NDA 212102/S-003

SUPPLEMENT 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 supplemental new drug application (sNDA) dated September 27, 2021, received September 27, 2021, and your amendments, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Fintepla (fenfluramine HCl) oral solution.

We acknowledge receipt of your risk evaluation and mitigation strategy (REMS) assessment dated September 27, 2021.

This Prior Approval sNDA provides for inclusion of a second indication for the treatment of seizures associated with Lennox-Gastaut syndrome (LGS) in patients who are 2 years of age and older and proposed modifications to the approved Fintepla REMS.

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, Instructions for Use, and Medication Guide), with the addition of any labeling changes in pending “Changes Being Effected” (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

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

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 from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that include labeling changes for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in Microsoft Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes. To facilitate review of your submission(s), provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

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

RISK EVALUATION AND MITIGATION STRATEGY (REMS) REQUIREMENTS

The REMS for Fintepla was originally approved on June 25, 2020. 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 proposed modifications to the REMS consist of changes to the REMS materials to align with the inclusion of the second indication for the treatment of seizures associated with LGS in patients who are 2 years of age and older and associated labeling changes pertaining to the risk for valvular heart disease and pulmonary arterial hypertension.

Your proposed modified REMS, submitted on September 27, 2021, amended and appended to this letter, is approved.

The timetable for submission of assessments of the REMS remains the same as that approved on June 25, 2020.

The revised 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.

[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.

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 Certification and Enrollment Statistics (provide for each reporting period and cumulatively)

a. Healthcare provider certification

i. The number of newly certified healthcare providers and the number of active (i.e., who have prescribed Fintepla at least once during the reporting period) healthcare providers stratified by healthcare 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 pharmacies, the number of active (i.e., have dispensed Fintepla at least once during the reporting period) pharmacies, and the number of 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 patients and the number of 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 wholesalers/distributors and the number of active (i.e., have shipped Fintepla at least once during the reporting period) wholesalers/distributors

3. 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 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 all 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.

4. 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 downloads and printings of each REMS 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 (which ever 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.

5. 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 prescribers 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 providers 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

6. 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 ECHO tests 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 receive 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

s. Key Performance Indicator: 99% of all dispensing will be from appropriately certified prescribers and pharmacies, to enrolled patients, and will occur only when the safe-use condition of an appropriately timed echocardiogram is obtained.

Knowledge

7. 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.

8. 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

9. 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 valvular heart disease or pulmonary arterial hypertension 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.

10. 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 to <5, 5 to <12, 12 to <18, 18 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)
     (i) 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)
   - Patient Age group (group by < 2 years of age, 2 to <5, 5 to <12, 12 to <18, 18 and older)
   - 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 reported cases of other new abnormality on ECHO (not previously reported), stratify to include:
   - Specified Reported Event Terms[3] on AE Form
   - 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 to <5, 5 to <12, 12 to <18, 18 and older)
   - 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.

[3] Sponsor to code verbatim terms to MedDRA Preferred Term (PT)

11. 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) of the FDCA. 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 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 that 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*

REMS modifications, 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 212102 REMS ASSESSMENT

or

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 REVISIONS 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, or website screenshots are only in PDF format, they may be submitted as such, but Word format is preferred.

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.

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]

You must submit final promotional materials and Prescribing Information, accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. 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).

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

Sincerely,

{See appended electronic signature page}

Nick Kozauer, M.D.
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

[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

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/s/

NICHOLAS A KOZAUER
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