CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

212102Orig1s000

PRODUCT QUALITY REVIEW(S)

U.S. FOOD & DRUG ADMINISTRATION

RECOMMENDATION: Approval

NDA 212102
Review #1

Drug Product Name	FINTEPLA (fenfluramine)
Dosage Form	Solution
Strength	2.2 mg/mL
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Applicant	Zogenix, Inc.
US agent, if applicable	N/A

QUALITY TEAM

Discipline	Primary Assessment	Secondary Assessment
Drug Substance	Rajan Pragani	Suong Tran
Drug Product	Stephanie Emory	Julia Pinto
Manufacturing	Tianhong Tim Zhou	Aditi Thakur
Microbiology	Yan Zheng	Elizabeth Bearr
Biopharmaceutics	Parnali Chatterjee	Ta-Chen Wu
Regulatory Business Process Manager	Dahlia Walters/Kelly Ballard	
Application Technical Lead	Martha Heimann	
Laboratory (OTR)	N/A	N/A
Environmental	N/A	N/A

Submission(s)	Document Date	Discipline(s) Affected
SD-2, Original NDA	2/5/2019	All
SD-11, Resubmission after RTF	9/25/2019	Drug Product (labeling)
SD-25, Response to DMEPA IR	12/16/2019	Drug Product
SD-41, Response to IR	2/27/2020	Manufacturing
SD-55, General Correspondence	05/15/2020	Drug Product (labeling)

QUALITY ASSESSMENT DATA SHEET

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Assessed	Comments
(b) (4)	IV	(b) (4)		Adequate	3/31/2020	Reviewer: S. Emory
	III			N/A	N/A	Adequate information in NDA.
	III			N/A	N/A	Adequate information in NDA.
	III			N/A	N/A	Adequate information in NDA.

B. Other Documents: *IND, RLD, or sister applications*

Document	Application Number	Description
NDA	16618	Original approval of Pondimin® (fenfluramine) for weight loss. FDA requested drug be withdrawn from the market in 1997 due to heart valve damage in patients who used the drug.
IND	125797	Development of fenfluramine for treatment of Dravet syndrome.

2. CONSULTS

None

EXECUTIVE SUMMARY

I. RECOMMENDATIONS AND CONCLUSION ON APPROVABILITY

The Office of Product Quality (OPQ) review team recommends that the Agency **Approve** NDA 212102 for FINTEPLA (fenfluramine) oral solution. From a quality perspective, the application, as amended in response to Agency information requests (IRs), provides adequate information to ensure that the Applicant can consistently manufacture a product that is suitable for use by the intended patients.

II. SUMMARY OF QUALITY ASSESSMENTS

A. Product Overview

Fenfluramine is a substituted amphetamine analog that was approved in 1973, as Pondimin® (fenfluramine HCl) tablets for treatment of obesity (NDA 16618). It was withdrawn from the market for reasons of safety in 1997 due to heart valve damage in patients who used the drug.

The applicant, Zogenix, has developed an oral solution containing fenfluramine, for treatment of seizures associated with Dravet syndrome, a rare and severe form of epilepsy, in patients 2 years and older. The proposed product is a colorless, cherry-flavored solution containing 2.2 mg/mL fenfluramine, as 2.5 mg/mL of fenfluramine hydrochloride.

Key review issues included stability of the drug during long-term storage and in use, qualification of a specified degradation product, adequacy of preservatives, palatability, and compatibility of product with dosing devices and feeding tubes.

Proposed indication(s) including intended patient population	Treatment of Dravet syndrome in patients 2 years and older
Duration of treatment	Chronic
Maximum daily dose	(b) (4) mg
Alternative methods of administration	None

B. Quality Assessment Overview

Drug Substance: Adequate

The drug substance, fenfluramine hydrochloride, is a structurally simple, synthetic small molecule. (b) (4)

hydrochloride salt, that is sparingly soluble to soluble in aqueous media. The drug substance structure has been adequately characterized.

The manufacturing process has been sufficiently described and appears reasonable. (b) (4)

The proposed drug substance includes appropriate tests for critical quality parameters and the analytical procedures are adequately described and validated. No risks for mutagenicity were identified for potential process impurities or degradation products. All specified impurities have limits below ICH Q3A qualification threshold. Elemental impurities are not required to be included in the drug substance specification with adequate supporting data as per ICH Q3D and justification, and residual solvents are controlled with acceptable ICH Q3C limits.

Based on the stability data provided for the registration batches from the proposed commercial manufacturer, the proposed **retest date of** (b) (4) is acceptable for fenfluramine hydrochloride.

Drug Product: Adequate

The proposed product is an aqueous solution for oral use that will be marketed in multi-use bottles containing 30 mL or 360 mL. The formulation includes compendial excipients, including (b) (4) ethyl paraben and methyl paraben (b) (4) , sucralose (b) (4), hydroxyethylcellulose (b) (4) . The formulation also contains a noncompendial cherry flavor. Concentrations of compendial excipients result in maximum daily exposures (MDEs) that are consistent with approved oral products. The cherry flavor was reviewed under the supplier's drug master file (DMF) and is acceptable for the proposed use.

The product is intended for weight-based dosing. The pharmacy will provide the appropriate size calibrated oral syringe and insert a press-in bottle adapter (PIBA) prior to dispensing. Dose-accuracy, repeated use, in-use stability, and compatibility studies and a leachability risk assessment have been conducted, supporting the use of the bottle, cap, adapter, and syringes, including the 4 most common syringe materials of construction.

The proposed specification includes testing for all critical parameters appropriate to the dosage form. Analytical methods have been appropriately developed and validated. The principal impurity observed in the product (b) (4) . All other impurity limits are below the ICH Q3B qualification threshold. Based on the applicant's risk assessments, omission of testing for residual solvents and elemental impurities is acceptable.

The design of stability studies adequately encompassed all bottles sizes and upright/inverted orientations. Based on the data provided, a **36-month shelf-life is granted for product stored at controlled room temperature**. The solution should not be refrigerated or frozen (b) (4) While product performance is not adversely affected, a change to appearance can impact acceptability of the product to patient or caregiver. The proposed in-use period, (b) (4) days from bottle opening, is adequately supported by data provided in the application.

Labeling: Adequate

During the initial filing review, a mismatch between the established name, fenfluramine oral solution and the label potency 2.5 mg/mL (based on the hydrochloride salt form) was identified. The applicant has revised the labeling such that the label potency, 2.2 mg/mL is consistent with the established name. The proposed labeling is deemed adequate with minor revisions that will be implemented when labeling is finalized.

Manufacturing: Adequate

Fenfluramine oral solution is a simple aqueous solution containing water soluble excipients. The manufacturing process consists of (b) (4)

(b) (4)

All proposed commercial manufacturing and testing facilities are currently acceptable. During review of the NDA, it was determined that previous inspection of the drug product manufacturing facility, (b) (4)

(b) (4) Based on this factor and risks identified during the review, a pre-approval inspection (PAI) of the Drug Product facility was recommended. Due to the ongoing COVID-19 pandemic

and travel restrictions, an on-site inspection of the facility was not possible. In lieu of an on-site inspection, acceptability of the facility was determined based on review by ORA and CDER of documents requested from the applicant under Section 704(a)(4) of the FD&C Act.

Biopharmaceutics: Adequate

The proposed drug product is an oral solution that contains excipients that will unlikely alter the bioavailability and pharmacokinetic disposition of the highly soluble and highly permeable drug substance, fenfluramine. Two formulations were developed for clinical use. The initial formulation contained (b) (4) for Phase 3 clinical trials. The to-be-marketed formulation is the same as the Phase 3 clinical formulation and manufactured at the same facility. Thus, no bridging is needed.

Microbiology: Adequate

The drug product is a nonsterile oral solution. The in-use period after opening the bottle is up to (b) (4) days for solution stored at controlled room temperature. Ethyl paraben (b) (4) and methyl paraben (b) (4)

All microbiological tests for batch release and stability testing are deemed suitable for quality control.

Environmental: Adequate

The applicant claims a categorical exclusion under 21 CFR 25.31(b). Approval of the NDA will increase the use of the active moiety, but the estimated concentration of the substance at the point of entry into the aquatic environment will be below 1 part per billion. The claim for categorical exclusion is granted.

C. Risk Assessment

From Initial Risk Identification			Review Assessment		
Attribute/ CQA	**Factors that can impact the CQA**	**Initial Risk Ranking**	**Risk Mitigation Approach**	**Final Risk Evaluation**	**Comments**
Assay/impurities	Formulation Raw Materials Container Closure Process/Scale/Equipment Site	**L**	Drug substance is stable across a relatively wide pH range. No degradation observed in stability		
Polymorphism		**L**	Not applicable.	**Adequate**	
Solution stability		**L**	Precipitation of preservatives can occur at lower temperatures. Product labeling will include “Do not refrigerate or freeze” statement.	**Adequate**	
Dosing accuracy		**L**	Viscosity and delivered volume controlled in specification.	**Adequate**	Dispensing pharmacy to supply oral syringes.
Palatability		**M**	(b) (4)	**Adequate**	
Microbial Limits		**L**	(b) (4)	**Adequate**	
Leachables		**M**	No extractables of concern were identified for container closure system or commonly used delivery devices.	**Adequate**	

D. List of Deficiencies for Complete Response

Not applicable.

Application Technical Lead Name and Date:

Martha R. Heimann, Ph.D.
CMC Lead
Office of New Drug Products
Division of New Drug Products II

6/15/2020

Martha Heimann

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CHAPTER IV: LABELING

1.0 PRESCRIBING INFORMATION

Assessment of Product Quality Related Aspects of the Prescribing Information:

1.1 HIGHLIGHTS OF PRESCRIBING INFORMATION

Item	Information Provided in the NDA	Assessor's Comments
Product Title in Highlights		
Proprietary name	FINTEPLA™ (fenfluramine) oral solution, CIV	*Adequate*
Established name(s)		
Route(s) of administration		
Controlled substance designation		
Dosage Forms and Strengths Heading in Highlights		
Summary of the dosage form(s) and strength(s) in metric system.	Oral solution: 2.2 mg/mL fenfluramine (b) (4)	*Adequate*
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	N/A	*N/A*
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package.	N/A	*N/A*

1.2 FULL PRESCRIBING INFORMATION

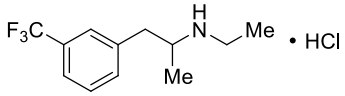
1.2.1 Section 2 (DOSAGE AND ADMINISTRATION)

Item	Information Provided in the NDA	Assessor's Comments
DOSAGE AND ADMINISTRATION section		
Special instructions for product preparation (e.g., reconstitution and resulting concentration, dilution, compatible diluents, storage conditions needed to maintain the stability of the reconstituted or diluted product)	A calibrated measuring device (either 3 mL or 6 mL oral syringe) will be provided by the pharmacy and is recommended to measure and administer the prescribed dose accurately [see How Supplied/Storage and Handling (16)]. A household teaspoon or tablespoon is not an adequate measuring device and should not be used. Discard any unused FINTEPLA (b) (4) FINTEPLA is compatible with commercially available gastric and nasogastric feeding tubes.	*Adequate*

1.2.2 Section 3 (DOSAGE FORMS AND STRENGTHS)

Item	Information Provided in the NDA	Assessor's Comments
DOSAGE FORMS AND STRENGTHS section		
Available dosage form(s) Strength(s) in metric system If the active ingredient is a salt, apply the USP Salt Policy per FDA Guidance	Oral solution: 2.2 mg/mL fenfluramine (b) (4)	*Adequate*
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting	No information	*Include description from Section 16: "FINTEPLA is a cherry flavored clear colorless liquid."*
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	N/A	*N/A*
For injectable drug products for parental administration, use appropriate labeling term (e.g., single-dose, multiple-dose, single-patient-use). Other package type terms include pharmacy bulk package and imaging bulk package.	N/A	*N/A*

1.2.3 Section 11 (DESCRIPTION)

Item	Information Provided in the NDA	Assessor's Comments
DESCRIPTION section		
Proprietary and established name(s) Dosage form(s) and route(s) of administration If the active ingredient is a salt, apply the USP Salt Policy and include the equivalency statement per FDA Guidance.	FINTEPLA contains 2.2 mg/mL fenfluramine, equivalent to 2.5 mg/mL of the hydrochloride salt.	*Revise to include dosage form and ROA: "FINTEPLA oral solution contains 2.2 mg/mL fenfluramine, equivalent to 2.5 mg/mL of the hydrochloride salt."*
List names of all inactive ingredients. Use USP/NF names. Avoid Brand names.	FINTEPLA contains the following inactive ingredients: water, potassium citrate, citric acid, hydroxyethylcellulose, methylparaben, sucralose, ethylparaben, and cherry flavor.	*Revise to list in alphabetical order.* *Listing "cherry flavor" is adequate. It is a proprietary mixture of over 60 individual components, therefore it is not feasible to list them here.*
Pharmacological/ therapeutic class	No information	*Revise to include pharmacological/ therapeutic class*
Chemical name, structural formula, molecular weight	The active ingredient, fenfluramine hydrochloride, is designated chemically as N-ethyl-α-methyl-3-(trifluoromethyl)phenethylamine hydrochloride. The structural Formula is:  	*Adequate*
Other important chemical or physical properties (such as pKa or pH)	FINTEPLA is a clear, colorless liquid. Fenfluramine hydrochloride is a white to off-white crystalline solid.	*Revise to include pKa of drug substance and pH of the drug product*

Section 11 (DESCRIPTION) Continued

Item	Information Provided in the NDA	Assessor's Comments
For oral prescription drug products, include gluten statement if applicable	FINTEPLA (b) (4) ingredient made from gluten-containing grain.	*Adequate.*
If radioactive, statement of important nuclear characteristics.	N/A	*N/A*
For parenteral injectable dosage forms, include the name and quantities of all inactive ingredients. For ingredients added to adjust the pH or make isotonic, include the name and statement of effect.	N/A	*N/A*
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	N/A	*N/A*
Statement of being sterile (if applicable)	N/A	*N/A*
Remove statements that may be misleading or promotional (e.g., "synthesized and developed by Drug Company X," "structurally unique molecular entity"	N/A	*N/A*

1.2.4 Section 16 (HOW SUPPLIED/STORAGE AND HANDLING)

Item	Information Provided in the NDA	Assessor's Comments
HOW SUPPLIED/STORAGE AND HANDLING section		
Available dosage form(s) Strength(s) in metric system	FINTEPLA contains 2.2 mg/mL fenfluramine.	*Revise to include dosage form: "FINTEPLA oral solution contains 2.2 mg/mL fenfluramine."*
Available units (e.g., bottles of 100 tablets)	No information	*Revise to include available units (30 and 360 mL)*
Additional information	Before dispensing, the pharmacist will insert a press-in bottle adapter. The pharmacy will provide 3 mL or 6 mL calibrated oral dosing syringes. (b) (4) (b) (4)	*Adequate*
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number Include information about child-resistant packaging	FINTEPLA is cherry flavored clear colorless liquid supplied in white plastic bottle with a child resistant closure.	*Revise to include NDC numbers*
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	N/A	*N/A*
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package.	N/A	*N/A*

Section 16 (HOW SUPPLIED/STORAGE AND HANDLING) (Continued)

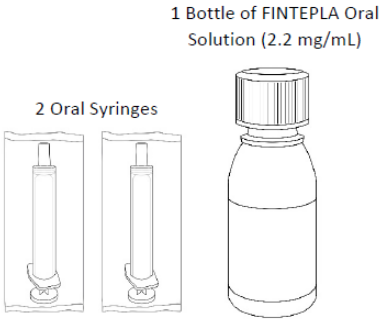
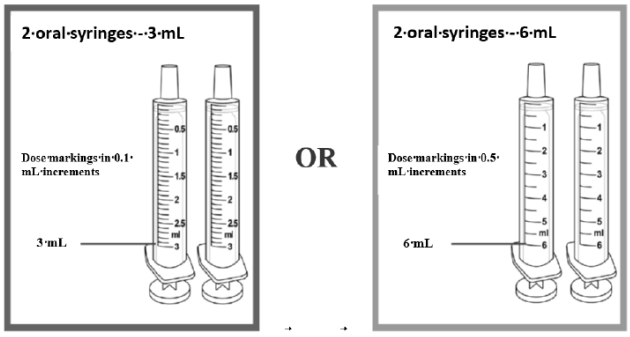
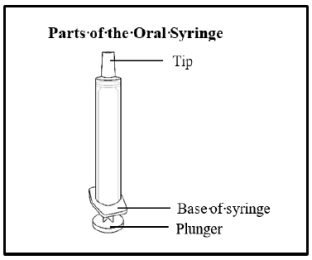
Item	Information Provided in the NDA	Assessor's Comments
Storage conditions. Where applicable, use USP storage range rather than storage at a single temperature.	Store FINTEPLA at room temperature between 68°F to 77°F (20°C to 25°C); excursions are permitted between 59°F to 86°F (15°C to 30°C). Do not refrigerate or freeze. [See USP Controlled Room Temperature.] Store the bottle and syringe together. Discard any unused (b) (4)	*Move USP reference to directly follow temperature ranges, preceding the statement "Do not refrigerate or freeze," because the USP definition does not apply to this statement.*
Special handling about the supplied product (e.g., protect from light, refrigerate). If there is a statement to "Dispense in original container," provide reason why (e.g. to protect from light or moisture, to maintain stability, etc.)		
If the product contains a desiccant, ensure the size and shape differ from the dosage form and desiccant has a warning such as "Do not eat."	N/A	*N/A*
Latex: If product does not contain latex and manufacturing of product and container did not include use of natural rubber latex or synthetic derivatives of natural rubber latex, state: "Not made with natural rubber latex. Avoid statements such as "latex-free."	N/A	*N/A*

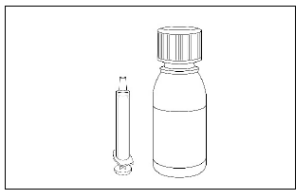
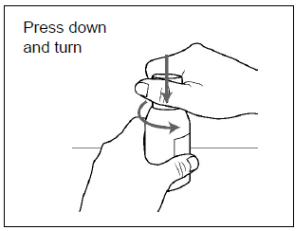
1.2.5 Manufacturing Information After Section 17 (for drug products)

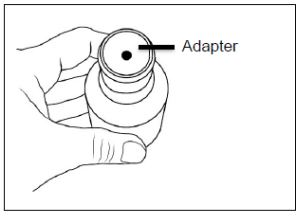
Item	Information Provided in the NDA	Assessor's Comments
Manufacturing Information After Section 17		
Name and location of business (street address, city, state and zip code) of the manufacturer, distributor, and/or packer	Marketed by: Zogenix Inc. 5959 Horton Street, Suite 500, Emeryville CA, 94608	*Adequate*

2.0 PATIENT LABELING

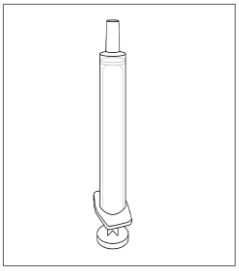
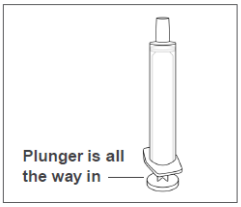
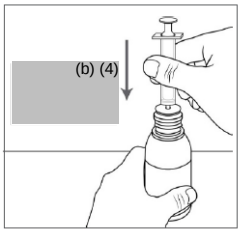
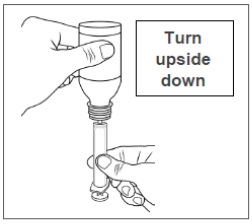
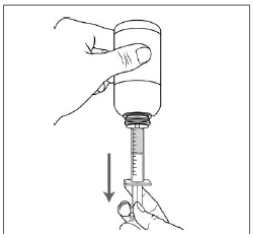
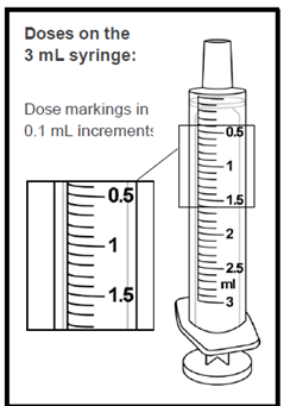
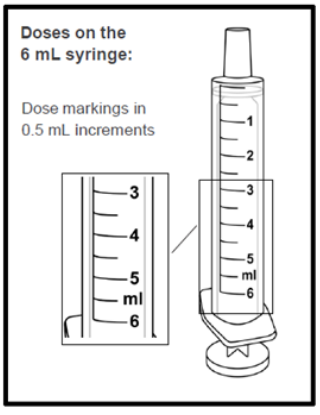
Item	Information Provided in the NDA	Assessor's Comments
Medication Guide		
How should I take FINTEPLA?	• Read the Instructions for Use on the right way to use FINTEPLA. • Measure your dose of FINTEPLA using the dosing syringe that is provided by the pharmacy. Do not use a household teaspoon or tablespoon. • FINTEPLA [redacted] (b) (4) gastric and nasogastric feeding tubes.	*Adequate*
How should I store FINTEPLA?	• Store FINTEPLA at room temperature between 68°F and 77°F (20°C and 25°C), excursions between 59°F and 86°F (15°C and 30°C) are acceptable. • Do not refrigerate or freeze • Discard any unused FINTEPLA [redacted] (b) (4) Keep FINTEPLA and all medicines out of the reach of children	*Adequate*
What are the ingredients in FINTEPLA?	**Active ingredient:** fenfluramine hydrochloride **Inactive ingredients:** water, potassium citrate, citric acid, hydroxyethylcellulose, methylparaben, sucralose, ethylparaben, and cherry flavor. FINTEPLA contains no ingredient [redacted] (b) (4) made from gluten-containing grain. Marketed by: Zogenix Inc. 5959 Horton Street, Suite 500, Emeryville CA, 94608	*Revise to list inactive ingredients in alphabetical order*

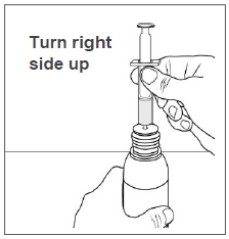
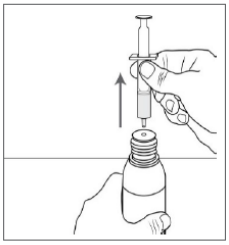
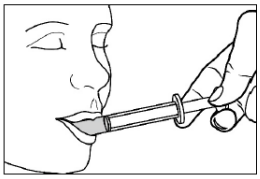
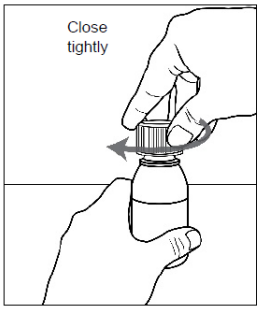
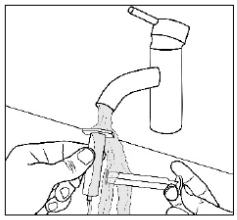
Item	Information Provided in the NDA	Assessor's Comments
Instructions for Use (IFU)		
WHAT IS INCLUDED WITH FINTEPLA	The following items are included to prepare and give an oral dose of FINTEPLA: • 1 bottle of FINTEPLA oral solution (2.2 mg/mL) • 2 reusable oral syringes 	*Adequate.*
ORAL SYRINGES PROVIDED WITH FINTEPLA BY THE PHARMACY	With FINTEPLA you will receive 2 reusable oral syringes. 2 oral syringes that can measure up to 3 mL **OR** 2 oral syringes that can measure up to 6 mL  	*Adequate*

<table>
<tr><td>IMPORTANT INFORMATION ABOUT FINTEPLA</td><td>• FINTEPLA is an oral medicine (taken by mouth) and is given twice daily. Follow your healthcare provider’s instructions for taking or giving doses of FINTEPLA.
• If you have questions about how to prepare or give FINTEPLA, contact your healthcare provider or call the pharmacist (b) (4) .
• Always use the oral syringes provided with FINTEPLA to make sure the right dose is given. If you need a new syringe contact your pharmacist.
(b) (4)</td><td>Adequate</td></tr>
<tr><td>PREPARING A DOSE</td><td> 
Step 1. Make sure you have:
• The bottle of FINTEPLA oral solution, and
• A clean, dry reusable syringe that was provided with FINTEPLA.
(b) (4)
Step 2. Check the “Discard After” date (MM/DD/YYYY).
• Do not use the medicine if the Discard After date has passed.
• If the date is near, contact your pharmacy or healthcare provider to get a refill or new prescription.
• If the date has passed, dispose of any unused FINTEPLA. (b) (4)
 

Step 3. Press down and turn the childproof cap to remove it from the bottle.
• Set the cap aside (do not throw away).
 

Step 4. Make sure the adapter is on the bottle.
• If the bottle does not have an adapter, contact the pharmacist.
• Always leave the adapter in place in the bottle of medicine.</td><td>Adequate</td></tr>
</table>

PREPARING A DOSE (CONTINUED)		**Step 5.** Remove an oral syringe from its packaging, if needed. Only use the oral syringes provided with FINTEPLA. **If an oral syringe is damaged, or you cannot read the dose markings**: • Use the other oral syringe provided, or • Contact the pharmacist to get a new one.	*Adequate*
		**Step 6.** Make sure the plunger is pushed all the way into the oral syringe.	
		**Step 7.** Hold the bottle of medicine firmly on a hard, flat surface. **Step 8.** Push the tip of the oral syringe into the opening of the adapter until it cannot be pushed further.	
PREPARING A DOSE (CONTINUED)		**Step 9.** Hold the oral syringe and bottle together and turn upside down.	*Adequate*
		**Step 10.** Slowly pull the plunger of the oral syringe to withdraw the prescribed dose.	
			

PREPARING A DOSE (CONTINUED)	 **Step 12.** Hold the oral syringe and bottle together and then turn [redacted] (b) (4)  **Step 13.** Holding the bottle firmly, gently pull the oral syringe out of the bottle adapter. **Step 14.** Make sure the dose in the oral syringe still matches the prescribed dose. If the dose does not match: • Put the syringe back into adapter. • [redacted] (b) (4) steps 9-11 to adjust the dose, as needed.	*Adequate*
GIVING FINTEPLA	 **Step 15.** Place the tip of the oral syringe against the inside of the patient's cheek. **Step 16.** Gently push the plunger until all the medicine in the oral syringe is given. • Do not squirt the medicine into the back of the throat [redacted] (b) (4) this may cause choking.  **Step 17.** Place the cap back on the bottle [redacted] (b) (4) until it stops. • Always leave the adapter in place in the bottle	*Adequate*
CLEANING THE SYRINGE	 **Step 18.** Rinse the oral syringe with clean water and allow it to air dry after each use. • Make sure you rinse the inside of the syringe and the plunger. **Cleaning Tips:** • The syringe is safe to clean in the dishwasher. [redacted] (b) (4) • Make sure the syringe and plunger are completely dry before the next use.	*Adequate*

STORING FINTEPLA	(b) (4) • Store at room temperature between 68°F and 77°F (20°C and 25°C) (b) (4) • Keep out of reach of children • Keep the cap tightly closed and the bottle upright. • Do not refrigerate or freeze (b) (4). • Discard any unused FINTEPLA (b) (4) Marketed by: Zogenix Inc. 5959 Horton Street, Suite 500, Emeryville CA, 94608	*Move the statement "Do not refrigerate or freeze the medicine" to directly follow the statement "Store at room temperature…" for consistency with other labeling.*

3.0 CARTON AND CONTAINER LABELING

3.1 Container Label (30 mL shown)

3.2 Carton Labeling (360 mL shown)

Item	Information Provided in the NDA	Assessor's Comments about Labels
Proprietary name, established name, and dosage form (font size and prominence	See examples above	*Adequate*
Dosage strength	See examples above	*Adequate*
Route of administration	See examples above	*Adequate*
Controlled substance symbol	See examples above	*Adequate*
If the active ingredient is a salt, include the equivalency statement per FDA Guidance	See examples above	*Adequate*
Net contents (e.g. tablet count)	See examples above	*Adequate*
"Rx only" displayed on the principal display	See examples above	*Adequate*
NDC number	See examples above	*Adequate*
Lot number and expiration date	See examples above	*Adequate*
Storage conditions. If applicable, include a space on the carton labeling for the user to write the new BUD.	(b) (4)	

Item	Information Provided in the NDA	Assessor's Comments about Labels
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use)	No information	*Adequate*
Other package terms include pharmacy bulk package and imaging bulk package which require "Not for direct infusion" statement.	N/A	*N/A*
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	N/A	*N/A*
Bar code	See examples above	*Adequate*
Name of manufacturer/distributor	See examples above	*Adequate*
Medication Guide (if applicable)	N/A	*N/A*
No text on Ferrule and Cap overseal	N/A	*N/A*
When a drug product differs from the relevant USP standard of strength, quality, or purity, as determined by the application of the tests, procedures, and acceptance criteria set forth in the relevant compendium, its difference shall be plainly stated on its label.	N/A	*N/A*

ITEMS FOR ADDITIONAL ASSESSMENT

Prescribing Information:

1) *Section 3: Include product description "cherry flavored clear colorless liquid."*
2) *Section 11: Include dosage form, ROA, pharmacological/therapeutic class, pKa of drug substance, and pH of the drug product. List inactive ingredients in alphabetical order.*
3) *Section 16: Include dosage form, available units (30 and 360 mL), and NDC numbers. Move USP reference to directly follow controlled room temperature ranges.*

Medication Guide: *List inactive ingredients in alphabetical order.*

Instructions for Use: *Move the statement "Do not refrigerate or freeze the medicine" to directly follow the storage statement.*

Carton/container labels:

Overall Assessment and Recommendation:

Adequate, pending the revisions listed above.

Stephanie Emory

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Julia Pinto

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BIOPHARMACEUTICS

NDA: 212102-ORIG-1/Resubmission following Refusal-To-File (RTF)
Drug Product Name/Strength: Fintepla™ (fenfluramine hydrochloride oral solution)**,** 2.5 mg/mL
Route of Administration: Oral
Applicant Name: Zogenix, Inc.
Submission Dates: 02/05/2019, SDN 2 (Original); 09/25/2019, SDN 11 (Resubmission)
Primary Reviewer: Parnali Chatterjee, Ph.D.
Secondary Reviewer: Ta-Chen Wu, Ph.D.

EXECUTIVE SUMMARY:

Background: Zogenix, Inc. is seeking approval of Fintepla™ (fenfluramine hydrochloride oral solution)**,** 2.5 mg/mL, for the treatment of seizures associated with Dravet Syndrome in patients 2 years and older *via* the 505(b)(2) regulatory pathway. The submission received a Refuse-to-File (RTF) notification on 04/05/2019. The Applicant resubmitted the NDA 212012 on 09/25/2019 and requested a priority review and a Rare Pediatric Disease Priority Review Voucher for the proposed drug product. Note that the current submission does not reference any Listed Drug (LD). Additionally, it should be noted that Pondimin Tablets containing 20 mg and 60 mg fenfluramine hydrochloride that was approved by the FDA on 06/14/1973 under NDA 016618 as an appetite suppressant for the treatment of obesity in adults was withdrawn from the market in 1997 due to safety and effectiveness reasons.

The NDA 212102 is supported by a single and multiple-dose Study ZX008-1504 (Cohort 1, Part 1, DDI and Part 2, food effect) in pediatric patients 2-18 years of age associated with Dravet Syndrome, and Studies ZX008-1505 and ZX008-1604 in healthy adult subjects. The submission is also supported by several safety and efficacy studies; Study 1, Study 2, ZX008-1503 (open label), and a Phase 3 Study ZX008-1504 (Cohort 2) in pediatric patients 2-18 years of age associated with Dravet Syndrome.

- ***Dissolution Testing:***

The proposed drug product is an oral solution that contains excipients that do not alter the bioavailability and pharmacokinetic disposition of fenfluramine. Therefore, no dissolution testing is proposed for Fintepla™ (fenfluramine hydrochloride oral solution)**,** 2.5 mg/mL.

- ***Bridging of Batches Due to Manufacturing Site, Manufacturing Process, and Formulation Changes:***

Manufacturing Site Changes:
As the clinical and proposed TBM drug product was manufactured at the the proposed commercial manufacturer, (b) (4) no 'bridging' of the drug product batches is needed.

Manufacturing Process Changes:

(b) (4)

Formulation Changes:

(b) (4)

- ***Biopharmaceutics Risk Assessment:***

Fenfluramine hydrochloride exhibits high solubility and high permeability. The proposed drug product, Fintepla (fenfluramine hydrochloride oral solution)**,** 2.5 mg/mL, is an oral solution that contains excipients that will unlikely alter the bioavailability and pharmacokinetic disposition of fenfluramine. From the Biopharmaceutics perspectives, the proposed drug product is a low risk drug product.

OVERALL REVIEW RECOMMENDATION:

From the Biopharmaceutics perspective, NDA 2212102-ORIG-1 for Fintepla™ (fenfluramine hydrochloride oral solution)**,** 2.5 mg/mL is recommended for **APPROVAL.**

BIOPHARMACEUTICS ASSESSMENT

➢ LIST OF SUBMISSIONS BEING REVIEWED:

Submissions Reviewed	Reference ID
Original NDA 212102 Submission	Dated 02/05/2019, SDN 2 (\\cdsesub1\evsprod\nda212102\0002\m2\27-clin-sum\summary-biopharm.pdf)
Refuse-to-File (RTF)	Dated 04/05/2019, *DAARTS* (https://darrts.fda.gov/darrts/ViewDocument?documentId=090140af804eaade)
NDA 212102 Resubmission	Dated 09/25/2019, SDN 11 (\\cdsesub1\evsprod\nda212102\0011\m2\25-clin-over\clinical-overview.pdf)
Response to Information Request	Dated 12/13/2019, SDN 24 (\\cdsesub1\evsprod\nda212102\0024\m1\us\111-info-amend\resp-clin-ir-seizure-types-20191119.pdf)

➢ *DRUG SUBSTANCE*:

Fenfluramine hydrochloride [molecular weight: 267.72 grams/mole; molecular formula: $C_{12}H_{16}F_3N.HCl$] (b) (4)

(b) (4)

(b) (4)

(b) (4)

[redacted]

- ***DRUG PRODUCT*:**

The to-be-marketed (TBM) drug product is a colorless and cherry-flavored oral solution containing equivalent to 2.5 mg/mL fenfluramine hydrochloride (~2.2 mg/mL fenfluramine free base) in an aqueous vehicle. The composition of the proposed drug product is provided in **Table 3**.

The proposed TBM drug product contains 2.5 mg/mL fenfluramine hydrochloride (~2.2 mg/mL fenfluramine free base) as the active ingredient, sucralose (b) (4) methyl and ethyl paraben (b) (4), potassium citrate (b) (4) and citric acid (b) (4), and hydroxyethylcellulose (b) (4) (see **Table 3**).

(b) (4)

[redacted]

(b) (4)

Table 3. Composition of the proposed commercial, to-be-marketed drug product, Fintepla™ (fenfluramine hydrochloride) oral solution**,** 2.5 mg/mL

Ingredient	Function	Quality Standard	Amount (mg/mL)[a]
Fenfluramine HCl	Active	Manufacturer's standard.	2.5
Methylparaben	(b) (4)	USP-NF, Ph. Eur.	(b) (4)
Ethylparaben		Ph. Eur.	
Sucralose		USP-NF, Ph. Eur.	
Hydroxyethylcellulose		USP-NF, Ph. Eur.	
Cherry Flavoring		Supplier's standard	
Potassium citrate		USP, Ph. Eur.	
Citric acid		USP, Ph. Eur.	
Water		USP, Ph. Eur.	

(b) (4)

(b) (4)

Manufacturing Sites:

The formulation develpment for the proposed drug product was conducted at (b) (4), (b) (4). The manufacturing process for the clinical and proposed commercial drug product was then transfered to the proposed commercial manufacturer, (b) (4) with drug product batches (2.5 mg/mL) dosed in the various clinical studies.

Dissolution Testing:

As the proposed drug product, Fintepla™ (fenfluramine hydrochloride oral solution)**,** 2.5 mg/mL, is an oral solution that contains excipients including (b) (4) that will unlikely alter the bioavailability and pharmacokinetic disposition of fenfluramine, no dissolution testing is proposed for the proposed, Fintepla (fenfluramine hydrochloride oral solution)**,** 2.5 mg/mL drug product.

Bridging of Formulations Due to Formulation, Manufacturing Site, and Manufacturing Process Changes:

Manufacturing Site Changes:
As the clinical and proposed TBM drug product was manufactured at the the proposed commercial manufacturer, (b) (4) no 'bridging' of the drug product batches is needed.

Manufacturing Process Changes:

(b) (4)

Changes in the Composition of the Drug Product:

(b) (4)

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(b) (4)

- ***BIOPHARMACEUTICS RISK ASSESSMENT:***

Fenfluramine hydrochloride is a highly soluble and highly permeable drug substance, per FDA's BCS Guidance. The proposed drug product, Fintepla (fenfluramine hydrochloride oral solution)**,** 2.5 mg/mL, is an oral solution that contains excipients that will unlikely alter the bioavailability and pharmacokinetic disposition of fenfluramine. From the Biopharmaceutics perspectives, the proposed drug product is a low risk drug product. However, this review does not evaluate the safety and effectiveness of the proposed drug product.

Parnali Chatterjee

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Ta-Chen Wu

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CHAPTER VII: MICROBIOLOGY

IQA NDA Assessment Guide Reference

Product Information	
NDA Number	N212102
Assessment Cycle Number	MR01
Drug Product Name/ Strength	Fenfluramine Hydrochloride, 2.5mg/mL
Route of Administration	oral solution
Applicant Name	Zogenix, Inc
Therapeutic Classification/ OND Division	OND/ODEI/DNP
Manufacturing Site	(b) (4)
Method of Sterilization	N/A for non-sterile products.

Assessment Recommendation: **Adequate**

Assessment Summary:

Document(s) Assessed	Date Received
Original submission	02/05/2019

Highlight Key Issues from Last Cycle and Their Resolution: N/A

Remarks: This is eCTD submission. The original NDA submitted on 02/05/2019 was RTF due to non-micro issues. Submission dated after 02/05/2019 and resubmission dated 09/25/2019 do not contain additional information on product quality section.

Concise Description of Outstanding Issues
(List bullet points with key information and update as needed): None

Supporting Documents: N/A

S DRUG SUBSTANCE

The manufacturing process for the drug substance is not reviewed because the drug substance is non-sterile.

P.1 DESCRIPTION OF THE COMPOSITION OF THE DRUG PRODUCT

Product description: The subject drug product is colorless, cherry-flavored oral solution packaged in a white HDPE round bottle with 28mm screw neck. It is a

multi-dose, preserved, oral aqueous product. The strength of the product is 2.5mg/mL fenfluramine hydrochloride and the pH is (b) (4). There are (b) (4) product presentations filled in 30mL, (b) (4) 360mL, (b) (4) bottles.

Product composition:

Ingredient	Function	Quality Standard	Amount (mg/mL)[a]
Fenfluramine HCl	Active	Manufacturer's standard.	2.5
Methylparaben (b) (4	(b) (4)	USP-NF, Ph. Eur.	(b) (4)
Ethylparaben (b) (4		Ph. Eur.	
Sucralose		USP-NF, Ph. Eur.	
Hydroxyethylcellulose		USP-NF, Ph. Eur.	
Cherry Flavoring (b) (4		Supplier's standard	
Potassium citrate (b) (4)		USP, Ph. Eur.	
Citric acid (b) (4		USP, Ph. Eur.	
Water (b) (4)		USP, Ph. Eur.	
(b) (4)			

(Table reproduced from the submission, 3.2.P.1, pg. 1).

Summary Table of the proposed Container Closure System (3.2.P.7)

Component	Size	Description	Manufacturers
Bottle	30mL, (b) (4) (b) (4) 360mL (b) (4)	28mm neck white round HDPE bottle	(b) (4)
Closure	28mm	28mm child resistant tamper-evident closure	

The same closure is used on all bottles.

Assessment: Adequate

The product description is acceptable.

P.2 PHARMACEUTICAL DEVELOPMENT

P.2.5 MICROBIOLOGICAL ATTRIBUTES

Container/Closure and Package Integrity-N/A for non-sterile products.

Antimicrobial Effectiveness Testing (AET) (3.2.P.2, Microbiological attributes, pg. 1).

(b) (4)

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(b) (4)

Assessment: Adequate

The adventitious agent safety evaluation is acceptable.

Primary Microbiology Assessor Name and Date: Yan Zheng, Ph.D. 12/05/2019

Secondary Assessor Name and Date: Elizabeth Bearr, Ph.D., Acting Q.A.L.12/05/2019

Yan Zheng

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Elizabeth Bearr

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