

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**212102Orig1s000**

**RISK ASSESSMENT and RISK MITIGATION  
REVIEW(S)**



**Risk Evaluation and Mitigation Strategy (REMS) Memorandum**

**U.S. FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH  
Office of Neuroscience  
Division of Neurology 2**

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**NDA:** 212102  
**Products:** Fintepla (fenfluramine) oral solution  
**APPLICANT:** Zogenix, Inc.  
**FROM:** Alice T.D. Hughes, M.D.  
**DATE:** June 25, 2020

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Section 505-1 of the Federal Food, Drug, and Cosmetic Act (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 [section 505-1(a)]. Section 505-1(a)(1) provides the following factors:

- (A) The estimated size of the population likely to use the drug involved;
- (B) The seriousness of the disease or condition that is to be treated with the drug;
- (C) The expected benefit of the drug with respect to such disease or condition;
- (D) The expected or actual duration of treatment with the drug;
- (E) The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug;
- (F) Whether the drug is a new molecular entity (NME).

After consultations between the Office of New Drugs and the Office of Surveillance and Epidemiology, we have determined that a REMS that includes elements to assure safe use is necessary for Fintepla to ensure that the benefits of the drug outweigh the risks of valvular heart disease and pulmonary arterial hypertension. In reaching this determination, we considered the following:

- A. FINTEPLA will be approved for treatment of seizures associated with Dravet syndrome in patients 2 years and older. A review of published literature determined that the incidence of Dravet syndrome in the United States ranges from 1/40,000 live births to

1/15,700 live births.<sup>1,2</sup> We do not have an estimate of the percentage of such patients who might be treated with Fintepla.

- B. Dravet syndrome is a rare, serious, and potentially life-threatening epilepsy syndrome beginning in infancy that is associated with significant morbidity due to refractory seizures and cognitive impairment. Patients typically present prior to 2 years of age with a variety of disabling seizure types and developmental delay. The cognitive impairment is considered to be, at least in part, caused by the seizures, and even with treatment of the seizures, cognitive impairment persists and is lifelong. Mortality is higher in pediatric patients with Dravet syndrome than the general pediatric population or the overall population with epilepsy. Seizures and seizure-related events are frequent causes of death.
- C. Study 1 was a randomized, blinded, placebo-controlled, add-on study of FINTEPLA performed in pediatric patients with refractory seizures associated with Dravet syndrome. This study evaluated FINTEPLA 0.8 mg/kg/day and 0.2 mg/kg/day with a maximum dose of 30 mg/day compared to placebo in patients not taking concomitant stiripentol. Both doses of FINTEPLA were statistically superior to placebo in the reduction of convulsive seizure frequency over the treatment period. (Please note that the equivalent labeled doses are 0.7 mg/kg/day, 0.2 mg/kg/day, and maximum 26 mg/day, respectively, based on the difference between fenfluramine [label] and fenfluramine HCL [used in the study]).



- D. Patients will take FINTEPLA chronically, on a daily basis. If efficacy persists, treatment may be lifelong.
- E. Although no clinical cases have been reported in the development program thus far, FINTEPLA's most serious risks are already-known cardiovascular adverse reactions associated with the active ingredient, fenfluramine: valvular heart disease (VHD) and pulmonary arterial hypertension (PAH). Fenfluramine hydrochloride was originally approved in the US under the trade name Pondimin® in 1973 for use as an anorectic

<sup>1</sup> Hurst DL. Epidemiology of severe myoclonic epilepsy of infancy. *Epilepsia* 1990;31(4):397-400.

<sup>2</sup> Wu YW, Sullivan J, McDaniel SS, et al. Incidence of Dravet Syndrome in a US Population. *Pediatrics* 2015 Nov; 136(5):e1310-5

agent and was prescribed both alone and in combination with phentermine (“fen-phen”) as an appetite suppressant for the treatment of adult obesity. Fenfluramine and its d-enantiomer form (dexfenfluramine, Redux®) were voluntarily withdrawn from the U.S. market in November 1997 because an association was identified between these drugs and VHD. In 1998, FDA issued a Notice of Proposed Rulemaking proposing to include certain drug products on a list of drug products that had been withdrawn or removed from the market because such drugs products or components of such drug products had been found to be unsafe or not effective, and which could not be compounded under section 503A of the FD&C Act ([63 FR 54082](#)). FDA identified in that notice “all drug products containing fenfluramine hydrochloride.” The notice also noted that fenfluramine HCl tablets, formerly marketed as Pondimin tablets, were associated with valvular heart disease, and the manufacturer voluntarily withdrew the drug from the market. This proposed rule was finalized in [64 FR 10944](#) (March 8, 1999), [21 CFR 216.24](#). In September 2015, the FDA determined that Pondimin and Ponderex were withdrawn from the U.S. market due to reasons of safety or effectiveness.

The suspected mechanism for fenfluramine-induced cardiac valvulopathy is off-target activation of 5-HT<sub>2B</sub> receptors located in cardiac valves by norfenfluramine, the main metabolite of fenfluramine. Cardiac valve abnormalities were associated with either fenfluramine or dexfenfluramine based on evaluation of spontaneous reports to FDA<sup>3,4</sup> and a subsequent meta-analysis of thousands of potential cases to assess prevalence.<sup>5</sup>

In its analysis of these spontaneous reports, FDA defined drug-related cardiac valvulopathy as documented aortic regurgitation (AR) of mild or greater severity and/or mitral regurgitation (MR) of moderate or greater severity after exposure to these drugs.<sup>6</sup> Trace or mild MR and trace AR were not included in this definition because of their relatively common occurrence and because they are generally considered to be physiologic findings. Although much less common, fenfluramine-induced cardiac valvulopathy may develop in right-sided heart valves. A sizable proportion of patients who developed cardiac valvulopathy were asymptomatic. Cardiac valve changes were frequently irreversible, required medication management and/or valve replacement surgery in many patients, and led to death in a few patients.<sup>7</sup> Duration of use was predictive for development of FDA-defined valvulopathy in the meta-analysis and predictive for mild or greater AR, MR, and tricuspid regurgitation (TR) in a large

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<sup>3</sup> Connolly HM, et al. Valvular heart disease associated with fenfluramine-phentermine. *NEJM* 1997 Aug 28;337(9): 581-8

<sup>4</sup> CDC Morbidity and Mortality Weekly Report, 14 Nov 1997; 46(45): 1061-6

<sup>5</sup> Sachdev M, et al. Effect of fenfluramine-derivative diet pills on cardiac valves: A meta-analysis of observational studies. *Am Heart J* 2002; 144:1065-73

<sup>6</sup> CDC Morbidity and Mortality Weekly Report, 14 Nov 1997; 46(45): 1061-6

<sup>7</sup> Dahl CF, et al. Valvular regurgitation and surgery associated with fenfluramine use: an analysis of 5743 individuals. *BMC Medicine* 2008, 6:34

observational case series. Valvulopathy has been reported up to seven years after fenfluramine discontinuation in a few patients.<sup>8</sup>

Pulmonary arterial hypertension (PAH) was associated with fenfluramine and dexfenfluramine prior to the U.S. FDA approval of these drugs.<sup>9</sup> In 1996, an epidemiological case-control study calculated that the use of appetite suppressants (primarily fenfluramine and its derivatives) was associated with an increased risk of PAH, and the duration of exposure was a significant factor (23-fold increase when used for more than 3 months).<sup>10</sup> Fenfluramine's role in inducing PAH is thought to be due to increased serotonin levels increasing smooth muscle cell and fibroblast proliferation. Drug-induced PAH may be reversible with drug cessation; however, some patients may develop irreversible and progressive disease similar to idiopathic and heritable forms of PAH.

During Studies 1 (b) (4) (an open-label chronic safety study) in the FINTEPLA development program, no VHD or PAH attributed to study medication was observed. At the time of the interim cut-off for Study (b) (4) 1648 echocardiograms (ECHOs) had been performed in 280 patients, with 5.9 (2.55) mean (SD) number of ECHOs per patient, with a range of time on drug of 63 to 823 days. Of those patients with trace or greater MR, all but one had trace MR, and no patients had moderate or greater MR. The one patient in whom mild MR was identified was found to have had mild MR on the screening ECHO; therefore, this finding was not new, and his enrollment was a protocol violation. Trace AR was observed rarely, and no findings of AR more severe than trace were seen. Trace TR and pulmonary regurgitation (PR) were observed frequently among study patients across studies, but no patients developed moderate or severe TR or PR. Zogenix did not find any patients with reported valvular or non-valvular cardiac structural abnormalities.

Pulmonary artery systolic pressure (PASP) was estimated only from patients with measurable TR velocity jets. In Study (b) (4) 125/232 patients (53.9%) had a baseline PASP available and 109/232 patients (47.0%) were analyzed for mean change in estimated PASP from baseline. The threshold for PAH was an estimated PASP of at least 35 mmHg. The estimated mean (SD) end of study PASP was 19.2 (6.3) with mean change from baseline of 0.2 (7.2) mmHg. In the randomized placebo-controlled studies, there was no obvious dose-dependent relative increase from baseline in estimated PASP compared to placebo.

Although no cases of either cardiac valvulopathy or pulmonary hypertension have been reported to date during the Fintepla development program, these are serious, often

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<sup>8</sup> Greffe G, et al: Valvular heart disease associated with fenfluramine detected 7 years after discontinuation of treatment. *Ann Thorac Surg* 2007, 83:1541-1543

<sup>9</sup> Abenhaim L, et al. Appetite suppressant drugs and the risk of primary pulmonary hypertension. International Primary Pulmonary Hypertension Study Group. *NEJM*. 1996 Aug 29;335 (9):609-16.

<sup>10</sup> Prasad A, et al: Cardiac allograft valvulopathy: a case of donor-anorexigen-induced valvular disease. *Ann Thorac Surg* 1999, 68:1840-1841

irreversible, and potentially life-threatening adverse effects associated with the drug. As previously stated, patients may develop drug-induced VHD yet remain asymptomatic. Even if symptoms related to VHD or PAH are present, recognition of cardiac symptomatology may be especially challenging in the intended use population. Cognitive impairment is present in almost all patients with Dravet syndrome, making it difficult for caregivers and clinicians to assess symptoms of valvulopathy or pulmonary hypertension by history.

Because it is unclear if dose-exposure, duration of therapy, or both increase the risk for fenfluramine-induced VHD or PAH, it is not possible to identify patients at increased risk either before or during treatment. Moreover, FINTEPLA is intended for chronic use, possibly life-long in some patients. Therefore, baseline and recurring assessments by echocardiography (ECHO) are necessary to identify changes in valvular structure, valve function, and to estimate pulmonary artery pressures.

Because the duration of treatment rather than dose-exposure may increase the risk of development of VHD or PAH, any risks may not be mitigated by the lower absolute doses proposed in the labeling. Although the proposed maximum labeled doses of 17-26 mg/day are lower than the previously approved dosing (60-120 mg/day), it is unclear if the dose-exposures in the Dravet studies were significantly different than the dose-exposure of fenfluramine when it was used as an anorectic agent.

- F. FINTEPLA is not a new molecular entity. It was previously approved by U.S. FDA under NDA 016618 (Pondimin, 1973; Ponderex, 1973). It was withdrawn from the U.S. market voluntarily in 1997 because of association with valvular heart disease. Pondimin and Ponderex were determined to have been withdrawn from the U.S. market for reasons of safety or effectiveness in 2015.<sup>11</sup>

The elements of the REMS will be a communication plan, elements to assure safe use, including ETASU A (healthcare providers who prescribe Fintepla are specially certified), ETASU B (pharmacies that dispense Fintepla are specially certified), ETASU D (each patient using Fintepla has evidence or other documentation of safe-use conditions), ETASU E (each patient using Fintepla is subject to certain monitoring), and ETASU F (each patient using Fintepla is enrolled in a registry), an implementation system, and a timetable for submission of assessments of the REMS.

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<sup>11</sup> <https://www.federalregister.gov/documents/2015/09/29/2015-24619/determination-that-pondimin-fenfluramine-hydrochloride-tablets-20-milligrams-and-60-milligrams-and> (accessed June 5, 2020)

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/s/  
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ALICE HUGHES  
06/25/2020 05:23:05 PM

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**Division of Risk Management (DRM)**  
**Office of Medication Error Prevention and Risk Management (OMEPRM)**  
**Office of Surveillance and Epidemiology (OSE)**  
**Center for Drug Evaluation and Research (CDER)**

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| <b>Application Type</b>       | NDA  |
| <b>Application Number</b>     | 212102   |
| <b>PDUFA Goal Date</b>        | June 25, 2020  |
| <b>OSE RCM #</b>              | 2019-393   |
| <b>Reviewer Name(s)</b>       | Carlisha Gentles, PharmD, Risk Management Analyst<br>Anahita Tavakoli, MA, Health Communications Analyst<br>Charlotte Jones, MD, MSPH, REMS Assessment Analyst |
| <b>Team Leader</b>            | Laura Zendel, PharmD, Risk Management Team Leader<br>Shelly Harris, ScD, REMS Assessment Team Leader   |
| <b>Division Director</b>      | Cynthia LaCivita, PharmD   |
| <b>Review Completion Date</b> | June 25, 2020  |
| <b>Subject</b>                | Evaluation of Need for a REMS  |
| <b>Established Name</b>       | Fenfluramine   |
| <b>Trade Name</b>             | FINTEPLA   |
| <b>Name of Applicant</b>      | Zogenix, Inc.  |
| <b>Therapeutic Class</b>      | Anticonvulsant   |
| <b>Formulation(s)</b>         | 2.5 mg/mL Oral solution  |
| <b>Dosing Regimen</b>         | 0.35 mg/kg twice daily (not to exceed a total daily dose of 26 mg)   |

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## EXECUTIVE SUMMARY

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This review evaluates whether a risk evaluation and mitigation strategy (REMS) for Fintepla (fenfluramine) is necessary to ensure the benefits outweigh its risks. Zogenix, Inc. submitted a New Drug Application (NDA) 212102 for fenfluramine with the proposed indication for treatment of seizures associated with Dravet Syndrome in patients 2 years of age and older. The risks associated with fenfluramine include valvular heart disease and pulmonary arterial hypertension. The applicant's proposed REMS consists of a Medication Guide, communication plan (CP), elements to assure safe use (ETASU), an implementation system, and a timetable for submission of assessments.

Fintepla (fenfluramine) has historical safety concerns having been approved in the US under the trade name Pondimin® (NDA 016618) in 1973 for use as an anorectic agent for the treatment of adult obesity and was later withdrawn from the market due to risks of left-sided cardiac valvular disease and pulmonary arterial hypertension (PAH), which can be serious and potentially fatal. Although some changes were seen on echocardiogram (ECHO) in the clinical development program for Fintepla, no clinical cases of valvular heart disease (VHD) or PAH were reported. While the most concerning risks of VHD and PAH were not observed in the current clinical development program, prior history shows that both risks were associated with fenfluramine in the past. Therefore, due to the observations seen in the trials with regards to valvular changes as well as historical experience and lack of long-term data, the risk of VHD and PAH will be included in a boxed warning.

Despite fenfluramine providing effective therapy for patients with DS, DRM and DN2 agree that labeling is not sufficient to mitigate these risks and a REMS is necessary to ensure that the benefits outweigh the risks. The risks of VHD and PAH associated with fenfluramine are serious and it is necessary for prescribers to understand these risks, the importance of monitoring for them, and appropriate patient selection. While it is expected that neurologists are familiar with the importance of monitoring, they do not typically complete cardiac assessments or manage patients with VHD or PAH. In a condition that may be asymptomatic and among a patient population with cognitive impairment making the assessment of VHD and PAH symptoms difficult, a REMS that includes ETASU is necessary to ensure the benefits outweigh the risks.

The goal of the FINTEPLA REMS Program is to mitigate the risk of valvular heart disease and pulmonary arterial hypertension associated with Fintepla by:

1. Ensuring prescribers are educated on:
  - a. The risk of valvular heart disease and pulmonary arterial hypertension associated with FINTEPLA.
  - b. The need to counsel patients on how to recognize and respond to signs and symptoms of valvular heart disease and pulmonary arterial hypertension.
  - c. The need to enroll patients in the FINTEPLA REMS Program.
  - d. The need to submit documentation of baseline and periodic cardiac monitoring of patients to identify valvular heart disease and pulmonary arterial hypertension.
2. Ensuring prescribers adhere to the following:
  - a. Enroll patients in the FINTEPLA REMS.

- b. Submit documentation of baseline cardiac monitoring.
  - c. Submit documentation of periodic cardiac monitoring.
3. Ensuring patients are educated on the following:
  - a. How to recognize and respond to signs and symptoms of valvular heart disease and pulmonary arterial hypertension.
  - b. The need to have baseline and periodic cardiac monitoring.
4. Enrolling of all patients in a registry to further support long-term safety and safe use of FINTEPLA.

The Fintepla REMS includes the following elements: a communication plan, ETASU A (healthcare providers who prescribe Fintepla are specially certified), ETASU B (pharmacies that dispense Fintepla are specially certified), ETASU D (each patient using Fintepla has evidence or other documentation of safe-use conditions), ETASU E (each patient using Fintepla is subject to certain monitoring), and ETASU F (each patient using Fintepla is enrolled in a registry), an implementation system, and a timetable for submission of assessments of the REMS. Prescribers must certify and patients must enroll to ensure they are aware of the risks and the monitoring requirements, and pharmacies must certify, and verify that patients are enrolled and authorized to receive the drug prior to dispensing. Additionally, all patients must be enrolled in a registry to further support long-term safety and safe use of the drug.

Depending on the assessment findings combined with the results of the postmarketing requirement, FDA may modify the REMS or consider other regulatory actions particularly if reports of VHD or PAH occur beyond what was observed in the clinical trial or if there is evidence of insufficient monitoring. If the REMS assessments or other data indicate that prescribers have gained familiarity with the drug or that the outcomes of VHD or PAH have not occurred with long term use, FDA may, in the future, determine that elements of the REMS or the REMS in its entirety are no longer necessary.

## 1 Introduction

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This review evaluates whether a risk evaluation and mitigation strategy (REMS) for Fintepla (fenfluramine) is necessary to ensure the benefits outweigh its risks. Zogenix submitted a New Drug Application (NDA) 212102 for Fintepla (fenfluramine) 2.5 mg/ml oral solution with the proposed indication for treatment of seizures associated with Dravet Syndrome in patients 2 years of age and older. This application is under review in the Division of Neurology (DN) 2. The applicant's proposed REMS consists of a Medication Guide, communication plan (CP), elements to assure safe use (ETASU), an implementation system, and a timetable for submission of assessments to ensure the benefits of fenfluramine outweigh the risks of valvular heart disease (VHD) and pulmonary arterial hypertension (PAH).

## 2 Background

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### 2.1 PRODUCT INFORMATION

Fintepla (fenfluramine), is an anti-epileptic drug proposed for treatment of seizures associated with Dravet Syndrome in patients 2 years of age and older. Fenfluramine, a racemic compound containing dexfenfluramine and levofenfluramine, is proposed as a 2.5 mg/ml oral solution dosed at 0.1 mg/kg to

0.35 mg/kg twice daily (as expressed in the labeling). Patients will take Fintepla chronically, on a daily basis. If efficacy persists, treatment may be lifelong.

The mechanisms by which fenfluramine exerts its therapeutic effects in the treatment of seizures associated with Dravet syndrome are unknown. Fenfluramine and the metabolite, norfenfluramine, increase extracellular levels of serotonin through interaction with serotonin transporter proteins and exhibit agonist activity at serotonin 5HT-2 receptors.

Fenfluramine is not currently approved in any jurisdiction, however, fenfluramine was originally approved in the US under the trade name Pondimin® (NDA 016618) in 1973 for use as an anorectic agent and was prescribed both alone and in combination with phentermine (“fen-phen”) as an appetite suppressant for the treatment of adult obesity. Fenfluramine and its d-enantiomer form (dexfenfluramine, Redux®) were voluntarily withdrawn from the U.S. market in November 1997 because a causal relationship was identified between these drugs and left-sided cardiac valvular disease and PAH. In September 2015, the FDA determined that fenfluramine was deemed “withdrawn from the U.S. market due to reasons of safety.”

## **2.2 REGULATORY HISTORY**

The following is a summary of the regulatory history for NDA 212102 relevant to this review:

- 01/18/2016: Fast track designation granted.
- 10/24/2018: Applicant informed at pre-NDA meeting that a REMS for fenfluramine was needed.
- 09/25/2019: NDA 212102 submission for treatment of Dravet’s Syndrome received that included a complete REMS proposal.
- 03/18/2020: The Agency notified the Applicant via teleconference that the Agency concurs with the need for a REMS with ETASU to ensure the benefits outweigh the risks. The Agency informed the Applicant to remove the Medication Guide as an element of the REMS and retain it as part of the labeling. The Agency requested that Applicant develop a separate inpatient pharmacy enrollment form and separate the prescriber-pharmacy guide into a prescriber guide and a pharmacy guide. Finally, the Agency informed the Applicant of the addition of a registry to be included as an element of the REMS.
- 04/07/2020: The Agency sent comments based on DRM review of proposed REMS program and as discussed at the 3/18/2020 teleconference.
- 04/23/2020: Applicant resubmitted materials in response to the Agency’s interim comments of April 7, 2020.
- 05/26/20: The Agency sent comments to the Applicant on the REMS document, and REMS materials except for the Patient Status Form, Cardiovascular Adverse Event Reporting Form, and the REMS Assessment Plan.
- 05/28/20: The Agency sent comments to the Applicant on the Patient Status Form, Cardiovascular Adverse Event Reporting Form and the Assessment Plan.

- 06/01/20: The Applicant resubmitted materials in response to the Agency comments from May 26, 2020 and May 28, 2020.
- 06/04/20: Information Request (IR) sent to Applicant based on REMS Amendment received on 06/01/2020.
- 06/08/20: Applicant responded to the IR and resubmitted materials.
- 06/15/20: The Agency sent comments on the REMS document and REMS materials
- 06/18/20: Applicant resubmitted materials in response to the Agency comments from June 15, 2020
- 06/22/20: The Agency sent comments to the Applicant on the REMS document, REMS materials and the Assessment Plan
- 06/23/20: Applicant resubmitted materials in response to the Agency comments from June 22, 2020
- 6/23/20: The Agency informed the Applicant that the resubmission was incomplete due to missing updated materials and to resubmit the full REMS proposal
- 06/24/20: Applicant resubmitted materials in response to the Agency comments from June 22, 2020

### 3 Therapeutic Context and Treatment Options

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#### 3.1 DESCRIPTION OF THE MEDICAL CONDITION

Dravet syndrome (DS) is a rare, serious, and potentially life-threatening epilepsy syndrome beginning in infancy that is associated with significant morbidity due to refractory seizures and cognitive impairment. Estimates of DS in the US range between 1/40,000 to 1/15,700 live births.<sup>1,a</sup> Patients typically present prior to 2 years of age with a variety of disabling seizure types and developmental delay. Over time other seizure types including myoclonic, absence, and partial seizures may occur. Frequent hospitalization for status epilepticus is common in the early years of the disorder when seizures may be a daily occurrence. The cognitive impairment is considered to be, at least in part, caused by the seizures, and even with treatment of the seizures, cognitive impairment persists and is lifelong. Children with DS are developmentally normal prior to seizure occurrence, however after the first year, developmental delays become evident along with autistic behaviors, ataxia, and other motor symptoms.<sup>2,3</sup> Independent living during adulthood is the exception for patients with Dravet Syndrome.<sup>4</sup> Mortality is higher in pediatric patients with DS than the general pediatric population or the overall population with epilepsy. In individuals with DS, up to 21% experience premature mortality.<sup>5</sup> Seizures

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<sup>a</sup> Section 505-1 (a) of the FD&C Act: FDAAA factor (A): The estimated size of the population likely to use the drug involved.

and seizure-related events are frequent causes of death. Sudden unexpected death in epilepsy (SUDEP) and status epilepticus are the most common causes of death accounting for 81% of deaths in patients with DS.<sup>6,b</sup>

### **3.2 DESCRIPTION OF CURRENT TREATMENT OPTIONS**

Dravet syndrome is a highly drug resistant epilepsy with most patients rarely achieving seizure freedom. There are two FDA approved therapies to treat seizures associated with Dravet Syndrome, Epidiolex (cannabidiol) and Diacomit (stiripentol). Both anticonvulsants were approved in 2018 and demonstrated statistically significant reduction of convulsive seizures compared to baseline vs placebo in randomized, placebo-controlled clinical trials. Risks associated with stiripentol include anorexia, weight loss, somnolence, and neutropenia. A risk associated with cannabidiol includes hepatocellular injury.<sup>7</sup>

Valproic Acid (VPA) and Clobazam (CLB) are identified as first line therapy by experts in the field and clinical practice, although neither has a specific indication for DS. Topiramate and the Ketogenic Diet are identified as recommended second line therapies for patients who do not respond to Valproic Acid or Clobazam.<sup>8,9</sup> The ketogenic diet is a low carbohydrate, high fat diet. Side effects include weight loss, bone loss, nephrolithiasis, and hyperlipidemia. The diet is very restrictive and may be difficult to maintain for the patient and family. Commonly used anticonvulsants carbamazepine, oxcarbazepine, phenytoin, and lamotrigine may exacerbate seizures in patients with DS and should be avoided. With two FDA approved therapies on the market and a few other therapy alternatives, an unmet need still exists due to seizures in patients with DS being severe and often refractory to multiple medications.

## **4 Benefit Assessment**

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The efficacy and safety of fenfluramine for the treatment of seizures associated with DS in patients 2 years of age and older was demonstrated in two pivotal phase 3 trials (Study 1- NCT02682927 and Study 1504-c2 – NCT029226898). Additional safety information was obtained from Study 1504-c1, an open label pharmacokinetic dosing study, and Study 1503, an ongoing open label extension study that recruited patients from Study 1 and Study 1504-c1 and 1504-c2.

Studies 1 and 1504-c2 were similar in design: randomized, double-blind, and placebo-controlled. Study 1 compared fenfluramine 0.8 mg/kg/day and 0.2 mg/kg/day with placebo in patients who were not receiving stiripentol. Study 1504-c2 compared fenfluramine 0.5 mg/kg/day with placebo in patients who were receiving stiripentol and either clobazam, valproate, or both. In both studies, patients had a clinical diagnosis of DS and were inadequately controlled on at least one antiepileptic drug or other anti-seizure treatment including vagal nerve stimulation or ketogenic diet. Both trials had a 6-week baseline period followed by randomization into a 2-week (Study 1) or 3-week (Study 1504-c2) titration period and a subsequent 12-week maintenance period where the dose of fenfluramine remained stable.

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<sup>b</sup> Section 505-1 (a) of the FD&C Act: *FDAAA factor (B): The seriousness of the disease or condition that is to be with treated with the drug.*

The primary efficacy endpoint in both studies was the change from baseline in the frequency of convulsive seizures. Both studies also had the same key secondary endpoints: proportion of subjects who achieve a  $\geq 50\%$  reduction from baseline in convulsive seizure frequency and comparison between treatment and placebo groups in the longest convulsive seizure-free interval during treatment and maintenance phase.

#### **4.1 RESULTS OF STUDY 1 AND STUDY 1504-c2**

In Study 1, 119 subjects were randomized to receive placebo (N=40), fenfluramine 0.2mg/kg/day (N=39), or fenfluramine 0.8mg/kg/day (N=40) over a 22-week treatment period. The fenfluramine 0.2mg/kg/day group demonstrated a -31.7% (P=0.043) reduction in seizure frequency, and the 0.8mg/kg/day group demonstrated a -70% (P<0.001) reduction in seizure frequency relative to placebo.

In Study 1504-c2, 87 participants were randomized to fenfluramine 0.5mg/kg/day (N=43) or placebo (N=44) over a 22-week treatment period. The fenfluramine group 0.5mg/kg/day plus stiripentol and at least one other anti-epileptic drug demonstrated a -59.5% (P<0.001) reduction in seizure frequency relative to placebo.

The reduction in seizure frequency was significantly greater for all dose groups of fenfluramine compared to placebo.<sup>10</sup> Per the clinical reviewer, the fenfluramine groups demonstrated a statistically significant reduction in convulsive seizures from baseline to the treatment period. The clinical reviewer further highlights that this reduction is clinically meaningful.<sup>11</sup> All key secondary efficacy endpoints were also statistically significant for all fenfluramine doses in both studies. The clinical reviewer concluded that, while the secondary analyses were statistically significant and generally supportive of the primary efficacy endpoints, they do not provide information separate from the primary efficacy endpoint.

## **5 Risk Assessment & Safe-Use Conditions**

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In placebo controlled trials, the most common adverse reactions of fenfluramine with incidence at least 10% or greater than placebo included decreased appetite, somnolence, sedation, lethargy, diarrhea, constipation, abnormal echocardiogram (ECHO), fatigue, malaise, asthenia, ataxia, balance disorder, gait disturbance, increased blood pressure, drooling, salivary hypersecretion, pyrexia, upper respiratory tract infection, vomiting, decreased weight, fall, and status epilepticus. The rates of discontinuation as a result of any adverse reaction were 13% and 7% for patients treated with fenfluramine 0.8 mg/kg/day and 0.2 mg/kg/day, and 6% for patients treated with fenfluramine 0.5mg/kg/day in combination with stiripentol, respectively, compared to 6% for patients on placebo. The most frequent adverse reaction leading to discontinuation in patients treated with any dose of fenfluramine was somnolence (N=3, 3%).

A total of 33 serious adverse events (SAEs) occurred in 21 patients in the placebo-controlled trials. The incidence of SAEs was similar in the Fintepla group (11 patients, 9%) compared to the placebo group (10 patients, 10%). SAEs reported in the Fintepla group included status epilepticus (4 [3.3%]), somnolence (3 [2.5%]), and seizure, lower respiratory tract infection, adverse drug reaction, decreased appetite, diarrhea, hypoxia, osteochondritis, and weight decreased which all occurred in a single patient. The clinical reviewer notes that the types and frequencies of SAEs reported are similar to those seen in other trials of refractory epilepsy in pediatric patients. The risks of decreased appetite and decreased weight,

somnolence, sedation, and lethargy, suicidal behavior and ideation, withdrawal of antiepileptic drugs, serotonin syndrome, increase in blood pressure and glaucoma will be communicated in the Warnings and Precautions section of the labeling to note the occurrence of SAEs and to align with class wide labeling for other antiepileptic therapies.

### **Deaths**

Four deaths were reported during the development with one occurring during the controlled trials. All deaths were attributed to SUDEP. Per the clinical reviewer, these patients were often ill with complex, chronic multisystem disease and complicated courses and SUDEP is common in the DS population. Therefore, these deaths are unlikely to be attributed to fenfluramine.

### **5.1 VALVULAR HEART DISEASE (VHD) AND PULMONARY ARTERIAL HYPERTENSION (PAH)**

Fenfluramine and dexfenfluramine were removed from the market in 1997 due to previously unidentified association between these drugs and left-sided cardiac valvulopathy combined with the association with PAH noted with these products prior to approval.<sup>12</sup> Prior to being removed from the market, fenfluramine was approved as an anorectic agent at a dose of 60 mg to 120 mg/day. Cardiac valve abnormalities were not identified in this application's clinical or nonclinical studies prior to approval of fenfluramine.<sup>13,14</sup> The suspected mechanism for fenfluramine-induced cardiac valvulopathy is off-target activation of 5-HT<sub>2B</sub> receptors located in cardiac valves by norfenfluramine, the main metabolite of fenfluramine. Fenfluramine's role in inducing PAH is thought to be due to increased serotonin levels increasing smooth muscle cell and fibroblast proliferation. Drug-induced PAH may be reversible with drug cessation; however, some patients may develop irreversible and progressive disease similar to idiopathic and heritable forms of PAH.

Because of fenfluramine's known risks of VHD and PAH, the Applicant conducted a prospective cardiac monitoring program throughout the clinical development program with FDA input. Echocardiograms (ECHOs) were performed at regular intervals during the controlled and uncontrolled studies as follows:

- Study 1: screening, Week 6, Week 14, and 3 months after the final dose
- Study 1504-c1: screening, Week 6, Week 12, Week 26, and 3 months after the final dose
- Study 1504-c2: screening, Week 6, Week 12, and 3 months after the final dose
- Study 1503: screening, months 1, 3, 6, 9, 12, 15, 18, 21, and 3 months after the final dose

As part of the Applicant's NDA submission, an Integrated Summary of Cardiovascular Safety (ISS-CV) was submitted with the purpose of characterizing the cardiovascular safety in the fenfluramine development program. The primary focus of the ISS-CV was the ECHO in assessment of mitral and aortic valves (particularly for regurgitation). Other analyses included measurements of pulmonary artery systolic pressure (PASP) and assessment of tricuspid and pulmonic valves. Including the 120-day safety update, the ISS-CV included ECHO data from a total of 330 patients enrolled in Study 1, 1504-c1, 1504-c2 and 1503. DN2 consulted The Division of Cardiology and Nephrology (DCN) to assist in review of the ISS-CV.<sup>15</sup>

No patient exhibited ECHO findings consistent with FDA-defined valvulopathy during the studies.<sup>c</sup> Overall, the proportion of trace or greater mitral regurgitation during double-blind treatment is larger in the pooled double-blind fenfluramine treatment group 26/122 (21.3%) than in the placebo group, 8/84 (9.5%). The clinical reviewer notes that the differences between the groups were mainly due to trace regurgitation which is not considered pathologic in the absence of structural valve abnormalities. There was no consistent relationship between the duration of treatment and prevalence of trace or greater mitral regurgitation. Additionally, no cases of PAH were identified through the cutoff date for the 120 Day Safety Update.

The clinical reviewer and the cardiology reviewer concluded that although neither VHD nor PAH have been observed to date in the Fintepla development program, both of the disorders have been associated with the active ingredient in Fintepla and thus patients with DS who are prescribed Fintepla are at risk of developing fenfluramine-associated VHD or PAH. VHD and PAH are serious, often irreversible, and potentially life-threatening adverse effects associated with the drug. Patients may develop drug-induced VHD or PAH without symptoms as many of the documented cases were asymptomatic and identified via ECHO. Despite a lack of findings of VHD or PAH in the fenfluramine clinical development program, there is concern about the risks of VHD and PAH in the intended population. The labeling will include a Boxed Warning stating that because of the association between serotonergic drugs with 5-HT<sub>2B</sub> receptor agonist activity, including fenfluramine, and VHD or PAH, cardiac monitoring is required via ECHO. Because of the serious risks of VHD and PAH, a REMS is necessary to ensure that the benefits of Fintepla outweigh the risks and to ensure that regular cardiac monitoring occurs to potentially identify evidence of PAH or VHD prior to a patient becoming symptomatic, aiding in early detection of these conditions.

## 6 Expected Postmarket Use

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Fenfluramine is likely to be prescribed by neurologists, pediatric neurologists, and epileptologists who have experience with anticonvulsants and the risks associated with anticonvulsants. In addition, the proposed REMS will require that patients are evaluated by a cardiologist with periodic ECHO as per labeling. Fenfluramine is likely to be used in both the outpatient and inpatient healthcare settings.

## 7 Risk Management Activities Proposed by the Applicant

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### 7.1 REVIEW OF APPLICANT'S PROPOSED REMS

To mitigate the risk of regurgitant aortic or mitral valvular heart disease, the Applicant submitted prescribing information that contained a boxed warning, a Medication Guide (MG) and a REMS.

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<sup>c</sup> Drug-related cardiac valvulopathy was defined by FDA as documented aortic regurgitation (AR) of mild or greater severity and/or mitral regurgitation (MR) of moderate or greater severity after exposure to the drug. Trace or mild MR and trace AR were not included in this definition due to their relatively common occurrence.

The FDA received the Applicant's REMS submission on September 25, 2019. The proposed REMS included a MG, communication plan, elements to assure safe use (ETASU) that included prescriber certification (A), pharmacy certification (B), documentation of safe use conditions (D), and monitoring (E), an implementation system, and a timetable for submission of assessments of the REMS. The Applicant did not propose any other risk management activities outside of the prescribing information and the proposed REMS.

The Applicant's proposed REMS incorporates monitoring based on the clinical trial protocols used during the clinical development program and the history of VHD and PAH associated with fenfluramine. In response to comments and IR's from the agency on April 8, 2020, May 26, 2020, May 28, 2020, June 4, 2020, June 15, 2020, June 17, 2020, and June 22, 2020, the proposed REMS was amended on April 23, 2020, June 1, 2020, June 8, 2020, June 23, 2020 and June 24, 2020. The final REMS document, REMS materials, and REMS supporting document were submitted on June 24, 2020. The final REMS includes a communication plan, elements to assure safe use (ETASU) that include prescriber certification (A), pharmacy certification (B), documentation of safe use conditions (D), monitoring (E), and a registry (F), an implementation system, and a timetable for submission of assessments of the REMS. Below is an overview of the Applicant's proposed REMS submitted on September 25, 2019 and the changes made during the review of the application.

### 7.1.1 Medication Guide

The Applicant originally proposed to include a Medication Guide (MG) as an element of the REMS, but removed it as recommended by the Agency. The MG will be retained as a part of the final approved labeling and dispensed with each Fintepla prescription in accordance with 21CFR 208.24. The MG will be packaged with each unit of use and will be available to all stakeholders via the Fintepla REMS website or Fintepla product website.

***Reviewer Comments:** The MG contains information for the patient that is beyond the risks the REMS is intended to mitigate and therefore is not required as an element of the REMS, as there will be patient materials developed that are focused specifically on the REMS risk. The Office of Medical Policy Patient Labeling team reviewed the MG under their review of the label for NDA 212102.*

### 7.1.2 REMS Goals

Zogenix, Inc. originally proposed the following goal for the Fintepla REMS:

The goal of the Fintepla Risk Evaluation and Mitigation Strategy (REMS) program is to mitigate the potential risk of regurgitant aortic or mitral valvular heart disease associated with fenfluramine, the active ingredient in Fintepla, by ensuring that:



**Reviewer Comments:** *The Applicant updated the goals based on comments from the Agency. DRM concurs with the proposed goal of the REMS:*

*The goal of the Fintepla REMS Program is to mitigate the risk of valvular heart disease and pulmonary arterial hypertension associated with Fintepla by:*

1. *Ensuring prescribers are educated on:*
  - a. *The risk of valvular heart disease and pulmonary arterial hypertension associated with Fintepla.*
  - b. *The need to counsel patients on how to recognize and respond to signs and symptoms of valvular heart disease and pulmonary arterial hypertension.*
  - c. *The need to enroll patients in the Fintepla REMS Program.*
  - d. *The need to submit documentation of baseline and periodic cardiac monitoring of patients to identify valvular heart disease and pulmonary arterial hypertension.*
2. *Ensuring prescribers adhere to the following:*
  - a. *Enroll patients in the Fintepla REMS.*
  - b. *Submit documentation of baseline cardiac monitoring.*
  - c. *Submit documentation of periodic cardiac monitoring.*
3. *Ensuring patients are educated on the following:*
  - a. *How to recognize and respond to signs and symptoms of valvular heart disease and pulmonary arterial hypertension.*
  - b. *The need to have baseline and periodic cardiac monitoring.*
4. *Enrolling of all patients in a registry to further support long-term safety and safe use of Fintepla.*

### **7.1.3 Communication Plan**

The Applicant proposes to send a *Letter for Healthcare Providers* to inform healthcare providers on the new drug approval, give the history of fenfluramine, and provide information about the risks of VHD and PAH associated with fenfluramine in the treatment of DS as well as information about the REMS Program. The Applicant proposes to disseminate the Letter for Healthcare Providers within 60 calendar days of the date Fintepla is first commercially distributed and again 6 months later.

**Reviewer's Comments:** *DRM concurs with the proposed Communication Plan of the REMS and that it is necessary to ensure prescribers are aware of the REMS associated with Fintepla's approval, to communicate the risks associated with Fintepla and the need for monitoring of the risks via echocardiogram. The Applicant's proposed timelines for the communications are acceptable. Comments on the letter were shared with the Applicant on April 8, 2020, May 26, 2020, and June 15, 2020. The letter submitted on June 24, 2020 is acceptable.*

#### 7.1.4 Elements to Assure Safe Use (ETASU)

The Applicant proposed the following ETASU as part of the REMS requirements: prescriber certification (A), pharmacy certification (B), documentation of safe-use conditions (D), and monitoring (E). After further review, the Agency determined the need to include a registry (ETASU F) as an element of the REMS. The ETASU are discussed in detail below.

##### **ETASU A: Prescriber Certification:**

Prior to prescribing, the healthcare provider must certify in the Fintepla REMS. To become a certified prescriber, the prescriber must review the prescribing information, the REMS Program Overview and Prescriber Training, successfully complete the Knowledge Assessment, complete the Prescriber Enrollment Form and submit these to the REMS program. Prior to initiating treatment with Fintepla, the prescriber must counsel the patient on the risks, the need for baseline and periodic cardiac monitoring via echocardiogram, provide the patient with the patient guide and enroll the patient into the REMS. Before the patient receives Fintepla and during treatment with Fintepla, the prescriber must review the results of the echocardiogram and determine the appropriateness of initiating or continuing therapy.

**Reviewer Comment:** *We agree that prescriber certification is necessary to ensure prescribers are educated on the drug's serious risks and comply with the requirements of the REMS. Prescriber certification will ensure prescribers are educated on the drug's serious risks and that they must adhere to counseling, enrollment and monitoring of patients, and that patients are informed on the risks and the need for cardiac monitoring. As these risks are not seen with other treatments for this disease state, cardiac monitoring and counseling about these risks may not be completed consistently by likely prescribers of the drug. An additional component of the prescriber certification will be the completion of a Prescriber Knowledge Assessment used to further ensure prescribers understand the risks and requirements in the REMS program. The Agency agrees that prescriber certification is necessary since the prescriber has the responsibility of assessing the patient's cardiac function and determining appropriateness of initiating treatment, continuing treatment or discontinuing treatment. Due to the historical nature of the risk and cardiac nature of the risk, the likely prescribers may be unfamiliar with the history of this drug prior to being withdrawn from the market and unfamiliar with managing VHD or PAH hence needing to be certified to ensure understanding in addition to completing prescriber knowledge assessment.*

*FDA conveyed to the Applicant on April 8, 2020, May 26, 2020, and June 15, 2020 that changes were needed to the Prescriber Enrollment Form. These changes included limiting the form to one-page front and back and updating the submission instructions on the form to include the various methods of submitting the form to the REMS. Changes were also made to the prescriber attestations. As a condition of certification, prescribers must attest on the Prescriber Enrollment Form that they agree to comply with the Fintepla REMS requirements which includes that they should counsel patients on the risk of VHD and PAH, successfully complete the Prescriber Knowledge Assessment, assess cardiac function via ECHO prior to treatment initiation, during treatment, and post-treatment as described in the Prescribing Information and enroll each patient into the Fintepla REMS Registry.*

*The FDA also determined to support safe use, that a patient registry was a necessary requirement of the REMS. In order to support a patient registry, when enrolling in the REMS the prescriber also agrees to complete and submit the Patient Enrollment Form, Patient Status Form, as well as the Cardiovascular Adverse Event Reporting Form if a case suggestive of VHD, PAH or other cardiac abnormalities occurs in a treated patient. See Section 7.1.7 for discussion and rationale for the Appended Materials.*

**ETASU B: Pharmacy Certification:**

The Applicant proposes that Fintepla should only be dispensed by certified pharmacies. Pharmacies must become certified by designating a representative who will on behalf of the pharmacy coordinate the activities of the REMS, by reviewing the training materials and ensure that all relevant staff are trained in the REMS program, obtain authorization to dispense Fintepla by contacting the REMS program to verify the prescriber is certified or the patient is under the care of a certified prescriber, the patient is enrolled, and the patient is authorized to receive treatment. Patient authorization status is determined by the Patient Status Form.

***Reviewer Comments:*** *We agree that pharmacies must be certified to ensure that prior to dispensing prescribers are certified, and that patients are enrolled and authorized to receive the drug. Certification will ensure that pharmacies dispensing Fintepla comply with only dispensing prescriptions from certified prescribers for enrolled patients that have completed the monitoring requirements. Having pharmacies certify allows for an additional system check for prescribers and patients ensuring the requirements are in place for fenfluramine to appropriately to ensure safe use.*

*Authorization to dispense fenfluramine is dependent on the successful enrollment of a patient into the REMS by a certified prescriber. Additionally, authorization to dispense will be linked to the prescriber indicating on the Patient Status form that treatment is appropriate and that the required monitoring and assessment have been completed. On April 8, 2020, May 26, 2020, June 15, 2020, and June 22, 2020, we provided comments to the Applicant to clarify the role of the certified pharmacy and REMS call center in terms of obtaining authorization to dispense, who will be contacting the prescriber and patient for a reminder, as well as if this information will need to be documented in the pharmacy's system.. The REMS call center will provide the patient's authorization status to the certified pharmacy based on receipt of the completed Patient Status Form. The patient is authorized to receive Fintepla if the prescriber is certified, the patient is enrolled and the patient has a patient status form on file and in this case, the pharmacy may dispense Fintepla. If the form is not received at 180 calendar days of the date of the last Patient Status Form, the REMS program places the patient's authorization status as Authorized-Warning. The pharmacy may still dispense Fintepla, however, the warning is to denote that the patient is within the 90-day grace period. The 90-day grace period was decided in order to minimize stakeholder burden, as scheduling of the ECHO or in some circumstances travel to obtain monitoring may be difficult. If the form is not received within 270 days (180 + 90 days grace period), the REMS call center designates the patient as not authorized to receive additional dispenses of the drug until the form is submitted by the prescriber with the necessary documentation. The pharmacy must not dispense Fintepla if the patient is categorized as not authorized. Further, FDA informed the Applicant that there needs to be separate processes and procedures for outpatient pharmacies versus inpatient pharmacies. The need to separate*

*the processes and procedures is to allow for flexibility in the inpatient setting when a patient needs to be continued on maintenance therapy and is already under the care of certified prescriber in the outpatient setting.*

#### *Inpatient Pharmacies*

*The process will be slightly different for the inpatient setting. If a patient is being initiated therapy in the inpatient setting, pharmacies must be certified to ensure that, prior to dispensing, prescribers are certified, and that patients are enrolled and authorized to receive the drug. If the patient is being continued on therapy from an outpatient setting, the pharmacy must verify that a patient is under the care of a certified prescriber by confirming the patient is enrolled in the REMS prior to dispensing and authorized to receive the drug. The inpatient prescriber is able to continue therapy under the certified prescriber that originally initiated therapy. In both scenarios, the patient is only allowed a max day supply of 15 days upon discharge from the inpatient facility. Additionally, a certified inpatient pharmacy is allowed to order Fintepla by contacting the REMS. Once the inpatient pharmacy's certification is verified, the wholesaler-distributor may process the order and ship Fintepla directly to the inpatient pharmacy. The ability for the inpatient pharmacy to order Fintepla in advance is to prevent delays in continuity of care for patients already on Fintepla in the outpatient setting.*

*In addition to the above requirements, the pharmacy's authorized representative for both inpatient and outpatient pharmacies will comply with the following REMS requirements:*

- *Agree not to distribute transfer, loan or sell Fintepla except to certified pharmacies*
- *Maintain records of dispensing information*
- *Maintain records documenting the staff's completion of training*
- *Maintain records that all REMS processes and procedures are in place and being followed*
- *If the authorized representative changes, have the new authorized representative enroll in the REMS*

#### **ETASU D: Safe Use Conditions**

The Applicant proposed to include patient enrollment in the Fintepla REMS to ensure that patients have been counseled by their prescriber on the drug's risks, understand the monitoring requirements and how to recognize signs and symptoms of VHD and PAH.

***Reviewer Comments:*** *FDA agrees with the Applicant's proposal to include patient enrollment. Patient enrollment as a measure of safe use conditions ensures that only patients who have enrolled in the REMS, received counseling from the prescriber and, acknowledge the need for monitoring by getting ECHO every 6 months are dispensed Fintepla.*

#### **ETASU E: Monitoring**

The Applicant proposed to include required cardiovascular monitoring using echocardiogram at baseline, every 6 months for two years and then annually thereafter as outlined in the Prescribing

Information. The Applicant changed the proposed monitoring requirement schedule following the comments provided on April 8, 2020 to before treatment initiation, every 6 months during treatment, and once 3-6 months following treatment discontinuation.

***Reviewer Comments:*** FDA agrees that required monitoring via ECHO is necessary to ensure safe use of this product. Prescribers must assess the patient's cardiac function and determine appropriateness of continuing treatment as described in the Prescribing Information. Prescribers will attest that the required monitoring and assessments were completed, and that continuation of treatment is appropriate using the Patient Status Form, which will be submitted to the REMS program every 180 days during treatment. Documentation of this monitoring will also confer authorization for dispensation of the drug at the pharmacy. The 6-month interval for monitoring beyond baseline was decided based on how the monitoring occurred during the clinical development program and the clinical team deeming that cardiac abnormalities would not be seen rapidly as to necessitate more frequent monitoring than every 6 months. Further, more frequent monitoring and submission of the form increases burden on prescribers and patients that may likely cause an increase in missing and incomplete forms, resulting in loss of access for patients for whom continuation of treatment is appropriate. Additionally, one of our concerns of the REMS centers around the patient's ability to comply with the monitoring. Therefore, the submission schedule utilized in this REMS has been chosen with an emphasis on maintaining patient access to the treatment with the expectation that prescribers will comply with the REMS requirements and their clinical practice responsibilities to the patient.

In addition to completing the Patient Status Form following each ECHO every 6 months, if any new or worsening of signs of VHD, PAH, or other cardiac abnormalities are noted by the prescriber, the REMS program will follow up with the prescriber. The prescriber will provide further information to the REMS program using the Cardiovascular Adverse Event Reporting Form. Following the Agency's comments on April 8, 2020, the Applicant proposed separating the Cardiovascular Adverse Event Reporting Form from the Patient Status Form due to the concern that reporting adverse events using the Patient Status Form could result in delay of completion of the form and therefore delay in medication being shipped to patient. Per the Applicant, a reason for delay in completing the cardiovascular adverse event section if imbedded within the Patient Status Form included the potential need to consult with the cardiologist or other specialists regarding the patient's ECHO report which may take some time. Therefore, the Applicant favored separating the adverse event reporting to a separate form that the REMS program would use to follow up with the prescriber after submission of the Patient Status Form. The Agency agreed with the Applicant and noted that the information collected on the Cardiovascular Adverse Event Reporting Form was not necessary for the prescriber to determine appropriateness of continuing therapy with Fintepla and may take additional time to complete.

#### **ETASU F: Registry**

Although not part of the Applicant's initial proposal, FDA determined that a registry was a necessary REMS requirement. The Applicant has added a patient registry to the REMS to further characterize the long-term risks of Fintepla. Information from the Patient Enrollment Form, Patient Status Form, and Cardiovascular Adverse Event Reporting Form will be used to collect data for the registry.

**Reviewer Comments:** *As it is uncertain if the dose-exposure, duration of therapy or both increase the risk of VHD and PAH; therefore, all patients will be enrolled in a registry to obtain data to further inform long-term safety for the drug in this population and to help determine if the risk mitigation efforts are adequate. The data that will be collected includes baseline cardiovascular status, number of patients, current dose of Fintepla, length of time patients receive Fintepla, findings of VHD, PAH or any new cardiac valve abnormalities, and outcome from findings of VHD, PAH or other cardiac valve abnormalities.*

*The components of the registry include:*

- *Patient Enrollment Form: to be completed prior to treatment initiation including patient demographic information.*
- *Patient Status Form: to be completed at baseline, every 6 months during treatment, and once 3-6 months following treatment discontinuation.*
- *Cardiovascular Adverse Event Reporting Form: to be completed if any new or worsening signs of VHD, PAH, or other cardiac abnormalities are noted on the Patient Status Form.*

*The registry can also be used to identify patients receiving Fintepla and offer them an opportunity to participate in a post marketing study that evaluates the incidence of VHD and PAH.*

### **7.1.5 Implementation System**

For successful implementation of the REMS, the Applicant proposes to maintain a REMS Call Center to support patients, prescribers, pharmacies, and wholesalers in interfacing with the REMS. The Applicant will ensure that Fintepla is only distributed to certified pharmacies by wholesalers who are compliant with distributing Fintepla as outlined in the REMS. To ensure compliance with the REMS, the Applicant will maintain processes and procedures to maintain adequate records to demonstrate that REMS requirements are being met including records of drug distribution and dispensing, certification of prescribers and pharmacies, and audits of certified pharmacies. These records must be readily available for FDA inspections. The Applicant will establish monitoring and audit procedures on an ongoing basis to ensure that the requirements of the REMS are being met and take corrective measures if non-compliance is identified.

**Reviewer Comment:** *FDA agrees with the Applicant's proposal to include an implementation system. We provided comments on April 8, 2020, May 26, 2020, June 15, 2020, and June 22, 2020 that added additional actions that the Applicant must include in the implementation system. This includes establishing and maintaining a registry and ensuring that the Applicant follows up with the healthcare provider to obtain all data required for complete adverse event reporting related to VHD, PAH, or other cardiac abnormalities. Additionally, the schedule for authorization for a patient to receive Fintepla based on receipt of the Patient Status Form was clarified to note the expectation that the Patient Status Form is completed every 180 days and also account for the 90-day grace period incorporated into the required monitoring schedule. The Applicant authorizes dispensing for each patient based on receipt of the Patient Status Form prior to initiation of treatment, and for subsequent dispensing, within 270 calendar days from the date of receipt of the last Patient Status Form. If a complete Patient Status Form is not*

*received within 270 calendar days, the patient is not authorized to receive the drug until a completed form is received. To ensure compliance, the Applicant ensures that the patient is not authorized to initiate treatment until the first Patient Status Form is received. For subsequent dispensing, if the Patient Status Form is not received with 180 calendar days of the date of receipt of the last Patient Status Form, the Applicant ensures that the REMS call center contacts the Prescriber to obtain the form.*

*Additionally, the following Applicant requirements were incorporated into the implementation system:*

- *Provide certified prescribers and pharmacies with access to the database of certified prescribers, certified pharmacies, and enrolled patients.*
- *Notify stakeholders within 2 business days after they are certified or enrolled in the REMS*
- *Ensure the Applicant follows up with healthcare providers to complete a Cardiovascular Adverse Event Reporting Form to obtain required data for the registry once a report suggestive of VHD or PAH is received.*
- *Ensure pharmacies are able to obtain authorization to dispense online and by phone.*
- *Audit pharmacies and wholesalers-distributors no later than 90 days after certification and have received at least one shipment, and annually thereafter.*

*The Applicant agreed with the changes and the proposed Implementation System is acceptable.*

#### **7.1.6 Timetable for Submission of Assessments**

Zogenix proposes to submit assessments to the FDA at 6 months and 12 months post approval of the REMS and annually thereafter from the date of the initial approval of the Fintepla REMS.

**Reviewer's Comments:** The proposed timetable for submission of assessments is acceptable.

#### **7.1.7 REMS Materials & Key Risk Messages**

The Applicant included the following materials as part of the original submission of the REMS:

- Letter for Healthcare Providers: serves to inform healthcare providers of the new drug approval for Fintepla, the serious risk associated with Fintepla for the treatment of DS, and prescriber requirements of the REMS Program.
- Prescriber Enrollment Form: serves to enroll the prescriber in the REMS and have prescribers attest that they understand the requirements of the REMS (i.e. training, patient enrollment, cardiac monitoring & documentation, patient counseling, and reporting adverse events and treatment discontinuation) as part of the process to become certified to prescribe fenfluramine.
- Prescriber and Pharmacy Guide (revised to Prescriber Training and separate Pharmacy Guide): serves to inform the prescriber and pharmacy of the serious risk associated with fenfluramine therapy, the requirements of the REMS Program, and the responsibilities of the prescriber and pharmacies
- Patient Status Form: documents cardiac monitoring and that the prescriber authorizes continuation of treatment for the patient, due at baseline, every 6 months, and 3-6 months after treatment discontinuation.

- Patient Enrollment Form: completed by the prescriber and patient to enroll the patient into the REMS Program, and has patients attest to understanding the requirements under the REMS (i.e., reviewing the Patient Guide, being counseled, and completing the required monitoring).
- Patient Guide: serves to inform the patient on the serious risks associated with fenfluramine therapy, the REMS Program, and the requirement for regular cardiac monitoring.
- Pharmacy Enrollment Form (revised to an Outpatient Pharmacy Enrollment Form and Inpatient Pharmacy Enrollment Form): completed by the pharmacy's authorized representative on behalf of the pharmacy to enroll and certify into the REMS Program.
- Website: an information source for stakeholders. It will allow healthcare providers, pharmacies and patients to enroll and certify into the REMS program. Prescribers will be able to complete a Knowledge Assessment and also complete and submit a Patient Status Form [and cardiovascular adverse event reporting form]. Pharmacies will be able to obtain authorization to dispense online. The REMS appended materials, including a link to the Prescribing Information and Medication Guide will be accessible from the REMS website and available in a format that can be downloaded.

**Reviewer Comments:** FDA agrees with the Applicant's proposed REMS materials, but also communicated on April 8, 2020, May 26, 2020, June 15, 2020 and June 22, 2020, that changes were needed to the proposed materials and additional materials were necessary to support the various requirements of the REMS. The following additional REMS materials were developed by the Applicant upon the Agency's request:

- Cardiovascular Adverse Event Reporting Form: Adverse event reporting of a cardiovascular event can also occur via this form at the time the form is due to the REMS Program.
- Separate Outpatient and Inpatient Pharmacy Enrollment Forms: the pharmacy enrollment form was separated into an inpatient and outpatient form to account for the different requirements for inpatient vs. outpatient pharmacy settings.
- Separate Prescriber Training and Pharmacy Guide: the Prescriber Training and Pharmacy Guide were separated to account for the different requirements for prescribers and pharmacies.
- REMS Program Overview: briefly describes the requirements of the REMS and the role and responsibilities of each relevant stakeholder (prescribers, pharmacies, and patients) in the REMS Program.
- Prescriber Knowledge Assessment: ensures prescribers understand the risk and requirements in the REMS program

The Applicant did not include key risk messages with their submissions of the REMS materials. See Section 8 of this review for DRM's proposed key risk messages.

### 7.1.8 REMS Assessment Plan

The Applicant included a REMS assessment plan for the proposed REMS in their supporting document in their initial submission on September 25, 2019.

The Applicant's initial Assessment Plan was reviewed and found to not accurately capture all the necessary data metrics, to not align with the draft guidance "REMS Assessment: Planning and Reporting" and to not align with the Agency's goal to be able to compare reported metrics to prespecified thresholds. The applicant was sent a revised assessment plan on May 22, 2020 with content that the Agency determined should be captured as part of the assessment of the Fintepla REMS.

On June 2, 2020 the Applicant submitted a REMS Supporting document with a revised Assessment Plan. The Applicant had accepted many of the Agency's proposals including identifying a threshold for "a demonstration of sufficient compliance if 99.9% of Fintepla prescriptions are dispensed in accordance with the REMS prescribing, distribution, and dispensing requirements by the fourth year of REMS operations. The compliance threshold of 99.9% corresponds to 1 noncompliance event per 1,000 attempts (prescriptions dispensed). Prior to the fourth year of REMS operations, while improvement activities are being undertaken the REMS is expected to function with a failure rate of 1 noncompliance event per 100 attempts (99.0%) and gradually increase to the 99.9% threshold."

On June 17, 2020 the Applicant was sent a redlined version of the Fintepla Assessment Plan with proposed changes and the inclusion of the proposed Safety Outcomes and Surrogate Health Care Outcomes.

On June 19, 2020 the Applicant submitted a Supporting Document with the Fintepla REMS Assessment Plan included based on the Agency's June 17, 2020, comments.

On June 22, 2020, the Applicant was sent comments on the Assessment Plan that should be included in the REMS Supporting Document. We had provided changes that included combining several of the metrics as well as formatting and editorial changes. The REMS Assessment Plan attached to this review includes the assessment metrics but does not include additional details found in the Applicant's Supporting Document.

On June 23, 2020 the Applicant submitted a Supporting Document with the Fintepla REMS Assessment Plan included based on the Agency's June 22, 2020, comments which is acceptable to the Agency.

**Reviewer's Comments:** We provided a revised assessment plan to the Applicant on April 8, 2020, June 17, 2020 and June 22, 2020. The Applicant provided an updated assessment plan that was acceptable on June 23, 2020. The REMS Assessment Plan review is included in Section 8. The final and agreed upon assessment plan can be found in Appendix 10.1 of this review.

### **7.1.9 Summary of OPDP Recommendations of REMS Materials**

The Office of Prescription Drug Promotion (OPDP) was consulted on May 7, 2020 and completed a consult review on June 2, 2020 by Dhara Shah. DRM agrees with all of OPDP's comments and made revisions to the REMS materials with the exception of the following:

#### **Letter for Healthcare Providers:**

- OPDP suggests revising the Header and Subject Line of the Healthcare Provider Letter to be consistent with the *Guidance of Industry and FDA Staff: Dear Health Care Provider Letter: Improving Communication of Important Safety Information*

*DRM Response: DRM is not in agreement with OPDP’s comment. The Healthcare Provider Letter intended as a REMS material is considered a REMS Letter and therefore does not need to be consistent with the referenced guidance above. OPDP acknowledged via email that we were not in agreement with the comment regarding the Healthcare Provider Letter.*

### **Prescriber Training and Pharmacy Guide**

- Page 5 and Page 2, respectively: “In clinical trials of Fintepla for the treatment of Dravet syndrome, no cases of valvular heart disease or pulmonary hypertension were reported”. Per OPDP, this statement minimizes the REMS risks of the drug and omits important material facts. Specifically, Section 6 of the draft PI includes the header, “Echocardiographic Safety Assessments of Valvular Regurgitation and Pulmonary Arterial Hypertension,” which states, “In Study 1 and Study 2, 16% of patients taking Fintepla compared to 6% of patients taking placebo were reported to have trace mitral regurgitation, and 3% of patients taking Fintepla and no patients taking placebo were found to have trace aortic regurgitation. During the open-label extension study, trace mitral regurgitation and trace aortic regurgitation were reported in 14% and 0.4%, respectively, of patients taking Fintepla.” OPDP recommends revising to include this material information.

*DRM Response: DRM, DCN, and DN2 are not in agreement with OPDP’s comment. Per DCN and DN2, emphasizing valvar regurgitation that would otherwise be found in a normal population might falsely imply FDA had concerns these physiologic findings could be manifestations of VHD. DCN and DN2 propose and DRM will update the Prescriber Training and the Pharmacy Guide to include the language below to address OPDP’s concern while maintaining consistent messaging about the REMS risk:*

*“In clinical trials of Fintepla for the treatment of Dravet syndrome, no cases of valvular heart disease or pulmonary hypertension were reported. Across clinical trials of Fintepla for the treatment of Dravet syndrome, 0.4-16% of patients taking Fintepla were found to have trace aortic or mitral regurgitation compared to 0-6% of patients taking placebo. Trace aortic or mitral regurgitation are considered physiologic or normal findings in the absence of valvular abnormalities.”*

## **7.2 OTHER PROPOSED RISK MANAGEMENT ACTIVITIES**

The applicant did not propose risk management activities other than labeling and the REMS.

*Reviewer’s Comments: DN2 determined that a Postmarketing Requirement (PMR) will be necessary and that the REMS registry, will provide pool of potential patients can be recruited for the PMR. DRM notes that the PMR deemed necessary by the Agency is outside of the scope of the REMS program and defer to Division of Pharmacovigilance for review and input.*

## 8 Discussion of Need for a REMS

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The Clinical Reviewer recommends approval of Fintepla on the basis of the efficacy and safety information currently available.<sup>16</sup> Seizures caused by DS are associated with severe morbidity and functional limitations in patients.

The most concerning risks associated with Fintepla are valvular heart disease and pulmonary arterial hypertension which can be serious and potentially fatal. Although some changes were seen on ECHO in the clinical development program, no clinical cases of VHD or PAH were reported. The risks of VHD and PAH associated with fenfluramine are well known as the drug was voluntarily withdrawn in 1997 and officially withdrawn from the market by the FDA due to safety reasons in 2015. Therefore, due to the observations seen in the trials with regards to valvular changes as well as historical experience and lack of long-term data, the risk of VHD or PAH will be included in a boxed warning.

Despite the potential benefits of Fintepla for patients with DS, DRM and DN2 determined that labeling is not sufficient to mitigate these risks and a REMS is necessary to ensure that the benefits outweigh the risks of VHD and PAH. While it is expected that the likely prescribers, such as neurologists, are familiar with the importance of monitoring, they do not typically perform cardiac assessments or manage VHD or PAH. In a condition that may be asymptomatic, among a patient population with cognitive impairment, the assessment of VHD or PAH symptoms may be difficult; therefore, a REMS that includes ETASU is necessary to ensure the benefits outweigh the risk for Fintepla.

On January 9, 2020, this Application was discussed at the REMS Oversight Committee (ROC)<sup>d</sup> Meeting. The ROC concurred that a REMS with elements to assure safe use that included prescriber certification (ETASU A), pharmacy certification (ETASU B), safe-use conditions-patient enrollment (ETASU D), monitoring (ETASU E), and a patient registry (ETASU F) is necessary to ensure the benefits of Fintepla outweigh the risks of VHD and PAH. The REMS will also include a targeted communication plan to inform prescribers of the risks and that Fintepla is approved with a REMS that includes restricted distribution.

The minimum necessary REMS elements required include:

1. Prescriber certification (ETASU A) to ensure that prescribers are educated about the risks, the need to enroll and counsel patients, the need to monitor patients, and the need to report events of VHD and PAH to the REMS Program.
2. Pharmacy certification (ETASU B) to ensure that prescribers are certified, and patients are enrolled and authorized to receive the drug prior to dispensing.

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<sup>d</sup> As per the 21<sup>st</sup> Century review process, all REMS with elements to assure safe use (ETASU) are discussed at the REMS Oversight Committee (ROC), which consists of senior-level management from the Offices of New Drugs, Surveillance and Epidemiology, and Regulatory Policy.

3. Safe-use conditions (ETASU D) to ensure that fenfluramine is only dispensed to patients who have been enrolled in the REMS, who have received counseling from the prescriber about the risks and monitoring requirements, and who have completed the monitoring requirements.
4. Patient monitoring (ETASU E) to ensure prescribers attest and document that they have completed monitoring of the patient's cardiac function at baseline, and every 6 months, and have assessed appropriateness of initiating treatment, and during ongoing therapy the appropriateness of continuing treatment. Should fenfluramine be discontinued, patient monitoring is required after discontinuation with submission of the prescriber's documentation within 3-6 months after treatment was discontinued.
5. Patients who receive fenfluramine will be enrolled in a patient registry (ETASU F) to inform us as to whether or not the REMS is mitigating the risk as designed and to further support collection of long-term safety data and safe use of fenfluramine. Because less is known about the long-term cardiotoxic effects of fenfluramine, enrollment of all patients in a registry is necessary to assess the safe use and chronic and potentially irreversible VHD and PAH associated with fenfluramine.

Appended materials will include: a letter for healthcare providers, prescriber enrollment form, prescriber guide, prescriber knowledge assessment, a program overview, outpatient pharmacy enrollment form, inpatient pharmacy enrollment form, pharmacy guide, patient enrollment form, patient guide, patient status form, cardiovascular adverse event reporting form, and a website. Enrollment forms will include attestations for each relevant stakeholder regarding knowledge of the REMS risks, as well as the safe use conditions required before dispensing and periodic monitoring. The letter for healthcare providers will notify likely prescribers about the new drug approval for Fintepla as well as the serious risks and prescriber requirements for the REMS. The prescriber knowledge assessment will ensure that prescribers understand the key messages included in the prescriber training at the time they take the assessment. The prescriber training and pharmacy guide inform the respective stakeholders about the risks associated with Fintepla therapy and the requirements and responsibilities of each stakeholder within the REMS. The Program Overview will be a concise document for any stakeholder to reference for REMS program operations and requirements. Patient directed materials include a patient guide to present information about the risk, how to recognize and respond to symptoms of VHD and PAH, and the importance of baseline and periodic cardiovascular monitoring. The patient status form will be used to document the required patient monitoring and the prescriber's determination of appropriateness of initiating or continuing therapy. The cardiovascular adverse event reporting form will be used to document any follow-up information for any new or worsening signs of VHD, PAH, or other cardiac abnormalities noted on the patient status form. Finally, a REMS website will assist in operationalizing the program by having all materials available and having online enrollment available. Further, an implementation system and timetable for submission of assessments will be requirements included in this REMS.

DRM concludes that based on the review of the proposed REMS received on June 24, 2020, that the REMS will support actions that will mitigate the risks of VHD and PAH and will further assess the long-term safety of Fintepla. Depending on the assessment findings combined with the results of the PMR, FDA may modify the REMS or consider other regulatory actions particularly if reports of VHD or PAH occur beyond

what was observed in the clinical trial, if there is evidence of insufficient monitoring or undue burden to stakeholders. If the REMS assessments or other data indicate that prescribers have gained familiarity with the drug or that the outcomes of VHD or PAH have not occurred with long term use, FDA may, in the future, determine that elements of the REMS or the REMS in its entirety are no longer necessary.

## 8.1 REMS MATERIALS AND KEY RISK MESSAGES

The following REMS materials will provide education and support the risks messages of the REMS:

- REMS Letter to Healthcare Providers
- REMS Program Overview
- Prescriber Training
- Prescriber Knowledge Assessment
- Prescriber Enrollment Form
- Outpatient Pharmacy Enrollment Form
- Inpatient Pharmacy Enrollment Form
- Pharmacy Guide
- Patient Guide
- REMS website
- Patient Enrollment Form
- Patient Status Form
- Cardiovascular Adverse Event Reporting Form

### Key Risk Messages for Healthcare Providers

Fintepla can cause valvular heart disease and pulmonary arterial hypertension

Prescribers must do the following:

#### **Before treatment initiation (*first dose*):**

- Enroll in the REMS by completing the ***Prescriber Enrollment Form***
- Successfully complete the ***Prescriber Knowledge Assessment*** and submit it to the REMS
- Counsel the patient (using the ***Patient Guide***) on:
  - The risks of valvular heart disease and pulmonary arterial hypertension
  - How to recognize and respond to signs and symptoms of valvular heart disease and pulmonary arterial hypertension
  - **How an echocardiogram (ECHO) can identify evidence of PAH or valvular heart disease prior to a patient becoming symptomatic**
  - The need for cardiac monitoring via ECHO
    - At baseline (treatment initiation)
    - Every 6 months during treatment, and
    - Once 3 to 6 months after treatment discontinuation
- Provide the patient with the ***Patient Guide***.
- Enroll the patient by completing and submitting the ***Patient Enrollment Form*** to the REMS and retaining a completed copy in the patient's record.
- Assess the patient's cardiovascular status and the appropriateness of initiating treatment by obtaining the results of the patient's baseline ECHO. Document and submit the results and appropriateness for treatment to the REMS using the ***Patient Status Form***.

### **During treatment; every 6 months**

- Counsel the patient (using the **Patient Guide**) on:
  - The need for cardiac monitoring via ECHO
    - Every 6 months during treatment, and (b) (4)
- Assess the patient's cardiovascular status and the appropriateness of continuing treatment by obtaining the results of the patient's ECHO. Document and submit the results and appropriateness of continued treatment to the REMS using the **Patient Status Form**.

### **After treatment discontinuation; 3 to 6 months**

- Assess the patient's cardiovascular status by obtaining the results of the patient's ECHO. Document and submit the results to the REMS using the **Patient Status Form**.

### **At all times**

- Report adverse events suggestive of valvular heart disease and/or pulmonary arterial hypertension on the **Cardiovascular Adverse Event Reporting Form** to the REMS.
- Report treatment discontinuation or transfer of care to the REMS.

## **Key Risk Messages for Pharmacists (Outpatient Pharmacies)**

Pharmacies must be certified in order to dispense Fintepla.

Outpatient Pharmacies must:

- Designate an authorized representative to carry out the certification process and oversee implementation and compliance with the REMS on behalf of the pharmacy.
- Have the authorized representative review the **Pharmacy Guide** and **REMS Program Overview**.
- Have the authorized representative enroll in the REMS by completing the **Outpatient Pharmacy Enrollment Form** and submitting it to the REMS.
- Train all relevant staff involved in the dispensing of Fintepla on the REMS requirements using the **Pharmacy Guide**. Train all relevant staff involved in the dispensing of Fintepla on the REMS requirements using the **Pharmacy Guide**.

### **Before dispensing:**

- Obtain authorization to dispense by contacting the REMS Program to verify that the prescriber is certified, the patient is enrolled, and the patient is authorized to receive the drug.

### **To maintain certification to dispense:**

- Have a new authorized representative enroll in the REMS Program by completing the **Outpatient Pharmacy Enrollment Form** and submitting it to the REMS if the authorized representative changes.

### **At all times:**

- Not distribute, transfer, loan, or sell Fintepla, except to certified pharmacies.
- Maintain records of dispensing information.
- Maintain records documenting staff's completion of REMS training.
- Maintain records that all REMS processes and procedures are in place and are being followed.

- Comply with audits carried out by Zogenix or a third party acting on behalf of Zogenix to ensure all processes and procedures are in place and are being followed.

### **Key Risk Messages for Pharmacists (Inpatient Pharmacies)**

Inpatient Pharmacies must:

- Designate an authorized representative to carry out the certification process and oversee implementation and compliance with the REMS on behalf of the pharmacy.
- Have the authorized representative review the ***Pharmacy Guide*** and ***REMS Program Overview***.
- Have the authorized representative enroll in the REMS by completing the ***Inpatient Pharmacy Enrollment Form*** and submitting it to the REMS.
- Train all relevant staff involved in the dispensing of Fintepla on the REMS requirements using the ***Pharmacy Guide***.

#### **Before dispensing:**

- For patients initiating treatment: obtain authorization to dispense each prescription by contacting the REMS Program to verify that the prescriber is certified, and the patient is enrolled and authorized to receive the drug.
- For patients continuing treatment: obtain authorization to dispense each prescription by contacting the REMS program to verify that the patient is enrolled and authorized to receive the drug.

#### **At discharge:**

- Dispense no more than 15 days' supply.

#### **To maintain certification to dispense:**

- Have the new authorized representative enroll in the REMS Program by completing the ***Inpatient Pharmacy Enrollment Form*** and submitting it to the REMS if the authorized representative changes.

#### **At all times:**

- Not distribute, transfer, loan, or sell Fintepla.
- Maintain records of dispensing information.
- Maintain records documenting staff's completion of REMS training.
- Maintain records that all REMS processes and procedures are in place and are being followed.
- Comply with audits carried out by Zogenix or a third party acting on behalf of Zogenix to ensure all processes and procedures are in place and are being followed.

### **Key Risk Messages for Patients**

Patient must do the following:

#### **Before treatment initiation (first dose)**

- Review the ***Patient Guide***.
- Enroll in the REMS Program by completing the ***Patient Enrollment Form*** with prescriber.



## Program Outreach and Communication

**(Section 1) Communication Plan Metric:** The processes associated with these metrics are related to informing likely prescribers of Fintepla of the existence of the REMS. These metrics identify that REMS requirement as outlined in the REMS document (Communication Materials and Dissemination Plans) are completed. Specific thresholds for these metrics are not identified as they are not felt to be critical to the ensuring the goals of the REMS are met.

## Program Implementation and Operations

**(Section 2) REMS Program Implementation:** The processes associated with these metrics are related to when the REMS website and call center are functioning. These metrics identify that the REMS website and call center are functional as required in the REMS document.

**(Section 3a) Healthcare Provider Certification metrics:** These metrics are associated with the REMS requirement that healthcare providers are certified. The requirement for healthcare provider certification supports the goal that healthcare providers are educated. Health care providers attest to being aware of the cardiovascular risk of Fintepla and the goals of the Fintepla REMS when they complete the Fintepla REMS Prescriber Enrollment Form. The metrics relate to health care provider certification provide context for the use of Fintepla, allow the review team to assess for evidence of unanticipated burden and problems with access. The demographic metrics can be used to confirm the representativeness of survey respondents to the population of prescribers. The metrics for completed healthcare provider certification also provide important context when assessing noncompliance with healthcare provider certification.

**(Section 3b) Pharmacy Certification metrics:** These metrics are associated with the REMS requirement that inpatient and outpatient pharmacies are certified. Pharmacies' authorized representatives commit to ensuring the REMS requirements are met prior to dispensing Fintepla on the Fintepla Pharmacy enrollment forms. The metrics related to pharmacy certification provide context for the use of Fintepla, allow the review team to assess for evidence of unanticipated burden and problems with access. The metrics for certified pharmacy provides important context when assessing noncompliance with pharmacy certification and assessing the completeness of pharmacy audits.

**(Section 3c) Patient enrollment metrics:** These metrics are associated with the REMS requirement that patients are enrolled. The requirement for patient enrollment supports the goal that patients are educated. Patients acknowledge that they have been counseled on the risk of developing heart valve problems and high blood pressure in their lung arteries and the requirement to have echocardiograms obtained by signing the Fintepla REMS Patient Enrollment Form. Patients are provided written information on the risks of Fintepla on the Fintepla REMS Patient Enrollment Form. Patients acknowledge they have received the Patient Guide that provides education on the risks of Fintepla and the requirements for obtaining echocardiograms. The metrics related to patient enrollment provide context for the use of Fintepla, allow the review team to assess for evidence of unanticipated burden and problems with access, and can help confirm the representativeness of survey respondents to the

population of patients. The metrics for completed patient enrollment also provides important context when assessing noncompliance with patient enrollment.

**(Section 3d) Wholesaler/Distributor enrollment metrics:** These metrics are associated with the REMS requirement that wholesalers/distributors are enrolled. The metrics for wholesaler/distributor enrollment provides context when assessing noncompliance with wholesaler/distributor enrollment and assessing the completeness of wholesaler distributor audits.

**(Section 4) Utilization metrics:** These metrics provide context for the use of Fintepla, allow the review team to assess for evidence of unanticipated burden and problems with access. Two metrics in utilization, prescriptions that are not dispensed and prescriptions where dispensing was delayed may act as balancing measures. These balancing metrics (measures) may allow the review team to determine if the restrictions in place as part of the REMS are associated with the inability or unintended delays in patients receiving their anticonvulsant. The need to avoid unnecessarily limiting access to an anticonvulsant is of concern to the Agency. A threshold for these metrics has not been identified a priori but will be assessed in the context of the risk of valvular heart disease and pulmonary arterial hypertension as it is currently understood and as the benefit risk assessment is reassessed over time.

**(Section 5a & 5b) REMS Infrastructure and Performance metric:** These metrics include the metrics related to calls to the Call Center and Website Activities. The metrics related to calls to the Call Center allow the review team to assess for evidence of unanticipated burden and problems with access. There are metrics in this category that provide information on the downloading of REMS materials. Metrics related to adverse events are included in this category and may provide additional safety surveillance data. Finally, these metrics can serve a role in quality assurance as complaints related to the REMS, and corrective actions related to the functioning of the call center are collected. A threshold for these metrics that would identify a problem has not been identified a priori. The requirement for the Applicant to identify corrective actions resulting from identified issues may make a threshold unnecessary if issues are appropriately identified and addressed to the Agency's satisfaction.

**(Section 6) REMS Compliance metrics:** The compliance metrics identify that dispensing of Fintepla is limited to certified healthcare providers, certified pharmacies and enrolled patients as required in the REMS. Limiting to certified healthcare providers and enrolled patients is one of the mechanisms that the Fintepla uses to verify that healthcare providers and patients are educated as required in the REMS document and supported by the REMS materials. A threshold has been agreed to by the Applicant and the Agency as described in the following description. "It will be considered a demonstration of sufficient compliance if 99.9% of FINTEPLA prescriptions are dispensed in accordance with the REMS prescribing, distribution, and dispensing requirements by the fourth year of REMS operations. The compliance threshold of 99.9% corresponds to 1 noncompliance event per 1,000 attempts (prescriptions dispensed). Prior to the fourth year of REMS operations, while improvement activities are being undertaken the REMS is expected to function with a failure rate of 1 noncompliance event per 100 attempts (99.0%) and gradually increase to the 99.9% threshold." The assumption underlying the threshold of 99.9% is that at year four the system is and has been stable. The stability of the REMS system can be affected by various events that may include changes in labeling, new safety information, new REMS material, or a REMS

modification. Noncompliance metrics are collected that provide context to any noncompliance and may cause the Applicant and Agency to reassess the underlying assumptions informing the thresholds in the REMS. This context is provided in part by root cause analysis, which may allow the review team to assess for evidence of unanticipated burden and problems with access. These metrics also serve in quality assurance, assuring the processes in the REMS system function as designed.

**Audits:** Specific metrics for audits are a requirement of the REMS Assessment Plan. The Assessment plan identifies critical events in the REMS audit include dispensing to a non-enrolled patient or dispensing a prescription written by a non-certified healthcare provider. As all pharmacies will be audited the audits will not be used to determine the need for a population-based intervention however the threshold identified above will apply to noncompliance with dispensing requirements.

### **Safe Use Behaviors**

**(Section 7) Patient status form metrics:** These metrics are associated with the REMS requirement that prescribers document cardiac monitoring. The requirement for the patient status form completion supports the goal that prescribers submit the documentation of the cardiac monitoring. The metrics relate to documentation of safe use prior to the initial dispense and at the time of dispensing at 6 months are covered by the threshold for dispensing in accordance with the REMS requirements. The requirement for cardiac monitoring is an important risk mitigation tool as an echocardiogram can identify evidence of valvular heart disease or pulmonary arterial hypertension prior to a patient becoming symptomatic. The results of the echocardiogram also support the prescriber and patient making an informed decision when considering the benefit risk balance for Fintepla. A metric for the submission of patient status forms 3-6 months after discontinuation of Fintepla is included in the assessment plan. A threshold for failure to document cardiac monitoring after discontinuation has not been identified a priori since obtaining the post discontinuation echocardiogram is not influenced by the patient's need to obtain additional drug. The Agency anticipates that the Applicant's efforts to ensure that post discontinuation cardiac monitoring is obtained will be a major factor in determining if further actions are required or if the system is functioning as designed and within the REMS ability to impact. However, at the time of this review, the post discontinuation echo is felt to be important to the safe use of Fintepla to ensure that the long-term risks of Fintepla are understood and to ensure the Fintepla REMS is able to support the long-term use and safety of Fintepla. For example, if patients and providers elect to discontinue Fintepla due to changes seen on the echocardiogram it is important for the Agency to know the impact of drug discontinuation on valvular heart disease and pulmonary hypertension.

In addition to the metrics that identify that patient status forms are submitted as required, metrics related to the patient status forms provide context for issues related to failure to obtain or document cardiac monitoring and allow the review team to assess for evidence of unanticipated burden and problems with access. These metrics also inform quality assurance, assuring the processes in the REMS system function as planned. Starting at the time of the 2- year assessment the Applicant has agreed to include a metric on the estimated travel time for patients to the Echocardiogram site and the certified prescriber's office to assess the travel times for patients by this safe use condition as a potential

assessment of access and unanticipated burden. Based on expert opinion, the clinical review team concluded that obtaining echocardiograms would not be problematic for the population of patient's receiving Fintepla who are already seeing specialists (neurologists) but this will allow further evaluation of the accuracy of that assumption.

### **Knowledge**

The knowledge metrics for the REMS are divided into three categories:

**(Section 8) Healthcare Provider post training Knowledge Assessment:** Healthcare providers are required to successfully complete a post training knowledge assessment in order to become certified in the Fintepla REMS.

The Knowledge surveys (9a and 9b) can be used in determining whether the REMS meets the goal of educating providers and patients however they are not sufficient on their own to ensure those goals are met. The enrollment of patients and providers and the assessment of the safe use behavior are necessary to determine the REMS is meeting its overarching goal of mitigating the risk of valvular heart disease and pulmonary hypertension associated with Fintepla. The enrollment of prescribers and patients ensure that they have reviewed the risk of Fintepla and the safe use conditions of ensuring echocardiograms are completed is the major intervention that contributes to an informed benefit risk assessment by the prescriber and the patient.

**(Section 9a) Prescriber Surveys:** The Assessment plan requires the Applicant to undertake prescriber surveys which will assess a sample of health care providers who have prescribed Fintepla. The surveys will assess whether the REMS is meeting the goal of educating healthcare providers about the risk associated with Fintepla and the need for cardiac monitoring, as well as their awareness and use of the REMS materials, understanding of and adherence to the REMS requirements, and attitudes and beliefs related to the burden of the REMS. The thresholds for survey key risk messages will be submitted with the survey methodology 90 days after approval of the product. The Applicant was advised to include the expected baseline knowledge for healthcare providers and patients/caregivers of the risk of pulmonary hypertension and valvular heart disease on May 22, 2020. The Agency is aware that Fintepla use in the Dravet population both in terms of efficacy and risk are in both the medical literature and on websites of support groups for patients with Dravet. This pre-existing knowledge may impact the influence the REMS has on educating healthcare providers and patients although the magnitude and direction of this effect is unknown.

**(Section 9b) Patient/Caregiver Surveys:** The Assessment plan includes that the Applicant undertake patient surveys which will assess a sample of patients (caregivers) who have used Fintepla. The surveys will assess whether the REMS is meeting the goal of educating patients about the risk associated with Fintepla and the need for cardiac monitoring. The thresholds for survey key risk messages will be submitted with the survey methodology 90 days after approval of the product.

### **Health Outcomes and/or surrogates of health outcomes**

The metrics for health outcomes are divided into three categories:

**(Section 10) Health Outcomes Compliance:** These metrics are associated with the requirement that prescribers complete cardiac adverse event forms if cardiac adverse events are identified on the patient safety form. This requirement is identified in the REMS document and healthcare providers attest they will do so to become certified.

**(Section 11) Safety Surveillance metrics:**

**(Section 11 a)** A summary of known or suspected adverse events from multiple sources: These metrics are associated with the occurrence of known or suspected adverse events and whether the monitoring identified in the prescribing information and required by the REMS was followed.

**(Section 11 b)** Registry metrics: The REMS require the Applicant to establish and maintain a registry of all patients that includes a reporting and collection system for all patients to provide information on patient outcomes and the incidence of valvular heart disease and pulmonary hypertension. The review team led by members of the Division of Cardiology, the Division of Neurology-2 with the Division of Pharmacovigilance and the Division of Risk Management identified the metrics based on the data included in the cardiovascular adverse event report form that were felt to be necessary to achieve the goal of the Fintepla REMS registry.

### **Considerations in the overall assessment of the Fintepla REMS:**

The enrollment of patients and providers and the assessment of the safe use behavior with the restricted distribution linked to these activities are necessary and may be sufficient to determine the REMS is meeting its overarching goal of mitigating the risk of valvular heart disease and pulmonary hypertension associated with Fintepla. The enrollment forms ensure that patients and prescribers have reviewed the risk of Fintepla. The safe use conditions of ensuring an echocardiogram is completed before the initial dispensing of Fintepla and with ongoing dispensing are the major factors that contribute to an informed benefit risk assessment by the prescriber and the patient, when considering the risk of pulmonary hypertension and valvular heart disease in the setting of Dravet syndrome, a “catastrophic” epilepsy with a significant risk of mortality in the setting of ongoing seizures.<sup>17,18,19</sup> The Agency considers that the patient and healthcare provider survey data is supportive and on its own not sufficient to determine if the REMS is meeting its overarching goal of mitigating the risk of valvular heart disease or pulmonary hypertension.

## **9 Conclusions & Recommendations**

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The risks of VHD and PAH associated with fenfluramine are serious and it is necessary for prescribers to understand these risks, the importance of monitoring for them, and appropriate patient selection. Based on the severity of VHD or PAH, and the uncertainty of the long-term cardiotoxic effects that may occur

with chronic fenfluramine therapy, we agree that requiring a REMS consisting of a communication plan, prescriber certification, pharmacy certification, safe-use conditions – patient enrollment, monitoring of patients, and enrollment of all patients receiving fenfluramine in a registry is necessary to ensure that the benefits outweigh the risk. Additionally, the REMS will require an implementation system and timetable for submission of assessments.

DRM finds the Applicant’s proposed REMS received on June 24, 2020 to be acceptable and is appended to this review.

## 10 Appendices

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### 10.1 FINTEPLA REMS ASSESSMENT PLAN

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, 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)

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CARLISHA C GENTLES on behalf of ANAHITA TAVAKOLI  
06/25/2020 04:06:57 PM

CHARLOTTE T JONES  
06/25/2020 04:08:03 PM

LAURA A ZENDEL  
06/25/2020 04:15:43 PM

SHELLY L HARRIS  
06/25/2020 04:18:12 PM

CYNTHIA L LACIVITA  
06/25/2020 04:38:47 PM

**Division of Risk Management (DRM)**  
**Office of Medication Error Prevention and Risk Management (OMEPRM)**  
**Office of Surveillance and Epidemiology (OSE)**  
**Center for Drug Evaluation and Research (CDER)**

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|-------------------------------|--|
| <b>Application Type</b>       | NDA  |
| <b>Application Number</b>     | 212102   |
| <b>PDUFA Goal Date</b>        | June 25, 2020  |
| <b>OSE RCM #</b>              | 2019-393   |
| <b>Reviewer Name(s)</b>       | Carlisha Gentles, PharmD<br>Anahita Tavakoli, MA<br>Charlotte Jones, MD, PhD, MSPH |
| <b>Team Leader</b>            | Laura Zendel, PharmD   |
| <b>Review Completion Date</b> | June 12, 2020  |
| <b>Subject</b>                | Evaluation of Need for a REMS  |
| <b>Established Name</b>       | Fenfluramine   |
| <b>Trade Name</b>             | Fintepla   |
| <b>Name of Applicant</b>      | Zogenix  |
| <b>Therapeutic Class</b>      | Anti-convulsant  |
| <b>Formulation(s)</b>         | 2.5 mg/ml Oral Solution  |
| <b>Dosing Regimen</b>         | 0.2 mg/kg to (b) (4) mg/kg twice daily   |

## 1 Introduction

---

The following comments and the attached redlined REMS document and appended materials are based on the Agency's review of the proposed REMS amendment for Fintepla submitted to NDA 212102 April 22, 2020 and most recently amended on June 16, 2020. Zogenix, Inc. submitted a New Drug Application (NDA) 212102 for Fintepla with the proposed indication to treat seizures associated with Dravet Syndrome (DS) in patients 2 years of age and older. To facilitate further review, we ask that the Applicant revise the REMS proposal based on the following comments and redlined documents then resubmit a complete REMS amendment within 1 calendar days, by COB on Tuesday, June 23, 2020.

## 2 Comments for the Applicant

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The following comments and the attached redlined REMS document and appended materials are based on the Agency's review of the proposed REMS amendment for Fintepla submitted to NDA 212102 on June 16, 2020. To facilitate further review, we ask that you revise your REMS proposal based on the following comments and resubmit your complete REMS amendment within 1 calendar day. We are providing what we consider final comments of the REMS Document, REMS Supporting Document, and appended materials.

### 2.1 GENERAL COMMENTS

Further changes are required to the REMS to be found acceptable. See comments below and attached redlined materials. We do not have any additional comments on the following appended materials at this time: FINTEPLA REMS Enrollment Forms for the Prescriber, Pharmacy and Patient, Patient Status Form, Letter for Healthcare Providers, or Prescriber Knowledge Assessment.

### 2.2 REMS DOCUMENT

Wholesaler-Distributor Section: Delete “(b) (4)” Retain this information within the supporting document.

### 2.3 REMS APPENDED MATERIALS

Revisions to the REMS appended materials are needed for the REMS to be acceptable. All REMS materials must align with the final labeling and REMS document. We have provided edits in tracked changes as well as additional comments that must be addressed in your materials. Ensure that all of your word versions of the appended materials align with the mock-up pdf versions of your materials. See attached redlined documents.

Additional specific changes are outlined below.

#### FINTEPLA REMS Program Overview

FINTEPLA REMS Resources Table: Delete “(b) (4)” before the name of each material to avoid redundancy.

#### FINTEPLA REMS Prescriber Training

- Page 5:
  - Delete the word “(b) (4)” when describing the Prescribing Information.
  - Replace the 1<sup>st</sup> bullet with the following statement: “There is an association between serotonergic drugs with 5 HT<sub>2B</sub> receptor agonist activity, including fenfluramine (the active ingredient in FINTEPLA), and valvular heart disease and pulmonary arterial hypertension” to align with the Boxed Warning.
  - Replace the 2<sup>nd</sup> bullet with the following statement: “In clinical trials of FINTEPLA for the treatment of Dravet syndrome, no cases of valvular heart disease or pulmonary hypertension were reported. Across clinical trials of FINTEPLA for the treatment of Dravet syndrome, 0.4-16% of patients taking Fintepla were found to have trace aortic or mitral regurgitation compared to 0-6% of patients taking placebo. Trace aortic or mitral regurgitation are considered physiologic or normal findings in the absence of valvular abnormalities.”

FINTEPLA REMS Pharmacy Guide

Under the “Risk of valvular heart disease and pulmonary arterial hypertension,” delete the following statements:



Replace the above listed statement with the following statement to align with labeling:

- There is an association between serotonergic drugs with 5HT<sub>2B</sub> receptor agonist activity including fenfluramine (the active ingredient in FINTEPLA), and valvular heart disease and pulmonary arterial hypertension. In clinical trials of FINTEPLA for the treatment of Dravet Syndrome, no cases of valvular heart disease or pulmonary hypertension were reported. Across clinical trials of FINTEPLA for the treatment of Dravet Syndrome, 0.4-1.6% of patients taking FINTEPLA were found to have trace aortic or mitral regurgitation compared to 0-6% of patients taking placebo. Trace aortic or mitral regurgitation are considered physiologic or normal findings in the absence of valvular abnormalities.

Inpatient Pharmacy Section, before dispensing, change #2 as follows to align with the REMS document:

- To continue maintenance therapy: Obtain authorization to dispense FINTEPLA by contacting the REMS to verify that the patient is under the care the care of a certified prescriber, the patient is enrolled and the patient is authorized to receive the drug.

FINTEPLA REMS Patient Guide

Make the following changes to the document to ensure the REMS risks of the drug is not minimized, promotional in tone or makes representations of an unapproved uses of the drug.

- On page 2, delete the phrase “(b) (4)” Align the “What is the most serious risk of FINTEPLA” section with the final Agency approved Medication Guide.
- On page 3, change “The Medication Guide explains how to take FINTEPLA and has information about other potential side effects” to “The Medication Guide explains how to take FINTEPLA and has

information about other serious risks and potential side effects.”

#### Cardiovascular Event Reporting Form

- Retain box for “death” under the section to capture the outcome of the cardiovascular adverse event.

#### FINTEPLA REMS Website Screenshots

The REMS website, in its entirety should be updated to align with the most recent version of the REMS document and REMS materials (i.e. guides, and forms). Make the following changes to the document to ensure the REMS risks of the drug are not minimized.

- Select Signing Reason:
  - The drop-down options are confusing. Please explain the need for the Select Signing Reason section, and the need for each option. Make it clearer within the website for the stakeholders as to the purpose and meaning of each option.
- Dispense Authorization Sections:
  - Ensure the pop-up boxes the pharmacy receives align with the proposed dispense authorization statuses described throughout the REMS, i.e. “Authorized,” “Authorized-Warning,” and “Not Authorized.” We agree with including the explanations for each authorization status and directions for the pharmacy within the pop-up box. Provide an example of each pop-up box a pharmacy may receive.
- Page 28:
  - Delete “(b) (4)” to align this section with the Medication Guide.
  - change “The Medication Guide explains how to take FINTEPLA and has information about other potential side effects” to “The Medication Guide explains how to take FINTEPLA and has information about other serious risks and potential side effects.”

In addition, in the Prescriber section, is there functionality within the website that allows the prescriber to see a patient’s history of Patient Status Forms and include the date for when the next Patient Status Form is due?

Submit a complete set of REMS website screenshots showing all content and functionality of the website. Both a .pdf and a word version should be submitted for review. If any website screenshots that are necessary to show all content and functionality of the website are proprietary in nature, you may include them separate from the public facing website screenshots as an appendix within the supporting document so that they may remain non-public.

The REMS-related webpages should not be a means to promote FINTEPLA or any other Zogenix product.

## **2.4 REMS SUPPORTING DOCUMENT**

In this version of the assessment plan, we have made additional formatting changes and have also updated some of the language in the assessment plan to more closely align with current assessment plan language. See underlined text for language that was added, changed and/or combined.

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06/22/2020 05:19:25 PM

**Division of Risk Management (DRM)**  
**Office of Medication Error Prevention and Risk Management (OMEPRM)**  
**Office of Surveillance and Epidemiology (OSE)**  
**Center for Drug Evaluation and Research (CDER)**

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|-------------------------------|--|
| <b>Application Type</b>       | NDA  |
| <b>Application Number</b>     | 212102   |
| <b>PDUFA Goal Date</b>        | June 25, 2020                                    |
| <b>OSE RCM #</b>              | 2019-393   |
| <b>Reviewer Name(s)</b>       | Carlisha Gentles, PharmD<br>Anahita Tavakoli, MA |
| <b>Team Leader</b>            | Laura Zendel, PharmD                             |
| <b>Review Completion Date</b> | June 15, 2020                                    |
| <b>Subject</b>                | Evaluation of Need for a REMS                    |
| <b>Established Name</b>       | Fenfluramine                                     |
| <b>Trade Name</b>             | Fintepla   |
| <b>Name of Applicant</b>      | Zogenix  |
| <b>Therapeutic Class</b>      | Anti-convulsant                                  |
| <b>Formulation(s)</b>         | 2.5 mg/ml Oral Solution                          |
| <b>Dosing Regimen</b>         | 0.2 mg/kg to 0.8 mg/kg twice daily               |

# 1 Introduction

---

The following comments and the attached redlined REMS document and appended materials are based on the Agency’s review of the proposed REMS amendment for Fintepla submitted to NDA 212102 April 22, 2020. Zogenix, Inc. submitted a New Drug Application (NDA) 212102 for Fintepla with the proposed indication to treat seizures associated with Dravet Syndrome (DS) in patients 2 years of age and older. To facilitate further review, we ask that the Applicant revise the REMS proposal based on the following comments and redlined documents then resubmit a complete REMS amendment within 3 calendar days, by close of business (COB) June 18, 2020.

## 2 Comments for the Applicant

---

The following comments and the attached redlined REMS document and appended materials are based on the Agency’s review of the proposed REMS amendment for Fintepla submitted to NDA 212102 on April 22, 2020 and amended on June 1, 2020 and June 8, 2020. To facilitate further review, we ask that you revise your REMS proposal based on the following comments and resubmit your complete REMS amendment within 3 calendar days. We are providing what we consider final comments on the REMS document. Review of the REMS Supporting Document, and appended materials are ongoing and therefore, these comments should not be considered final.

### 2.1 GENERAL COMMENTS

Further changes are required to the REMS to be found acceptable. Align attestations in each individual form with the REMS document. See comments below and attached redlined materials.

### 2.2 REMS DOCUMENT

Revisions to the REMS document are necessary to be acceptable. Please see attached redlined document.

- Add an attestation to both the inpatient and outpatient pharmacy sections to “Maintain records of dispensing information” to correspond with the added attestations on the enrollment forms.
- We have provided additional editorial changes for clarity and to align with the Format and Content of a REMS Document Guidance.

### 2.3 REMS APPENDED MATERIALS

Revisions to the REMS appended materials are needed for the REMS to be acceptable. All REMS materials must align with the final labeling and REMS document. We have provided edits in tracked changes as well as additional comments that must be addressed in your materials. Ensure that all of your word versions of the appended materials align with the mock-up pdf versions of your materials. See attached redlined documents.

Additional specific changes are outlined below.

[FINTEPLA REMS Program Overview](#)

Simplify and re-organize the Program Overview to align with the REMS document and other appended materials. Incorporate editorial changes throughout the document to further simplify this material. Additionally, insert a table of Fintepla REMS Resources at the end of this document similar to the resources page on the website.

#### FINTEPLA REMS Enrollment Forms for Prescriber, Pharmacy, and Patients:

Update all attestations within the enrollment forms to reflect requirements in the REMS document.

#### FINTEPLA REMS Prescriber Training

Ensure that the prescriber training aligns with revisions made to the REMS document and other REMS materials. For example, there are several questions in the Prescriber Knowledge Assessment that are not addressed in the Prescriber Training. Add further details within the training to further explain the prescriber's responsibilities and incorporate the importance of regular monitoring via echocardiogram (ECHO) for early detection of the conditions.

#### FINTEPLA REMS Pharmacy Guide

The footnote describing the authorization to dispense is easy to miss. Make this information more prominent and more detailed so that pharmacies understand the meaning of the authorization statuses. Also, it remains unclear how pharmacies will obtain authorization to dispense via fax. Update accordingly in the Pharmacy Guide and in the Supporting Document. Additionally, provide rationale for requiring inpatient pharmacies to fax the course of therapy to the REMS at discharge and if there will be a call or online option to fulfill this request.

#### FINTEPLA REMS Patient Guide

Incorporate editorial changes throughout the document to make it more patient friendly. Additionally, add language to emphasize the importance of ECHO monitoring for early detection of the conditions. These comments were provided in a previous round of comments but were not incorporated.

#### Patient Status Form

- Add height, weight, and BMI as optional data points to collect for patients.
- Incorporate editorial changes for clarity

#### Cardiovascular Event Reporting Form

- Include a section to capture the outcome of the cardiovascular adverse event.
- Incorporate additional information on the form as requested by the agency.

#### FINTEPLA REMS Program Letter for Healthcare Providers

Incorporate language to emphasize the importance of obtaining an ECHO to monitor for changes in cardiac function or disease and early detection of the conditions: An ECHO can identify evidence of valvular heart disease or pulmonary arterial hypertension prior to a patient becoming symptomatic.

#### FINTEPLA Prescriber Knowledge Assessment

Incorporate an editorial change at the beginning of the document. Remove the word “ (b) (4) ” from question #4. The responses to the knowledge assessment should be added to the Prescriber Training.

#### FINTEPLA REMS Website Screenshots

The REMS website, in its entirety should be updated to align with the most recent version of the REMS document and REMS materials (i.e. guides, and forms). Include the date of last ECHO under the patient and provider information heading of the dispense authorization number section. Additional editorial changes are needed throughout the screenshots.

Submit a complete set of REMS website screenshots showing all content and functionality of the website. Both a .pdf and a word version should be submitted for review. If any website screenshots that are necessary to show all content and functionality of the website are proprietary in nature, you may include them separate from the public facing website screenshots as an appendix within the supporting document so that they may remain non-public.

The REMS-related webpages should not be a means to promote FINTEPLA or any other Zogenix product.

#### **2.4 REMS SUPPORTING DOCUMENT**

Changes to the Supporting Document are necessary. In general, revisions should be made to ensure the Supporting Document aligns with the REMS document and the revisions made to the appended materials.

Monitoring for Valvular Heart Disease and Pulmonary Arterial Hypertension During Treatment with Fintepla Section:

- Add a reference for the following: Of the 132 spontaneous reports reviewed by FDA, 113 (86%) met the FDA case definition of valvulopathy.
- Edit the following paragraph as shown:



- Retain the language: (b) (4)  
(b) (4)  
(b) (4) at the end of the second to last paragraph.

## Prescriber Section

- Clarify if prescribers will be notified via other means (e.g. email) when patient enrollment is complete and the patient can receive Fintepla.
- Clarify the requirements for the timing of the follow-up ECHO for patients initiating Fintepla. We recommend simplifying the timing to be based on the date of receipt of the Patient Status Form.
- When the REMS provides reminders to the prescriber at 60 and 30 days prior to the next ECHO due date, we recommend to also include a phone, mail, or email reminder in addition to fax.
- The statement, “ [REDACTED] (b) (4) [REDACTED] ” is confusing as it implies that a patient may be allowed therapy past the grace period. Please clarify the intent.

Further clarification is needed regarding the outpatient and inpatient pharmacy process. Specifically:

- Provide clarification regarding the online verification process to be used in the pharmacy which has been added per your website screenshots. Explain how the pharmacy uses the unique authorization number.
- Incorporate your resubmission response on 6/8/20 regarding inpatient pharmacy process of obtaining Fintepla from the wholesaler-distributor into the Supporting Document
- Further detail is needed to outline the outpatient and inpatient pharmacy requirements for verification and documentation procedures. Include further explanation of how the pharmacies obtain authorization to dispense for fax, phone and online, what responsibilities the pharmacy, Zogenix or the REMS Coordinating Center have for each scenario (Authorized, Authorized-Warning, and Not-Authorized), and how prescribers and patients are notified when the patient status form is due or past-due and how the notification is documented.
- Include an algorithm to outline when the REMS Coordinating Center will send the Cardiovascular Adverse Event Reporting Form for follow-up based on responses on the Patient Status Form. See comments within the Patient Status Form for reference.
- Describe how the REMS will identify patients “ [REDACTED] (b) (4) ” and if this is limited to the inpatient setting.
- Describe further how you will distinguish between “ [REDACTED] (b) (4) ” and “discontinuation,” specifically is there a timeframe that determines treatment interruption vs. discontinuation or is interruption transient while discontinuation permanent?

Further explain your distribution requirements and how wholesaler-distributors become authorized to distribute.

- Add “Wholesaler-distributors must identify an authorized representative to carry out the enrollment processes and oversee implementation and compliance with the REMS on behalf of the wholesaler-distributor.

#### Implementation System

- Note that the REMS will also contact the patient to be made aware when they are within the grace period for their ECHO.
- Include further details about when the cardiovascular adverse event reporting form is sent as outlined in your 6/8/20 IR response.

#### **2.4.1 Assessment Plan**

Update the Assessment Plan based on the changes to the REMS document and appended materials. Additional comments will be provided in the next round of comments.

#### Resubmission Instructions

- Your complete REMS proposal should be submitted as separate documents in the same submission, to include both a Word tracked changes version, a Word clean version as well as a .pdf version of each of the previously mentioned documents and appended materials.
- Include all final formatting when submitting REMS materials in your next submission, including any logos, coloring, shading, or other design features.

Additionally, we refer you to the [REMS@FDA](mailto:REMS@FDA) website, which references multiple approved REMS programs which you may find useful.

Please submit your complete REMS proposal by June 16, 2020.

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CARLISHA C GENTLES  
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ANAHITA TAVAKOLI  
06/15/2020 09:59:47 AM

LAURA A ZENDEL  
06/15/2020 10:26:05 AM

# Internal Consults

\*\*\*\*Pre-decisional Agency Information\*\*\*\*

**Please Note: The following review is for DRISK only and should not be used to provide comments to the sponsor.**

To: Anahita Tavakoli, Health Communications Analyst,  
Division of Risk Management (DRM),  
Office of Surveillance and Epidemiology (OSE)

From: Dhara Shah, Regulatory Review Officer, OPDP

CC: Aline Moukhtara, Team Leader, OPDP  
Casmir Ogbonna, Safety Regulatory Project Manager, OSE  
Laura Zendel, Team Leader, DRM  
Carlisha Gentles, Risk Management Analyst, DRM  
Doris Auth, Associate Director, DRM  
Jina Kwak, OPDP  
Michael Wade, OPDP  
CDER-OPDP-RPM

Date: June 12, 2020

Re: NDA 212102  
FINTEPLA™ (fenfluramine) oral solution, CIV

Comments on draft Risk Evaluation and Mitigation Strategies (REMS)  
Materials (Submission date: June 2, 2020)

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## **Materials Reviewed**

OPDP has reviewed the following proposed REMS materials for FINTEPLA™ (fenfluramine) oral solution, CIV (Fintepla):

- Healthcare Provider (HCP) REMS Materials:
  - Prescriber Enrollment Form
  - Outpatient Pharmacy Enrollment Form
  - Inpatient Pharmacy Enrollment Form
  - Prescriber Training
  - REMS Program Overview
  - Prescriber Knowledge Assessment
  - Pharmacy Guide
  - Patient Status Form
  - Cardiovascular Adverse Event Reporting Form
  - Healthcare Provider Letter
  
- Direct-to-Consumer (Patient) REMS Materials:
  - Patient Enrollment Form
  - Patient Guide
  
- REMS Website Screenshots

The version of the draft REMS materials used in this review were sent from DRM (Anahita Tavakoli) via email on June 2, 2020. The draft REMS materials are attached to the end of this review memorandum. OPDP offers the following comments on these draft REMS materials Fintepla.

## **General Comments**

Please remind Zogenix that REMS materials are not appropriate for use in a promotional manner.

OPDP notes the link [www.FinteplaREMS.com](http://www.FinteplaREMS.com), and toll-free number 1-877-964-3649. OPDP recommends that these items represent a direct link to only REMS related information and not be promotional in tone. Furthermore, we remind Zogenix that the REMS specific website should not be the sole source of approved REMS materials.

## **REMS Materials**

OPDP does not object to including the following materials in the REMS program (please see Specific Comments below):

- Healthcare Provider (HCP) REMS Materials:
  - Prescriber Enrollment Form
  - Outpatient Pharmacy Enrollment Form

- Inpatient Pharmacy Enrollment Form
- Prescriber Training
- REMS Program Overview
- Prescriber Knowledge Assessment
- Pharmacy Guide
- Patient Status Form
- Cardiovascular Adverse Event Reporting Form
- Healthcare Provider Letter
- Direct-to-Consumer (Patient) REMS Materials:
  - Patient Enrollment Form
  - Patient Guide
- REMS Website Screenshots

### Specific Comments

OPDP considers the following statements promotional in tone and recommends revising them in the REMS piece:

#### **Patient Guide:**

- Page 2: “ [REDACTED] (b) (4) ”
  - **Risk**
    - This statement minimizes the REMS risks of the drug and is not included in the draft PI. OPDP recommends deletion.
  - **Benefit**
    - The phrase, “ [REDACTED] (b) (4) ” is promotional in tone and makes representations of an unapproved use of the drug. In addition, this information was deleted from the Box Warning of the draft PI. OPDP recommends deletion.
- Page 3: “The Medication Guide explains how to take FINTEPLA and has information about [REDACTED] (b) (4) ” (emphasis added)
  - **Risk**
    - The phrase “ [REDACTED] (b) (4) ” minimizes the non-REMS risks of the drug. OPDP recommends revising to this to state “other serious risks and potential side effects.”

#### **Pharmacy Guide:**

- Page 2: [REDACTED] (b) (4)  
[REDACTED] (in pertinent part)
  - **Benefit**
    - The phrase [REDACTED] (b) (4) ” is promotional in tone and makes representations of an unapproved use of the drug. In addition, this

information was deleted from the Box Warning of the draft PI. OPDP recommends deletion.

- This statement represents an assurance of safety about the drug by implying the Box Warning risk is only associated with Fintepla when used to treat (b) (4). In addition, this information is not included in the draft PI. The Box Warning of the draft PI states, (b) (4)  
(b) (4)  
(b) (4)  
OPDP recommends deleting the statement and revising to include this material information consistent with the draft PI.

- Page 2: (b) (4)  
(b) (4)

- **Risk**

- This statement minimizes the REMS risks of the drug and omits important material facts. Specifically, Section 6 of the draft PI includes the header, “Echocardiographic Safety Assessments of Valvular Regurgitation and Pulmonary Arterial Hypertension,” which states, “In Study 1 and Study 2, 16% of patients taking FINTEPLA compared to 6% of patients taking placebo were reported to have trace mitral regurgitation, and 3% of patients taking FINTEPLA and no patients taking placebo were found to have trace aortic regurgitation. During the open-label extension study, trace mitral regurgitation and trace aortic regurgitation were reported in 14% and 0.4%, respectively, of patients taking FINTEPLA.” OPDP recommends revising to include this material information.

### Prescriber Training:

- Page 5: (b) (4)  
(b) (4)

- **Benefit**

- The phrase “(b) (4)” is promotional in tone and makes representations of an unapproved use of the drug. In addition, this information was deleted from the Box Warning of the draft PI. OPDP recommends deletion.
- Please see similar comment above. This information is not included in the draft PI. The Box Warning of the draft PI states, (b) (4)  
(b) (4)  
(b) (4)  
OPDP recommends deleting the statement

and revising to include this material information consistent with the draft PI.

- Page 5: [REDACTED] (b) (4)
  - **Risk**
    - This statement minimizes the REMS risks of the drug and omits important material facts. Specifically, Section 6 of the draft PI includes the header, “Echocardiographic Safety Assessments of Valvular Regurgitation and Pulmonary Arterial Hypertension,” which states, “In Study 1 and Study 2, 16% of patients taking FINTEPLA compared to 6% of patients taking placebo were reported to have trace mitral regurgitation, and 3% of patients taking FINTEPLA and no patients taking placebo were found to have trace aortic regurgitation. During the open-label extension study, trace mitral regurgitation and trace aortic regurgitation were reported in 14% and 0.4%, respectively, of patients taking FINTEPLA.” OPDP recommends revising to include this material information.

**Website:**

- Page 17: “The Medication Guide explains how to take FINTEPLA and has information about [REDACTED] (b) (4)” (emphasis added)
  - **Risk**
    - The phrase “[REDACTED] (b) (4)” minimizes the non-REMS risks of the drug. OPDP recommends revising to this to state “other serious risks and potential side effects.”
- **Risk**
  - Please see above comments regarding information pertaining to the REMS risk and revise forms, training and other materials located on the website to align with above recommended changes listed.

We have no additional comments on these proposed REMS materials at this time.

Thank you for your consult.

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**Division of Risk Management (DRM)**  
**Office of Medication Error Prevention and Risk Management (OMEPRM)**  
**Office of Surveillance and Epidemiology (OSE)**  
**Center for Drug Evaluation and Research (CDER)**

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|-------------------------------|--|
| <b>Application Type</b>       | NDA  |
| <b>Application Number</b>     | 212102   |
| <b>PDUFA Goal Date</b>        | June 25, 2020                                    |
| <b>OSE RCM #</b>              | 2019-393   |
| <b>Reviewer Name(s)</b>       | Carlisha Gentles, PharmD<br>Anahita Tavakoli, MA |
| <b>Team Leader</b>            | Laura Zendel, PharmD                             |
| <b>Review Completion Date</b> | May 28, 2020                                     |
| <b>Subject</b>                | Evaluation of Need for a REMS                    |
| <b>Established Name</b>       | Fenfluramine                                     |
| <b>Trade Name</b>             | Fintepla   |
| <b>Name of Applicant</b>      | Zogenix  |
| <b>Therapeutic Class</b>      | Anti-convulsant                                  |
| <b>Formulation(s)</b>         | 2.5 mg/ml Oral Solution                          |
| <b>Dosing Regimen</b>         | 0.2 mg/kg to 0.8 mg/kg twice daily               |

## 1 Introduction

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The following comments and the attached redlined appended materials are based on the Agency's review of the proposed REMS amendment for Fintepla submitted to NDA 212102 April 22, 2020. Zogenix, Inc. submitted a New Drug Application (NDA) 212102 for Fintepla with the proposed indication to treat seizures associated with Dravet Syndrome (DS) in patients 2 years of age and older in addition to the comments sent on May 26, 2020. These comments focus on the patient status form and the proposed addition of an adverse event reporting form. To facilitate further review, we ask that the Applicant revise the REMS proposal based on the following comments and redlined documents then resubmit a complete REMS amendment within 4 calendar days, by close of business (COB) June 1, 2020. Review of the REMS document, supporting document, and appended materials is ongoing and therefore, these comments should not be considered final.

## 2 Comments for the Applicant

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The following comments and the attached redlined appended materials are based on the Agency's review of the proposed REMS amendment for Fintepla submitted to NDA 212102 on April 22, 2020 in addition to the comments sent on May 26, 2020. To facilitate further review, we ask that you revise your REMS proposal based on the comments sent on May 26, 2020 and the following comments and resubmit your complete REMS amendment incorporating both sets of comments within 4 calendar days. Review of the REMS document, supporting document, and appended materials is ongoing and therefore, these comments should not be considered final.

### 2.1 REMS APPENDED MATERIALS

The Agency agrees with your proposal to separate reporting adverse events from the Patient Status Form and collect that information on the Cardiovascular Adverse Event Reporting Form, however, additional changes are needed to be acceptable. Align definitions of fenfluramine-associated VHD with the generally accepted case definition used by the FDA as noted in comments dated May 26, 2020.

Incorporate the following changes throughout all materials to align with changes to the REMS document:

- Change the risk from “ (b) (4) ” to “valvular heart disease and pulmonary arterial hypertension”

Please see attached redlined materials. Additional specific changes are outlined below.

#### Patient Status Form

- Remove the text (b) (4) ” to avoid situations in which the patient status form is submitted, but a patient's cardiac function had not been assessed via ECHO. Retain within the supporting document as

information to be collected when following up when the patient status form is not submitted on time.

#### Cardiovascular Adverse Event Reporting Form

- Add “or other cardiac findings” so that this form is used for follow-up of any cardiac findings on the ECHO, not limited to VHD or PAH.
- Remove the section that includes the (b) (4).
- Incorporate additional questions on the form as recommended by the agency.
- Provide rationale for (b) (4) reporting form to the REMS.

#### Resubmission Instructions

- Your complete REMS proposal should be submitted as separate documents in the same submission, to include both a Word tracked changes version, a Word clean version as well as a .pdf version of each of the previously mentioned documents and appended materials.
- Include all final formatting when submitting REMS materials in your next submission, including any logos, coloring, shading, or other design features.

Additionally, we refer you to the [REMS@FDA](mailto:REMS@FDA) website, which references multiple approved REMS programs which you may find useful.

Please submit your complete REMS proposal including these comments and comments received on May 26, 2020 by June 1, 2020.

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**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.**  
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/s/  
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CARLISHA C GENTLES  
05/28/2020 10:11:38 AM

ANAHITA TAVAKOLI  
05/28/2020 10:46:24 AM

LAURA A ZENDEL  
05/28/2020 11:06:36 AM

**Division of Risk Management (DRM)**  
**Office of Medication Error Prevention and Risk Management (OMEPRM)**  
**Office of Surveillance and Epidemiology (OSE)**  
**Center for Drug Evaluation and Research (CDER)**

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|-------------------------------|--|
| <b>Application Type</b>       | NDA  |
| <b>Application Number</b>     | 212102   |
| <b>PDUFA Goal Date</b>        | June 25, 2020  |
| <b>OSE RCM #</b>              | 2019-393   |
| <b>Reviewer Name(s)</b>       | Carlisha Gentles, PharmD<br>Anahita Tavakoli, MA<br>Charlotte Jones, MD, PhD, MSPH |
| <b>Team Leader</b>            | Laura Zendel, PharmD   |
| <b>Division Director</b>      | Cynthia LaCivita, PharmD   |
| <b>Review Completion Date</b> | May 22, 2020   |
| <b>Subject</b>                | Evaluation of Need for a REMS  |
| <b>Established Name</b>       | Fenfluramine   |
| <b>Trade Name</b>             | Fintepla   |
| <b>Name of Applicant</b>      | Zogenix  |
| <b>Therapeutic Class</b>      | Anti-convulsant  |
| <b>Formulation(s)</b>         | 2.5 mg/ml Oral Solution  |
| <b>Dosing Regimen</b>         | 0.2 mg/kg to 0.8 mg/kg twice daily   |

## 1 Introduction

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The following comments and the attached redlined REMS document, supporting document and appended materials are based on the Agency's review of the proposed REMS amendment for Fintepla submitted to NDA 212102 April 22, 2020. Zogenix, Inc. submitted a New Drug Application (NDA) 212102 for Fintepla with the proposed indication to treat seizures associated with Dravet Syndrome (DS) in patients 2 years of age and older. This application is under review in the Division of Neurology 2 (DN2). The Applicant's proposed REMS consists of elements to assure safe use (ETASU), an implementation system, and a timetable for submission of assessments to ensure the benefits of Fintepla outweigh the risks of regurgitant valvular heart disease (VHD) and pulmonary arterial hypertension (PAH). DRM and DN2 agree that a REMS with ETASU A (prescriber certification), B (pharmacy certification), D (safe use conditions), E (monitoring) and F (registry) is necessary to for the benefits of Fintepla to outweigh its risks. To facilitate further review, we ask that the Applicant revise the REMS proposal based on the following comments and redlined documents then resubmit a complete REMS amendment within 7 calendar days, by close of business (COB) May 29, 2020. Review of the REMS document, supporting document, and appended materials is ongoing and therefore, these comments should not be considered final.

## 2 Comments for the Applicant

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The following comments and the attached redlined REMS document, supporting document and appended materials are based on the Agency's review of the proposed REMS amendment for Fintepla submitted to NDA 212102 on April 22, 2020. To facilitate further review, we ask that you revise your REMS proposal based on the following comments and resubmit your complete REMS amendment within 7 calendar days. Review of the REMS document, supporting document, and appended materials is ongoing and therefore, these comments should not be considered final.

### 2.1 GENERAL COMMENTS

Further changes are required to the REMS to be found acceptable. Align attestations in each individual form with the REMS document. See comments below and attached redlined materials. The Patient Status Form and Cardiovascular Adverse Event Reporting Form are still under review. Additional comments will be forthcoming.

If fenfluramine is approved, provide a tentative timeline that Zogenix, Inc. plans to launch this product.

### 2.2 REMS DOCUMENT

Revisions to the REMS document are necessary to be acceptable. Please see attached redlined document. The goal has been revised to revise focus on the risk to valvular heart disease and pulmonary arterial hypertension (b) (4). Remove the language "(b) (4)" throughout the REMS document and appended materials.

Editorial formatting changes to align with the Format and Content of a REMS Document Guidance are also necessary. See attached redlined document. Incorporate additional changes made to the document as well as address areas where we have requested further clarification.

### 2.3 REMS APPENDED MATERIALS

Revisions to the REMS appended materials are needed for the REMS to be acceptable. After review, we note that most materials are quite text-heavy and there remains redundancy throughout the educational materials. Therefore, we request that you streamline the REMS materials with more concise messaging and information to prevent message fatigue and to be most effective. We have provided edits in tracked changes as well as additional comments that must be addressed in your materials, however there is a need to further streamline the materials and re-submit to the Agency for review. See attached redlined documents.

In addition, incorporate the following changes throughout all materials to align with changes to the REMS document:

- Change the risk from “ (b) (4) ” to “valvular heart disease and pulmonary arterial hypertension”
- Removal of “ (b) (4) ” when referring to the risk (b) (4)

Further, the definition of fenfluramine-associated VHD has been changed and needs to align with the generally accepted case definition used by the FDA as noted below:

The definition of fenfluramine-associated VHD has been changed and is no longer consistent with the generally accepted case definition used by FDA, used during the development program, and referenced in published articles. This new definition is more restrictive, requiring more abnormalities on ECHO and that patients be symptomatic to be considered to have fenfluramine-associated VHD. We do not believe that there is sufficient evidence to narrow the definition. Additionally, the more restrictive definition is inconsistent with that planned for the Boxed Warning in the labeling. Lastly, by making the definition of VHD more restrictive, patients may be misclassified as not having VHD and the risk vs. benefit may not be assessed appropriately, leaving patients at greater risk of negative outcome.

Please see attached redlined materials. Additional specific changes are outlined below.

#### FINTEPLA REMS Program Overview

The Program Overview has been reworded and reorganized to align with the REMS document and other appended materials. Incorporate editorial changes throughout the document.

By way of example, we suggest you review the FDA-approved PALYNZIQ REMS Program Overview and JYNARQUE REMS Program Overview in the public domain.

#### FINTEPLA REMS Enrollment Forms for Prescriber, Pharmacy, and Patients:

All attestations which are included in the enrollment forms should reflect the language in the REMS document and program requirements. Limit the length of the Prescriber and Patient Enrollment Forms to one page (front and back).

#### FINTEPLA REMS Prescriber Guide

Re-name this material to “Prescriber Training.” Streamline the content of the training and change to a presentation format. By way of example, we suggest you review the FDA-approved TURALIO REMS Prescriber Training in the public domain. In addition, incorporate the importance of completion of patient monitoring (echocardiogram (ECHO)) for early detection of the conditions.

#### FINTEPLA REMS Pharmacy Guide

Streamline the content of this guide to make it more user friendly. Add information regarding the pharmacy process for obtaining authorization to dispense Fintepla (and therefore verification of prescriber certification, patient enrollment and receipt of patient status form) and what the pharmacy must do once the authorization status is received, specifically detailing situations when an updated patient status form is not on file, when the pharmacy is given an “Authorized-Warning” alert or a “Not Authorized” alert.

#### FINTEPLA REMS Patient Guide

Incorporate editorial changes throughout the document. Re-arrange the content to focus on the risk messaging at the beginning of the guide. Incorporate language to emphasize the importance of monitoring (ECHO) for early detection of the conditions.

#### FINTEPLA REMS Program Letter for Healthcare Providers

Streamline the content within the healthcare provider letter and limit to one page if possible.

#### FINTEPLA Prescriber Knowledge Assessment

Add an additional question to assess the prescriber’s understanding of the importance to have ECHO performed for early detection of the conditions due to some patients being asymptomatic. Also, incorporate editorial changes throughout the document. Further, the knowledge assessment questions should be revised to reflect the final version of the label and REMS Document.

#### FINTEPLA REMS Website Screenshots

The REMS website, in its entirety should be updated with the most recent version of the REMS document and REMS materials (i.e. guides, and forms). Additional revisions are included below:

**REMS website home page:** Remove the deleted language [REDACTED] <sup>(b) (4)</sup> and replace with language below:

#### **What is the FINTEPLA REMS (Risk Evaluation and Mitigation Strategy)?**

A REMS is a strategy to manage known or potential risks associated with a drug and is required by the U.S. Food and Drug Administration (FDA) to ensure that the benefits of

the drug outweigh its risks. FINTEPLA is available only through a restricted distribution program called the FINTEPLA REMS because of the risk of regurgitant valvular heart disease and pulmonary arterial hypertension

Include the following language below “What is the FINTEPLA REMS”?

#### **FINTEPLA REMS Overview**

- Only certified healthcare providers can prescribe FINTEPLA.
- Only certified pharmacies can dispense FINTEPLA.
- Educate patients on the risks of developing problems with the heart valves or high blood pressure in the arteries of the lungs.
- Enroll all patients in the REMS.

Since online enrollment is an option, you must re-submit the screenshot(s) of what the new window(s) would look like as part of the functionality of your website submission. This would include the data fields to complete, and the information that pops up for the relevant stakeholders to read. Submit a complete set of REMS website screenshots showing all content and functionality of the website. Both a .pdf and a word version should be submitted for review.

The REMS-related webpages should not be a means to promote FINTEPLA or any other Zogenix product.

#### **2.4 REMS SUPPORTING DOCUMENT**

Changes to the supporting document are necessary. See the redlined document. In general, the supporting document should expand on information in the REMS document and provide additional information about the REMS such as rationale for the need of each of the REMS requirements. The goal should be updated to match the REMS document and the revisions made to the appended materials should align with supporting document as well. Additional details are needed to explain further how each stakeholder (prescribers, pharmacies, and patients) is engaged with the various elements of the REMS from a procedural standpoint. Specifically:

- ETASU section - Provide additional information for each requirement/element to expand on information in the REMS document such as the rationale for and supporting information about the design and implementation of the REMS.
- Detail is needed to outline the outpatient and inpatient pharmacy requirements verification and documentation procedures. Include further explanation of how the pharmacies obtain authorization to dispense, what responsibilities the pharmacy, Zogenix or the REMS Coordinating Center have for each scenario (Authorized, Authorized-Warning, and Not-Authorized), and how prescribers and patients are notified when the patient status form is due or past-due and how the notification is documented. Additional details regarding these processes should be incorporated in the supporting document.

- Further explain your distribution requirements and how wholesaler-distributors become authorized to distribute.
- Describe how the REMS will identify patients "not under the care of a certified Prescriber" and if this is limited to the inpatient setting
- Describe how you will distinguish between a "(b) (4)" and a "discontinuation of treatment"

### 2.4.1 Assessment Plan

Update the Assessment Plan based on the changes to the REMS document and appended materials. As submitted, the Fintepla REMS Assessment Plan does not accurately capture all required data metrics, does not align with the draft guidance "REMS Assessment: Planning and Reporting" and does not align with the Agency's goal to be able to compare reported metrics to prespecified thresholds. Therefore, we have created a new assessment plan with content that the Agency believes should be captured as part of the assessment of the Fintepla REMS. When you resubmit your materials, submit a new overview that aligns with your submitted assessment plan.

The Agency's preliminary proposal for the Fintepla REMS Assessment Plan is detailed below. Additional metrics and comments will be provided on the Health Outcomes and/or Surrogates of Health Outcomes and will be combined with the updated Cardiac Adverse Event Reporting Form in a future response to the Applicant. As we complete the review of the application, we anticipate there will be further comments and revisions that will be forthcoming.

#### 2.4.1.1 General Comments for the Assessment Plan

The assessment plan categories were identified in the overview, but those categories were not used as headings in the Assessment Plan. The Agency has aligned the assessment plan metrics with the draft guidance "REMS Assessment: Planning and Reporting".

A threshold of (b) (4) % for all metrics except surveys has been identified. A (b) (4) % threshold is aspirational but likely unattainable. The Agency proposes that the thresholds not be set at (b) (4) %. Initially, while opportunities for improvement of the system and iterative improvement activities are being undertaken the REMS is likely to be function with a failure rate of 10-2. By year 4 the Agency anticipates that those metrics of the REMS associated with restrictions to drug dispensing, will function at the 10-3 level and the threshold will be set at that level.<sup>1</sup> Please adjust accordingly.

You may submit evidence for alternative thresholds from other sources, including health service research and quality improvement projects, preferably nationwide and collaborative, that would align with the goals of the REMS. For example, identifying the compliance with American Heart Association recommendations on obtaining echocardiograms in pediatric patients with acute ischemic stroke might be a useful benchmark. A comparison of the impact of the Fintepla REMS compared with a guideline without restrictions that evaluated compliance with pediatric neurologists ordering echocardiograms may prove useful.<sup>2</sup>

As described in the draft guidance “Survey Methodologies to Assess REMS Goals That Relate to Knowledge: Guidance for Industry” released in January 2019, you should provide a rationale for survey thresholds for each key risk message on a case by case basis. The thresholds identified should consider the public health consequences of the risk being addressed and the educational level of the stakeholders being surveyed. In the rationale, provide evidence related to the expected baseline knowledge of the risks by stakeholders without the REMS and thresholds that can be obtained by the provision of educational material to the targeted stakeholders.

Tables, figures or flow diagrams may be used where appropriate. Flow diagrams similar to those used in Consort reporting may be modified to help clarify the exclusion and inclusion of stakeholders for appropriate metrics.<sup>3</sup>

We advise you to avoid the abbreviation “AR” in the supporting document, assessment plan, and assessment report due to the risk of misinterpretation. The abbreviation is currently used in the supporting document both to identify aortic regurgitation and assessment report. Additionally, AR is often used in REMS assessment reports to identify the Authorized Representative.

When “other” is a category identified in a REMS assessment metric provide sufficient categories and group similar responses so that no more than 10% of the responses are identified as “Other” in the REMS assessment report.

## **2.4.2 Assessment Plan**

As submitted, the Fintepla REMS Assessment Plan does not accurately capture all required data metrics, does not align with the draft guidance “REMS Assessment: Planning and Reporting” and does not align with the Agency’s goal to be able to compare reported metrics to prespecified thresholds. Therefore, we have created a new assessment plan with content that the Agency believes should be captured as part of the assessment of the Fintepla REMS. Please review, make edits as you see pertinent and re-submit with redlined and clean versions for review. Submit a new overview that aligns with your submitted assessment plan.

### 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 date(s) and number of REMS materials packets sent by method of distribution
  - d. The number of mailings successfully delivered, returned or undeliverable. The number of emails successfully delivered, opened, and unopened emails.

### 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 Fintepla website became live and fully operational
  - c. Date prescribers could become certified
  - d. Date when pharmacies could become certified

- e. Date when patients could become enrolled
  - f. Date when the REMS Coordinating Center was established and fully operational
3. REMS Certification and Enrollment Statistics (provide for each reporting period and cumulatively)
- a. Healthcare provider certification in the REMS
    - 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 of Osteopathic Medicine, Advanced Nurse Practitioner, Physician Assistant, Other) specialty, and geographic region (defined as US Census Regions)
    - ii. A summary of the methods of healthcare provider certification
    - iii. The number of healthcare providers who were unable to become certified, accompanied by the reason 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 in the REMS
    - i. The number of newly certified, active (i.e. have dispensed Fintepla), and recertified pharmacies stratified by pharmacy type (i.e. inpatient, outpatient) and geographic region (defined as US Census Regions)
    - ii. A summary of the methods of pharmacy certification
    - iii. The number of pharmacies that were unable to become certified, accompanied by the reason 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 in the REMS
    - i. The number of newly enrolled patients stratified by age, gender, race, ethnicity and geographic region (defined by US Census regions)
    - ii. The number of active patients by stratified by age, gender, race, ethnicity and geographic region (defined by US Census regions)
    - iii. A summary of the methods of patient enrollment
4. Fintepla Utilization Data (provide for each reporting period and cumulatively)
- a. Pharmacy and Wholesaler/Distributor data stratified by pharmacy type (i.e. outpatient including specialty pharmacies), inpatient)
    - i. The number of shipments sent to pharmacies stratified by quantity per shipment.
    - ii. The geographic distribution of the certified inpatient pharmacies and outpatient pharmacies (defined by US Census regions)
  - b. Prescriber data stratified by specialty, healthcare provider type, geographic region (defined by US census data)
    - i. The number of prescriptions (new and refills) stratified by quantity dispensed per prescription.
    - ii. The number of prescribers who wrote Fintepla prescriptions that were dispensed:
      - the number of dispensed prescriptions written by each prescriber

- the number of patients for whom dispensed prescriptions were written by each prescriber.
- iii. The number of prescriptions (new or refills) that were not dispensed with the reasons for the inability to dispense including but not limited to:
  - Prescriber not certified
  - Patient not enrolled
  - REMS program did not authorize dispense for other reasons (identify these reasons)
- iv. The number of prescriptions dispensing delays
  - whether the prescription was new or a refill
  - a measure of central tendency and variability for dispensing delays
  - listing and summary of all reasons for delays in prescription dispensing
  - including an assessment and rationale for why the reasons were related to the REMS and any additional information on reasons for delay including issues related to insurance payers.

Include in your supporting document a definition of dispensing delay with this metric and the rationale for identifying a specific time period as a delay).

- iii. The number of unique patients receiving Fintepla.

5. REMS Infrastructure and Performance (provide previous, current and cumulative reporting periods)

a. REMS Website

- i. The number of visits and unique visits to the REMS website
- ii. The number of REMS materials downloaded or printed for each material from the website.

b. REMS Coordinating Center

- i. The number of contacts received by the Fintepla REMS coordinating center, stratified by stakeholder type.
- ii. The number of REMS materials requested using the REMS call center. Summary of reasons for calls (e.g., enrollment question) and by reporter (stakeholder). The summary must account for 80% of calls by each stakeholder or the top five reasons for calls.
- iii. If the summary reasons for the call indicate access issues, unanticipated burden or adverse events provide a description of each call stratified by stakeholder.
- iv. Summary of corrective actions resulting from issues identified

6. REMS Compliance (provide previous, current and cumulative reporting periods)

a. Identify Thresholds for non-compliance for defined metrics

- b. Provide a copy of the non-compliance plan, including the criteria for non-compliance for each stakeholder, actions taken to address non-compliance for each case, and which event lead to de-certification from the REMS

- c. Provide a summary of non-compliance identified, including but not limited to:
- i. A unique ID for each stakeholder that was found to be in non-compliance or had a deviation identified to track this by unique stakeholder over time.
  - ii. The source of the noncompliance data
  - iii. The root cause analysis of noncompliance identified
  - iv. The number of shipments distributed to non-certified pharmacies. Also provide this metric as a percentage of all shipments distributed.
  - v. The number of dispensed prescriptions written by non-certified prescribers in the outpatient setting (also provide this metric as a percentage of all dispensed prescriptions in the outpatient setting).
    - Identify if the dispenses were for a 30 day or a 90 day dispense (when calculating the percentage for all dispensed prescriptions adjust all dispenses to 30 day dispense e.g. each 90 day dispense is equivalent to a three 30 day dispenses.)
    - If the echo had been obtained.
    - If the prescriber was later certified.
    - Time between the prescription dispense and the prescriber's certification. Provide a measure of central tendency and variability for this metric.
  - vi. The number of dispensed prescriptions written by non-certified prescribers for a patient not under the care of a certified prescriber in the inpatient setting (also provide this metric as a percentage of all dispensed prescriptions in the inpatient setting).
    - If the echo had been obtained or not
    - If the prescriber was later certified
    - Time between the prescription dispense and the prescriber's certification. Provide a measure of central tendency and variability for this metric.
  - vii. The number of prescriptions dispensed to non-enrolled patients (also provide this metric as a percentage of all dispensed prescriptions). Stratified by inpatient and outpatient pharmacies
    - If the echo had been obtained or not,
    - If the patient was later enrolled
    - The time between the prescription dispense and the prescriber's certification. This metric should be stratified by inpatient and outpatient pharmacies
  - viii. The number of prescriptions dispensed for non-enrolled patients written by a noncertified prescriber (also provide this metric as a percentage of all dispensed prescriptions) (Stratify by inpatient and outpatient pharmacies). Link these

cases so that the agency can identify how this data links with the specific root causes of dispensing from an uncertified prescriber and dispensing to a non-enrolled patient from the previous metrics.

- ix. The number of times that a Fintepla prescription was dispensed by a certified pharmacy that bypassed the REMS authorization process (provide this also as a percentage of all dispensed prescriptions) (Stratify by inpatient and outpatient pharmacy.
  - the status of the prescribers (certified or not) the status of the patient(s) (enrolled or not)
  - the presence of a current status form or not
  - If the echo had been obtained or not.
- x. The number of patients who received Fintepla who were not enrolled in the REMS registry.
  - Provide this metric as a percentage of all patients who were dispensed Fintepla
  - Provide this metric as a percentage of all patients enrolled in the REMS registry
- xi. The number of instances of noncompliance during the reporting period and cumulatively not identified previously, accompanied by a description of each instance and the reason for the occurrence (if provided).
- xii. Provide a copy of the current audit plan for each stakeholder, the number of active stakeholders targeted for audit, and the number who completed the audit.
  - i. Report of audit findings for each stakeholder (REMS Call Center, pharmacies and wholesalers/distributors)
    - The number of audits expected, and the number of audits performed
    - The number and types of deficiencies noted for each group of audited stakeholders
    - For those with deficiencies noted, report the number that successfully completed a corrective and preventive action (CAPA) plan within one month of audit
    - For those with deficiencies noted, report the number that successfully completed a corrective and preventive action (CAPA) plan within one month of audit
    - For any that did not complete the CAPA within one month of the audit, describe actions taken
    - Documentation of completion of training for relevant staff

- The existence of documented processes and procedures for complying with the REMS
- Verification that each audited stakeholder’s site that the designated authorized representative remains the same. If different, include the number of new authorized representatives and verification of the site’s recertification

Include in your supporting document that critical events in the audit must include a single occurrence of:

- Dispensing to a non-enrolled patient in the inpatient or outpatient setting.
- Dispensing a prescription written by a non-certified prescriber in the outpatient setting.
- Dispensing after obtaining a “Not Authorized” status.
- Dispensing after bypassing the Authorization process.

Include in your supporting document the protocol for all root cause analyses by stakeholder, and that a root cause analysis will identify the findings for the cause of the non-compliance(s) identified in the root cause analysis, any corrective actions taken to address findings, the status of corrective actions, and any resulting preventative actions taken.

#### Safe Use Behaviors

7. Patient Status Forms (provide previous, current, and cumulative data).
  - a. Provide a summary of safe use behaviors related to Patient Status Forms, including but not limited to:
    - i. The number of patients with a Patient Status Form who were dispensed a new prescription for Fintepla (Provide this metric as a percentage of all patients who were dispensed Fintepla) (Stratify by inpatient and outpatient)
    - ii. The number of patients without a Patient Status Form who were dispensed a new prescription for Fintepla.
      - Stratify as to whether the patient had an echo or not.
      - Reasons echo not obtained
      - Link this information to pharmacy noncompliance data so that the Agency can identify the RCA that is associated with these events occurring.
      - Provide the source(s) of this data

The number of patients who had a completed Patient Status Form submitted within 6 months of their most recent Patient status form (Provide this metric as a percentage of patients who were dispensed Fintepla and had not had a Patient Status form documenting discontinuation of Fintepla).

- The distribution of the time between the previous Patient Status Form on record with the REMS and the submission of a subsequent Patient Status Form. (Provide an appropriate measure of central tendency and an appropriate measure of variability)
- iii. The number of patients who did not have a completed Patient Status Form (Outstanding Patient Status Form) submitted within 6 months of their most recent Patient Status Form. Provide this number as a percentage of expected patient status forms.
  - Types and frequency and outcomes of outreach activities performed to obtain outstanding forms.
  - Provide the number of authorized warnings sent to pharmacies
- iv. The number of patients who had a Patient Status Form within 9 months of their most recent Patient Status Form. (Provide this metric as a percentage of patients who were due a Patient Status Form at 6 months and did not have one submitted).
  - The distribution of the time between the previous Patient Status Form on record with the REMS and the submission of a subsequent Patient Status Form. Include a measure of central tendency and variability of the data
- v. The number of patients who did not have a patient status form within 9 months of their most recent Patient Status Form who had not discontinued Fintepla within 72 hours of the day the patient status form was due. Provide this metric as a percentage of patients who were due a Patient Status Form at 6 months and did not have one submitted).
  - Stratify as to whether the patient had an echo or not. If the echo was not obtained provide a reason.
  - Link this information to the pharmacy noncompliance data so that the Agency can identify the RCA that is associated with these events.
- vi. The number of patients who were continually dispensed Fintepla for 9 months or more (inpatient dispensing included) who did not have a Patient Status Form submitted within 15 months of a previous Patient Status Form.
  - Stratify as the whether the patient had and echo or not. If the echo not obtained provide a reason.
  - Link this information to pharmacy noncompliance data so that the Agency can identify the RCA that is associated with these events occurring
- vii. The number of patients who had a complete Patient Status Form submitted within 3-6 months after discontinuing treatment with Fintepla. Also provide this metric as a percentage of all patients who were identified as discontinuing treatment based on

- a submitted Patient Status Form
  - no longer receiving dispenses of Fintepla for the past 6 months.
- viii. The number of patients who did not have complete Patient Status Form submitted within 3-6 months after discontinuing treatment with Fintepla. Also provide this metric as a percentage of all patients who were identified as discontinuing treatment based on
- a submitted Patient Status Form
  - no longer receiving dispenses of Fintepla for 6 months.

Include in your supporting document when Patient Status Forms are not obtained potential reasons for not obtaining an echocardiogram. Consider the following reasons; Echo could not be scheduled due to lack of availability at preferred location, Transportation issues with getting to echo, Cost issues (change in insurance, no insurance), Prescriber felt unnecessary, Patient lost to follow up, Patient changing prescribers, Patient lost to follow up, Patient did go for Echo but was unable to complete (reasons why), other reasons that may contribute to understanding of factors contributing to failure of REMS to ensure echocardiograms obtained on the required schedule. Identify if information came from patient or provider's perspective.

Include in your supporting document a mechanism to obtain feedback from prescribers the reason the patients status form was not completed and suggestions on reducing the paperwork burden associated with the patient status form. Consider the following suggestion options; incorporate form into electronic health record, allow prescriber to fax echo results directly to REMS, contact designated representative for results of echo.

- ix. Number of unique patients who experience a treatment interruption, duration of treatment interruption and reason for treatment interruption.
- Identify the definition of treatment interruption and compare to the definition of discontinued treatment.

Include in your supporting document potential reasons for a treatment interruption including cardiac toxicity, patient had not received echocardiogram, no status form received, prescriber elected to stop medication and then resumed, patient changed providers, and insurance issues. Identify the definition of treatment interruption and compare to the definition of discontinued treatment.

- x. Number of unique patients who were not authorized to receive Fintepla due to the Echo not being completed and the reason the Echo was not completed. Provide this metric as a percentage of all patients who were receiving Fintepla and were in compliance with the REMS requirements.
- xi. Beginning with the 2 year assessment provide an analysis of the estimated travel time for patients to a tertiary care site capable of providing the echocardiogram evaluation. Provide a similar analysis of the estimated travel time between patients, the certified prescribers who enrolled them, and a tertiary care site capable of providing the echocardiogram evaluation. Provide a measure of central tendency, variability, and extremes of the data

## Knowledge

8. Post-Training Knowledge Assessments (provide previous, current, and cumulative reporting periods)
  - a. Number of completed post-training Knowledge Assessments for prescribers including method of completion and number of attempts to complete
  - b. Summary of the most frequently missed Knowledge Assessment questions.
  - c. A summary of potential comprehension or perception issues identified with the Knowledge Assessment
9. Healthcare Provider Surveys
  - a. Surveys will be conducted among a random sample of healthcare providers who are certified to prescribe Fintepla. The purpose of the healthcare provider survey is to evaluate the effectiveness of the REMS in communicating the risk associated with Fintepla. Specifically, the survey will assess healthcare providers' understanding of the REMS key messages:
10. Patient/caregiver Surveys
  - a. Surveys will be conducted among a random sample of patients (or caregivers) who have used Fintepla to evaluate the effectiveness of the REMS in communicating the serious risks associated with Fintepla. Specifically, the survey will assess patients' (or caregivers') understanding of the REMS key risk messages:

## Health Outcomes and/or Surrogates of Health Outcomes

The metrics under this heading are currently under review and will be provided in the future.

## Resubmission Instructions

- Your complete REMS proposal should be submitted as separate documents in the same submission, to include both a Word tracked changes version, a Word clean version as well as a .pdf version of each of the previously mentioned documents and appended materials.
- Include all final formatting when submitting REMS materials in your next submission, including any logos, coloring, shading, or other design features.

Additionally, we refer you to the [REMS@FDA](mailto:REMS@FDA) website, which references multiple approved REMS programs which you may find useful.

Please submit your complete REMS proposal by May 29, 2020.

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<sup>1</sup> T. Nolan, R. Resar, C. Harden. Improving the Reliability of Health Care. In: IHI Innovation Series White Paper. Boston: Institute for Healthcare Improvement; 2004.

<sup>2</sup> Ferriero DM, Fullerton HJ, Bernard TJ, et al. Management of Stroke in Neonates and Children: A Scientific Statement From the American Heart Association/American Stroke Association. *Stroke*. 2019;50(3): e51-e96.

<sup>3</sup> Schulz KF, Altman DG, Moher D. CONSORT 2010 Statement: updated guidelines for reporting parallel group randomized trials. *BMJ (Clinical research ed)*. 2010;340:c332.

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**Division of Risk Management (DRISK)**  
**Office of Medication Error Prevention and Risk Management (OMEPRM)**  
**Office of Surveillance and Epidemiology (OSE)**  
**Center for Drug Evaluation and Research (CDER)**

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|-------------------------------|------------------------------------|
| <b>Application Type</b>       | NDA                                |
| <b>Application Number</b>     | 212102                             |
| <b>PDUFA Goal Date</b>        | June 25, 2020                      |
| <b>OSE RCM #</b>              | 2019-393                           |
| <b>Reviewer Name(s)</b>       | Carlisha Gentles, PharmD           |
| <b>Team Leader</b>            | Laura Zendel, PharmD               |
| <b>Division Director</b>      | Jamie Wilkins, PharmD              |
| <b>Review Completion Date</b> | April 7, 2020                      |
| <b>Subject</b>                | Evaluation of Need for a REMS      |
| <b>Established Name</b>       | Fenfluramine                       |
| <b>Trade Name</b>             | Fintepla                           |
| <b>Name of Applicant</b>      | Zogenix                            |
| <b>Therapeutic Class</b>      | Anti-convulsant                    |
| <b>Formulation(s)</b>         | 2.5 mg/ml Oral Solution            |
| <b>Dosing Regimen</b>         | 0.2 mg/kg to 0.8 mg/kg twice daily |

# 1 Introduction

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The following comments and the attached redlined REMS document, supporting document and appended materials are based on the Agency's review of the proposed REMS for Fintepla submitted to NDA 212102 on September 25, 2019. To facilitate further review, we ask that the Applicant revise the REMS proposal based on the following comments and redlined documents then resubmit a complete REMS amendment within 14 calendar days, by close of business (COB) April 21, 2020. Review of the REMS document, supporting document, and appended materials is ongoing; this should not be considered final.

## 2 Comments for the Applicant

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### 2.1 GENERAL COMMENTS

As discussed during a March 18, 2020 teleconference held between Zogenix and the Agency, the Agency agrees that a REMS is necessary for fenfluramine, however, we do not agree with the REMS requirements as initially proposed. The REMS requirements should include prescriber certification (ETASU A), pharmacy certification (ETASU B), safe use conditions to include patient counseling and enrollment (ETASU D), monitoring (ETASU E), a REMS registry (ETASU F) and a communication plan (CP). The Medication Guide should be removed as an element of the REMS but retained as part of the proposed labeling for Fintepla. We have revised the REMS document and appended materials as shown in the attached redlined documents. The recommendations provided here are based on the current proposed labeling. However, all communication materials must be revised to be consistent with the final FDA-approved labeling.

### 2.2 REMS DOCUMENT

Revisions to the REMS document are necessary to be acceptable.

#### REMS Goal:

The goal of the REMS have been revised to reflect changes in the REMS requirements.

#### Pharmacy Requirements:

Additionally, the REMS document should include details to outline requirements to establish processes and procedures for verification of safe use conditions and completion of monitoring requirements. The process should incorporate usage of a patient authorization prior to dispensing.

Further, there will need to be different processes and procedures for an inpatient pharmacy versus outpatient pharmacy. If continuing therapy for a currently enrolled patient, a prescriber may continue therapy as long as the patient is enrolled and therefore assumed to be under the care of a certified prescriber. See attached redlined document.

Review of the REMS document is ongoing; these comments should not be considered final.

### 2.3 REMS APPENDED MATERIALS

The Agency is requiring the following additional materials to be developed: FINTEPLA REMS *Program Overview* and a *Prescriber Knowledge Assessment*. Further, the Agency is requiring the pharmacy enrollment form to be split into an *Inpatient Pharmacy Enrollment Form* and an *Outpatient Pharmacy Enrollment Form* and the Prescriber and Pharmacy Guide to be split into a *Prescriber Guide* and a *Pharmacy Guide*. Separation of the inpatient and outpatient pharmacy enrollment forms as well as the pharmacy and prescriber guide will allow for greater details to be provided for each stakeholder to ensure that the requirements of the FINTEPLA REMS are being met and decrease confusion. Further, the Agency’s current thinking has changed regarding both the naming of the FINTEPLA REMS and referencing the titles of REMS materials within the content of the REMS materials. Using the term “Program” as part of the name of the FINTEPLA REMS is no longer necessary. In addition, repeating the prefix “FINTEPLA REMS Program” when referencing various materials within the content of the material is redundant, resulting in more text for the REMS participant to read making the information longer and more difficult to read. We request that you make these changes within all materials with the exception of the REMS Program Overview. You can leave that name as the FINTEPLA REMS Program Overview. Also, note that the title that appears at top of each material will still contain “FINTEPLA REMS Program” so that the material is identifiable. We are only requesting this change within the content of the materials.

#### FINTEPLA REMS Program Overview

The Agency requests that you create an overview that describes the requirements of the FINTEPLA REMS Program and the responsibilities of each relevant stakeholder including prescribers, pharmacies (pharmacist) and patients. Please limit the number of pages to a maximum of 2-4, or 1-page front and back, if possible.

The FINTEPLA REMS Program Overview should include the following subheadings:

**What is the FINTEPLA REMS?**

**How does the FINTEPLA REMS work?**

**What are the requirements of the FINTEPLA REMS?**

- Prescriber Requirements
- Pharmacy Requirements
- Patient Requirements

By way of example, we suggest you review the FDA-approved PALYNZIQ REMS Program Overview and JYNARQUE REMS Program Overview in public domain.

#### FINTEPLA REMS Prescriber Enrollment Form

See attached redlined version of the Prescriber Enrollment Form. The instructions should be simplified, and attestations adjusted to correspond with the REMS document.

FINTEPLA REMS Prescriber Guide

Separate the Prescriber and Pharmacy Guide into a separate Prescriber Guide and Pharmacy Guide. The new Prescriber Guide should reflect revisions made to the REMS Document. See the attached redlined version of the Prescriber and Pharmacy Guide.

The Prescriber Guide should include the following headings and subheadings:

**What is FINTEPLA?**

**Serious Risk of** [redacted] (b) (4)

- Additional Risks and Safety Information

**What is the FINTEPLA REMS?**

[redacted] (b) (4)

[redacted] (b) (4)

**What are the Requirements of the FINTEPLA REMS?**

**Prescriber** [redacted] (b) (4)

**How Does a** [redacted] (b) (4) **Become Certified in the FINTEPLA REMS?**

- [redacted] (b) (4)
- [redacted]
- At all times

[redacted] (b) (4)

By way of example, we suggest you review the FDA-approved PALYNZIQ REMS Prescriber in public domain.

FINTEPLA REMS Pharmacy Guide

The Agency requests that you create a Pharmacy Guide separate from the Prescriber Guide that describes the requirements of the FINTEPLA REMS Program, the responsibilities of each relevant stakeholder including prescribers, pharmacies (pharmacist) and patients, separate processes and procedures for the inpatient and outpatient pharmacy settings, and the verification process used to determine if patient is authorized to receive treatment. Align with revisions made to the REMS document.

The REMS Pharmacy Guide can include the following subheadings:

**What is the FINTEPLA REMS?**

## **Outpatient Pharmacy Overview of the FINTEPLA REMS**

## **Inpatient Pharmacy Overview of the FINTEPLA REMS**

## **What are the Requirements of the FINTEPLA REMS?**

## **How Does a Pharmacy Become Certified in the FINTEPLA REMS?**

- Before Dispensing FINTEPLA (to includes details on the verification process to be used)
- Dispensing FINTEPLA and During Treatment
- At all times

Additionally, the Pharmacy Guide should include the following detail regarding authorization status based upon how you intend to operationalize your system. The authorization status provided by your systems should include:

1. Authorized – proceed with dispensing prescription
2. Authorized– proceed with dispense (ex. Patient late on ECHO, but not outside of 3-month grace period) however, follow up with prescriber/patient with reminder for monitoring and date where dispensing will no longer occur
3. Not authorized – patient not authorized to receive medication (ex. Patient late on ECHO and is outside of 3-month grace period or prescriber has discontinued therapy)

Further, outline that in the inpatient setting, if continuing therapy for a currently enrolled patient, a prescriber may continue therapy as they are assumed to be under the care of a certified prescriber. New initiation of therapy does need to be completed by a certified prescriber.

By way of example, we suggest you review the FDA-approved Bosentan REMS Pharmacy Guide in public domain.

### FINTEPLA REMS Outpatient Pharmacy Enrollment Form

The Agency requests that you create a separate Outpatient Pharmacy Enrollment Form and Inpatient Pharmacy Enrollment Form. The proposed REMS Program Pharmacy Enrollment Form can be used as a basis for the Outpatient Pharmacy Enrollment Form. See the attached redlined version of Pharmacy Enrollment Form. By way of example, we suggest you review the FDA-approved JYNARQUE REMS Program Pharmacy Enrollment and PALYNZIQ REMS Program Pharmacy Enrollment in public domain.

### FINTEPLA REMS Inpatient Pharmacy Enrollment Form

The Agency requests that you create a separate Inpatient Pharmacy Enrollment Form. The proposed REMS Program Pharmacy Enrollment Form can be used as a basis for the Inpatient Pharmacy Enrollment Form. However, the Inpatient Pharmacy Enrollment Form will need to include information specific to the inpatient pharmacy and a pharmacy agreement with attestations addressing dispensing and verification requirements in the inpatient pharmacy setting. By way of example, we suggest that you review the FDA-approved Bosentan REMS Inpatient Pharmacy Enrollment Form in public domain.

#### FINTEPLA REMS Patient Enrollment Form

See the attached redlined version of the Patient Enrollment Form. The form should be limited to one page in length. The content should be updated to match the REMS document.

#### FINTEPLA REMS Patient Guide

See the attached redlined version of the Patient Guide. The title of this guide should be changed to “FINTEPLA REMS Patient Guide.” Consider creating an easy to read and understand flow chart with patient responsibilities before, during, and after treatment with the drug. Please refer to the JYNARQUE REMS Patient Guide, or PALYNZIQ REMS Patient Guide for examples. The information presented here should mirror the patient section of the REMS document.

#### FINTEPLA REMS Program Patient Status Form

See the attached redlined version of the Patient Status Form document. Outcome data obtained from patient monitoring will be necessary, therefore edits have been made to incorporate this information. The content should be updated to match the REMS document. Further, incorporate additional data fields to collect more information for the REMS registry.

#### FINTEPLA REMS Program Letter for Healthcare Providers

See the attached redlined version of the Letter for Healthcare Providers. The content should be updated to match the REMS document.

#### FINTEPLA REMS Website Screenshots

See the attached redlined version of the Websites Screenshots. Refer to Jynarque REMS Program or Palynziq REMS Program websites as examples. Update the content to match the REMS document and enrollment forms. Submit both a .pdf and a word version for review.

The REMS-related webpages should not be a means to promote FINTEPLA or any other Zogenix product.

## **2.4 REMS SUPPORTING DOCUMENT**

Changes to the supporting document are necessary. See the document for tracked changes. In general, the supporting document should expand on information in the REMS document and provide additional information about the REMS such as rationale for the need of each of the REMS requirements. The goal should be updated to match the REMS document. Detail is needed to outline the outpatient and inpatient pharmacy requirements to establish processes and procedures for verification of safe use conditions and completion of monitoring requirements. The system should have a dispensing

restriction, where the patient will no longer be able to receive FINTEPLA, at 9 months if patient did not complete the required monitoring in the last 6 months. If the patient has not completed monitoring at month 6, a warning should be provided, prescriber notified, and patient given a 3-month grace period. Verification that a patient is authorized to receive drug (i.e. monitoring requirements have been met) will need to be integrated into your pharmacy certification requirements. Three potential outcomes for patient authorization should be included so that there is a grace period built into dispensing should a patient experience access or scheduling issues to complete the mandatory monitoring (up to 90 days grace period). The three outcomes should be:

- Authorized – proceed with dispensing prescription
- Authorized– proceed with dispense (ex. Patient late on ECHO, but not outside of 3-month grace period) however, follow up with prescriber/patient with reminder for monitoring and date where dispensing will no longer occur
- Not authorized – patient not authorized to receive medication (ex. Patient late on ECHO and is outside of 3-month grace period or prescriber has discontinued therapy)

Additionally, there will need to be different processes/procedures requirements as mentioned above for an inpatient pharmacy versus outpatient pharmacy. With the inpatient pharmacy:

- If the patient is a new start, the standard procedures of prescriber certification, patient enrollment and pharmacy enrollment would occur.
- If continuing therapy for a currently enrolled patient, a prescriber may continue therapy as they are assumed to be under the care of a certified prescriber. New initiation of therapy does need to be completed by a certified prescriber.

Include whether the verification process will include a call to the REMS Center, usage of a portal, or usage of a switch system.

### **2.4.1 Assessment Plan**

Update the Assessment Plan based on the changes to the REMS document and appended materials. Additional comments will be provided after resubmission of the Assessment Plan with the aforementioned updates.

#### Resubmission Instructions

Your complete REMS proposal should be submitted as separate documents in the same submission, to include both a Word tracked changes version, a Word clean version as well as a .pdf version of each of the previously mentioned documents and appended materials.

Additionally, we refer you to the REMS@FDA website, which references multiple approved REMS programs which you may find useful.

Please submit your complete REMS proposal by April 21, 2020.

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