

RISK EVALUATION AND MITIGATION STRATEGY (REMS) Document FINTEPLA (fenfluramine) REMS Program

I. Administrative Information

Application Number: NDA 212102

Application Holder: Zogenix, Inc.

Initial REMS Approval: 06/2020

II. REMS Goals

The goal of the FINTEPLA Risk Evaluation and Mitigation Strategy (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.
 - 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 the long-term safety and safe use of FINTEPLA.

III. REMS Requirements

Zogenix, Inc. must ensure that healthcare providers, patients, pharmacies, and wholesaler-distributors comply with the following requirements:

1. Healthcare providers who prescribe FINTEPLA must:

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| To become certified to prescribe | <ol style="list-style-type: none">1. Review the drug's Prescribing Information.2. Review the following: Prescriber Training and REMS Program Overview.3. Successfully complete the Prescriber Knowledge Assessment and submit it to the REMS Program.4. Enroll in the REMS by completing the Prescriber Enrollment Form and submitting it to the REMS Program. |
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1. Healthcare providers who prescribe FINTEPLA must:

Before treatment initiation (first dose)	<ol style="list-style-type: none">5. Counsel the patient on the risks of valvular heart disease and pulmonary arterial hypertension, including how to recognize and respond to signs and symptoms of valvular heart disease and pulmonary arterial hypertension, and the need for cardiac monitoring via echocardiogram at baseline (treatment initiation), every 6 months during treatment, and once 3 to 6 months after treatment discontinuation using the Patient Guide.6. Provide the patient with the Patient Guide.7. Enroll the patient by completing and submitting the Patient Enrollment Form to the REMS.8. Assess the patient's cardiovascular status and the appropriateness of initiating treatment by obtaining an echocardiogram. Document and submit the results and authorization for treatment to the REMS Program using the Patient Status Form.
During treatment: Every 6 months	<ol style="list-style-type: none">9. Counsel the patient on the need for cardiac monitoring via echocardiogram every 6 months during treatment using the Patient Guide.10. Assess the patient's cardiovascular status and the appropriateness of continuing treatment by obtaining an echocardiogram. Document and submit the results and appropriateness of continued treatment to the REMS Program using the Patient Status Form.
After treatment discontinuation: 3 to 6 months	<ol style="list-style-type: none">11. Assess the patient's cardiovascular status by obtaining an echocardiogram. Document and submit the results to the REMS Program using the Patient Status Form.
At all times	<ol style="list-style-type: none">12. Report adverse events suggestive of valvular heart disease and/or pulmonary arterial hypertension on the Cardiovascular Adverse Event Reporting Form to the REMS Program.13. Report treatment discontinuation or transfer of care to the REMS Program.

2. Patients who are prescribed FINTEPLA:

Before treatment initiation	<ol style="list-style-type: none">1. Review the Patient Guide.2. Enroll in the REMS by completing the Patient Enrollment Form with the prescriber. Enrollment information will be provided to the REMS Program.3. Receive counseling from the prescriber on the risk of valvular heart disease and pulmonary arterial hypertension, including how to recognize signs and symptoms of valvular heart disease and pulmonary arterial hypertension, and the need to get an echocardiogram before treatment, every 6 months during treatment, and once 3 to 6 months after treatment discontinuation using the Patient Guide.4. Get an echocardiogram to check your heart.
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2. Patients who are prescribed FINTEPLA:

During treatment: Every 6 months	5. Receive counseling from the prescriber on the need to get an echocardiogram every 6 months during treatment using the Patient Guide .
	6. Get an echocardiogram to check your heart.
After treatment discontinuation: 3 to 6 months	7. Get an echocardiogram to check your heart.
At all times	8. Inform the prescriber if any signs or symptoms of valvular heart disease or pulmonary arterial hypertension develop.
	9. Inform all healthcare providers about this treatment.

3. Outpatient pharmacies that dispense FINTEPLA must:

To become certified to dispense	1. Designate an authorized representative to carry out the certification process and oversee implementation and compliance with the REMS Program on behalf of the pharmacy.
	2. Have the authorized representative review the Pharmacy Guide and REMS Program Overview .
	3. Have the authorized representative enroll in the REMS Program by completing the Outpatient Pharmacy Enrollment Form and submitting it to the REMS.
	4. Train all relevant staff involved in dispensing FINTEPLA on the REMS requirements using the Pharmacy Guide .
Before dispensing	5. Obtain authorization to dispense by contacting the REMS Program to verify that the prescriber is certified, and the patient is enrolled and authorized to receive the drug.
To maintain certification to dispense	6. Have the new authorized representative enroll in the REMS Program by completing the Outpatient Pharmacy Enrollment Form if the authorized representative changes.
At all times	7. Not distribute, transfer, loan, or sell FINTEPLA, except to certified pharmacies.
	8. Maintain records of dispensing information.
	9. Maintain records that all processes and procedures are in place and being followed.
	10. Maintain records documenting staff's completion of REMS training.
	11. Comply with audits carried out by Zogenix, Inc. or a third party acting on behalf of Zogenix, Inc. to ensure that all processes and procedures are in place and are being followed.

4. Inpatient pharmacies that dispense FINTEPLA must:

To become certified to dispense	1. Designate an authorized representative to carry out the certification process and oversee implementation and compliance with the REMS on behalf of the pharmacy.
	2. Have the authorized representative review the Pharmacy Guide and REMS Program Overview .

4. Inpatient pharmacies that dispense FINTEPLA must:

	<ol style="list-style-type: none">3. Have the authorized representative enroll in the REMS by completing the Inpatient Pharmacy Enrollment Form and submitting it to the REMS.4. Train all relevant staff involved in dispensing FINTEPLA on the REMS Program requirements using the Pharmacy Guide.
Before dispensing	<ol style="list-style-type: none">5. 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.6. 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	<ol style="list-style-type: none">7. Dispense no more than 15 days' supply
To maintain certification to dispense	<ol style="list-style-type: none">8. Have the new authorized representative enroll in the REMS Program by completing the Inpatient Pharmacy Enrollment Form if the authorized representative changes.
At all times	<ol style="list-style-type: none">9. Not distribute, transfer, loan, or sell FINTEPLA10. Maintain records of dispensing information.11. Maintain records that all processes and procedures are in place and being followed.12. Maintain records that document staff's completion of REMS training.13. Comply with audits carried out by Zogenix, Inc. or a third party acting on behalf of Zogenix, Inc. to ensure that all processes and procedures are in place and are being followed.

5. Wholesale-distributors that distribute FINTEPLA must:

To be able to distribute	<ol style="list-style-type: none">1. Establish processes and procedures to ensure that the drug is distributed only to certified pharmacies.2. Train all relevant staff involved in distributing FINTEPLA on the REMS requirements.
At all times	<ol style="list-style-type: none">3. Distribute FINTEPLA only to certified pharmacies.4. Maintain records of all distributions.5. Comply with audits carried out by Zogenix, Inc. or a third party acting on behalf of Zogenix, Inc. to ensure that all processes and procedures are in place and are being followed.

Zogenix, Inc. must provide training to healthcare providers who prescribe FINTEPLA.

The training includes the following educational materials: [Prescriber Training](#), [REMS Program Overview](#), and [Prescriber Knowledge Assessment](#). The training must be available online and in hard-copy format via fax and mail.

Zogenix, Inc. must provide training to pharmacies that dispense FINTEPLA.

The training includes the following educational materials: [Pharmacy Guide](#) and [REMS Program Overview](#). The training must be available online and in hard-copy format via fax and mail.

To inform healthcare providers about the REMS and the risks and safe use of FINTEPLA, Zogenix, Inc. must disseminate REMS communication materials according to the table below:

Target Audience	Communication Materials and Dissemination Plans
Healthcare providers who are likely to prescribe FINTEPLA	<p>REMS Letter: Letter for Healthcare Providers, with attachments: Prescribing Information, Prescriber Training, and REMS Program Overview</p> <ol style="list-style-type: none"> 1. Email within 60 calendar days of the date FINTEPLA is first commercially distributed and again 6 months later. <ol style="list-style-type: none"> a. Send by mail within 30 calendar days of the date of the first email if the healthcare provider’s email address is not available or the email is undeliverable. b. Send a second email within 30 calendar days of the date the first email was sent if the first email is marked as unopened. c. Send by mail within 30 calendar days of the date the second email was sent if the second email is marked as unopened. 2. Disseminate through field-based sales representatives and medical science liaisons during initial/follow-up discussion with healthcare providers for 12 months from the date FINTEPLA is first commercially distributed. 3. Disseminate through the following professional societies and request the letter or content be provided to their members. <ol style="list-style-type: none"> a. American Epilepsy Society; Child Neurology Society; American Academy of Neurology. 4. Disseminate and prominently display at professional meetings where Zogenix, Inc. has a presence for 12 months from the date FINTEPLA is first commercially distributed.

To support REMS Program operations, Zogenix, Inc. must:

1. Authorize dispensing for each patient based on receipt of the [Patient Status Form](#) on the following schedule: 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.
2. Establish and maintain a REMS Program website, www.FinteplaREMS.com. The REMS Program website must include the capability to complete prescriber certification, pharmacy certification, and enroll and manage patients online, to obtain authorization to dispense online, and the option to print the Prescribing Information, Medication Guide, and REMS materials. All product websites for consumers and healthcare providers must include REMS-specific prominent links to the REMS Program website. The REMS Program website must not link back to any promotional product websites.
3. Make the REMS Program website fully operational and make all REMS materials available through the REMS Program website and call center by the date FINTEPLA is first commercially distributed.
4. Establish and maintain a REMS Program call center for REMS participants at 1-877-964-3649.
5. Establish and maintain a validated, secure database of all REMS participants who are enrolled and/or certified in the FINTEPLA REMS Program.
6. Ensure prescribers are able to complete the certification process online, by fax and mail.

7. Ensure prescribers are able to enroll their patients in the REMS online, by fax and mail.
8. Ensure pharmacies are able to complete the certification process online, by fax and mail.
9. Ensure prescribers are able to submit the [Patient Status Form](#) to the REMS online, by fax, and by mail.
10. Ensure prescribers are able to report adverse events suggestive of valvular heart disease and pulmonary arterial hypertension via the [Patient Status Form](#) online, by fax, and by mail.
11. Ensure pharmacies are able to obtain authorization to dispense online and by phone.
12. Provide the [Prescriber Training](#), [REMS Program Overview](#), [Prescriber Enrollment Form](#), [Patient Enrollment Form](#), and Prescribing Information to healthcare providers who (1) attempt to prescribe FINTEPLA and are not yet certified or (2) inquire about how to become certified.
13. Provide the [Pharmacy Guide](#), [REMS Program Overview](#), and [Inpatient Pharmacy Enrollment Form](#) or [Outpatient Pharmacy Enrollment Form](#), as appropriate, to pharmacies that (1) attempt to dispense FINTEPLA and are not yet certified or (2) inquire about how to become certified.
14. Notify prescribers, patients, and pharmacies within 2 business days after they become enrolled and/or certified in the REMS Program.
15. Provide certified prescribers access to the database of certified pharmacies and enrolled patients.
16. Provide certified pharmacies access to the database of certified prescribers and enrolled patients.
17. Provide authorized wholesale-distributors access to the database of certified pharmacies.
18. Establish and maintain a registry for 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 arterial hypertension.
19. Ensure that, once a report suggestive of valvular heart disease or pulmonary arterial hypertension is received, Zogenix, Inc. follows up with the healthcare provider(s) to complete a [Cardiovascular Adverse Event Reporting Form](#), to obtain all required data related to the adverse event for the registry.

To ensure REMS participants' compliance with the REMS Program, Zogenix, Inc. must:

20. Ensure the [Patient Status Form](#) is received for each patient on the following schedule: For treatment initiation, the patient is not authorized to receive the drug until the form is received. For subsequent dispensing, if the [Patient Status Form](#) is not received within 180 calendar days of the date of receipt of the last [Patient Status Form](#), Zogenix, Inc. must contact the prescriber to obtain the form. If the form is not received within 270 calendar days, the patient is not authorized to receive the drug until the form is received.
21. Verify annually that the authorized representative's name and contact information corresponds to those of the current designated authorized representative for the pharmacy. If different, the pharmacy must be required to re-certify with a new authorized representative.
22. Maintain adequate records to demonstrate that REMS requirements have been met, including, but not limited to, records of FINTEPLA distribution and dispensing; certification of prescribers and pharmacies; enrollment and status of patients; documentation of completed [Patient Status Forms](#) and [Cardiovascular Adverse Event Reporting Form](#); and audits of REMS participants. These records must be readily available for FDA inspections.
23. Establish a plan for addressing noncompliance with REMS requirements.
24. Monitor prescribers, pharmacies, and wholesale-distributors on an ongoing basis to ensure the REMS requirements are being met. Take corrective action if noncompliance is identified, including decertification.
25. Audit pharmacies and wholesale-distributors no later than 90 calendar days after they become certified and have received at least one shipment, and annually thereafter, to ensure that REMS processes and procedures are in place, functioning, and support the REMS requirements.
26. Take reasonable steps to improve implementation of and compliance with the REMS requirements based on monitoring and evaluation of the FINTEPLA REMS.

IV. REMS Assessment Timetable

Zogenix, Inc. must submit REMS assessments at 6 months and 12 months from the date of the initial approval of the REMS and annually thereafter. To facilitate inclusion of as much information as possible while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment should conclude no earlier than 60 calendar days before the submission date for that assessment. Zogenix, Inc. must submit each assessment so that it will be received by the FDA on or before the due date.

V. REMS Materials

The following materials are part of the FINTEPLA REMS:

Enrollment Forms

Prescriber:

1. [Prescriber Enrollment Form](#)

Patient:

2. [Patient Enrollment Form](#)

Pharmacy:

3. [Outpatient Pharmacy Enrollment Form](#)
4. [Inpatient Pharmacy Enrollment Form](#)

Training and Educational Materials

Prescriber:

5. [Prescriber Training](#)
6. [REMS Program Overview](#)
7. [Prescriber Knowledge Assessment](#)

Patient:

8. [Patient Guide](#)

Pharmacy:

9. [Pharmacy Guide](#)
10. [REMS Program Overview](#)

Patient Care Forms

11. [Patient Status Form](#)
12. [Cardiovascular Adverse Event Reporting Form](#)

Communication Materials

13. [Letter for Healthcare Providers](#)

Other Materials

14. [REMS Website](#)