, Total Dose (Mean, Range), Daily Dose (mg/kg/day)
- Event Outcome, stratified by age, dosing, symptomatic/signs to include:
  - Number of cases requiring hospitalization
  - Number of cases requiring medication or interventional therapy
  - Number of cases reporting death
  - Number of cases reporting discontinuation of treatment due to CV AE

3. Of the reported cases of elevated pulmonary arterial systolic pressure (PASP > 35 mm Hg), stratify to include:
   - Number of cases reporting ECHO findings of PAH, sorted by Interventricular septal flattening, Elevated right heart/pulmonary artery pressure (pulmonary artery systolic pressure >35 mm Hg), Other

- Of those with Elevated right heart/pulmonary artery pressure (pulmonary artery systolic pressure >35 mm Hg)
  - Mean, Max and Min PASP reading (mm Hg)
- Number of cases reporting Patient Symptomatic
- Number of cases reporting Signs on Physical Exam
- Number of cases reporting patient is on Stiripentol
- Patient Age (Mean, Range)
- Total Dose (Mean, Range)
- Daily Dose (mg/kg/day)
- Cumulative Time to Event Analysis, stratified by Patient Age, Total Dose (Mean, Range), Daily Dose (mg/kg/day)
- Event Outcome, stratified by age, dosing, reporting symptomatic/signs to include:
  - Number of cases requiring hospitalization
  - Number of cases requiring medication or interventional therapy
  - Number of cases reporting death
  - Number of cases reporting discontinuation of treatment due to CV AE

4. Of the Other new abnormality on ECHO (not previously reported), stratify to include:
   - Specified Reported Event Terms on AE Form
   - Number reporting Patient Symptomatic
   - Number reporting Signs on Physical Exam
   - Number reporting patient is on Stiripentol
   - Age (Mean, Range)
   - Total Dose (Mean, Range)
   - Daily Dose (mg/kg/day)

- Cumulative Time to Event Analysis, stratified by Patient Age, Total Dose (Mean, Range), Daily Dose (mg/kg/day)

- Event Outcome, stratified by age, dosing, reporting symptomatic/signs to include:
  - Number of cases requiring hospitalization
  - Number of cases requiring medication or interventional therapy
  - Number of cases reporting death
  - Number of cases reporting discontinuation of treatment due to CV AE

c. Include an overall summary and discussion of whether the data warrants further detailed assessment, labeling changes, and/or communication

12. The requirements for assessments of an approved REMS under section 505-1(g)(3) include with respect to each goal included in the strategy, an assessment of the extent to which the approved strategy, including each element of the strategy, is meeting the goal or whether one or more such goals or such elements should be modified.

We remind you that in addition to the REMS assessments submitted according to the timetable in the approved REMS, you must include an adequate rationale to support a proposed REMS modification for the addition, modification, or removal of any goal or element of the REMS, as described in section 505-1(g)(4) of the FDCA.

We also remind you that you must submit a REMS assessment when you submit a supplemental application for a new indication for use as described in section 505-1(g)(2)(A). This assessment should include:

a) An evaluation of how the benefit-risk profile will or will not change with the new indication.

b) A determination of the implications of a change in the benefit-risk profile for the current REMS.

c) *If the new, proposed indication for use introduces unexpected risks*: A description of those risks and an evaluation of whether those risks can be appropriately managed with the currently approved REMS.

d) *If a REMS assessment was submitted in the 18 months prior to submission of the supplemental application for a new indication for use*: A statement about whether the REMS was meeting its goals at the time of the last assessment and if any modifications of the REMS have been proposed since that assessment.

e) *If a REMS assessment has not been submitted in the 18 months prior to submission of the supplemental application for a new indication for use:* Provision of as many of the currently listed assessment plan items as is feasible.

f) *If you propose a REMS modification based on a change in the benefit-risk profile or because of the new indication of use, submit an adequate rationale to support the modification, including*: Provision of the reason(s) why the proposed REMS modification is necessary, the potential effect on the serious risk(s) for which the REMS was required, on patient access to the drug, and/or on the burden on the health care delivery system; and other appropriate evidence or data to support the proposed change. Additionally, include any changes to the assessment plan necessary to assess the proposed modified REMS. *If you are not proposing a REMS modification*, provide a rationale for why the REMS does not need to be modified.

If the assessment instruments and methodology for your REMS assessments are not included in the REMS supporting document, or if you propose changes to the submitted assessment instruments or methodology, you should update the REMS supporting document to include specific assessment instrument and methodology information at least 90 days before the assessments will be conducted. Updates to the REMS supporting document may be included in a new document that references previous REMS supporting document submission(s) for unchanged portions. Alternatively, updates may be made by modifying the complete previous REMS supporting document, with all changes marked and highlighted. Prominently identify the submission containing the assessment instruments and methodology with the following wording in bold capital letters at the top of the first page of the submission:

NDA 212102 REMS ASSESSMENT METHODOLOGY
(insert concise description of content in bold capital letters, e.g., ASSESSMENT METHODOLOGY, PROTOCOL, SURVEY METHODOLOGIES, AUDIT PLAN, DRUG USE STUDY)

An authorized generic drug under this NDA must have an approved REMS prior to marketing. Should you decide to market, sell, or distribute an authorized generic drug

under this NDA, contact us to discuss what will be required in the authorized generic drug REMS submission.

We remind you that section 505-1(f)(8) of FDCA prohibits holders of an approved covered application with elements to assure safe use from using any element to block or delay approval of an application under section 505(b)(2) or (j). A violation of this provision in 505-1(f) could result in enforcement action.

Prominently identify any submission containing the REMS assessments or proposed modifications of the REMS with the following wording in bold capital letters at the top of the first page of the submission as appropriate:

NDA/BLA 212102 REMS ASSESSMENT

NEW SUPPLEMENT FOR NDA 212102/S-000
CHANGES BEING EFFECTED IN 30 DAYS
PROPOSED MINOR REMS MODIFICATION

or

NEW SUPPLEMENT FOR NDA 212102/S-000
PRIOR APPROVAL SUPPLEMENT
PROPOSED MAJOR REMS MODIFICATION

or

NEW SUPPLEMENT FOR NDA 212102/S-000
PRIOR APPROVAL SUPPLEMENT
PROPOSED REMS MODIFICATIONS DUE TO SAFETY LABELING CHANGES SUBMITTED IN SUPPLEMENT XXX

or

NEW SUPPLEMENT (NEW INDICATION FOR USE)
FOR NDA 212102/S-000
REMS ASSESSMENT
PROPOSED REMS MODIFICATION (if included)

Should you choose to submit a REMS revision, prominently identify the submission containing the REMS revisions with the following wording in bold capital letters at the top of the first page of the submission:

REMS REVISION FOR NDA 212102

To facilitate review of your submission, we request that you submit your proposed modified REMS and other REMS-related materials in Microsoft Word format. If certain documents, such as enrollment forms, are only in PDF format, they may be submitted as such, but the preference is to include as many as possible in Word format.

SUBMISSION OF REMS DOCUMENT IN SPL FORMAT

FDA can accept the REMS document in Structured Product Labeling (SPL) format. If you intend to submit the REMS document in SPL format, as soon as possible, but no later than 14 days from the date of this letter, submit the REMS document in SPL format using the FDA automated drug registration and listing system (eLIST).

For more information on submitting REMS in SPL format, please email FDAREMSwebsite@fda.hhs.gov.

REQUESTED PHARMACOVIGILANCE

We request that you perform postmarketing surveillance for cases of valvular heart disease and pulmonary arterial hypertension in patients exposed to Fintepla. Submit individual reports as 15-day expedited reports to your NDA and directly to the Division of Neurology 2. Include comprehensive summaries and analyses of these events quarterly as part of your required postmarketing safety reports (e.g., periodic safety update reports [PSURs]). In the analysis of each case, provide an assessment of causality, with documentation of risk factors and results of all assessments that support the diagnosis (e.g., ECHO reports, pulmonary hemodynamic parameters) or the causality, along with information about dose and dose titration, duration of Fintepla therapy, time of event in relation to duration of therapy, associated signs and symptoms, concomitant therapies, treatment given for the event, and outcome of each event.

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.*[6]

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.[7] Information and Instructions for completing the form can be found at FDA.gov.[8]

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

REPORTING REQUIREMENTS

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

If you have any questions, call Stephanie N. Parncutt, M.H.A., Senior Regulatory Health Project Manager, at (301) 796-4098 or email at Stephanie.Parncutt@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Nick Kozauer, M.D.
Acting Director
Division of Neurology 2
Office of Neuroscience
Center for Drug Evaluation and Research

ENCLOSURE(S):

- Content of Labeling
  - Prescribing Information
  - Medication Guide
  - Instructions for Use
- REMS

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/

NICHOLAS A KOZAUER
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