FINTEPLA® Training

MODULE 6: FINTEPLA Prescribing Information

This Help page describes how to use eHandbooks. Please note that some features described on this page may not be available with this particular eHandbook. Also, the availability of features described on this page may be dependent upon the capabilities of your specific viewing device, such as a PC or Mac® computer, or a tablet device, such as an iPad®.

Viewing this eHandbook on a PC or Mac computer:

Viewing your eHandbook: Viewing this eHandbook requires Adobe Acrobat Reader or Adobe Acrobat Professional version 8.0 and higher.

Using navigation buttons at top of screen: The buttons located at the top of each page allow you to navigate through this document. Click on these buttons to take you Back to view the last page you were on or to the Previous Page, Next Page, or Last Page. The Contents and Glossary buttons provide direct links to the table of contents and full glossary. The Help button brings you to this Help page.

Navigating via the table of contents: the bookmark panel on the left side of the screen provides a full Table of Contents for the document. Click on a header title to go to a specific page. Client (+) symbol to view the subtopics included underneath the main header.

Making electronic notations: eHandbooks are enabled to support the highlighting of text and the addition of pop-up notes using the Annotation toolset within Adobe Acrobat. Click on **Tools** from within Adobe Acrobat to use these features.

Viewing term definitions: Glossary terms are bolded throughout the document. To see a definition of a bolded term, click on the term.

Answering review questions: When answering review questions with writeable fields, click on the field and then type in your answer. When answering multiple-choice questions, click on a checkbox or radio button. To check your answers, click the Show Answers button.

Viewing this eHandbook on a Tablet Device

Viewing your eHandbook: Optimal viewing of your eHandbook on a tablet device requires the installation of a third-party application that enables the viewing of PDF documents. Check with your device manufacturer for more information on third party applications that support PDF viewing.

Navigating with swipe and zoom features: Swipe pages to move forward or backward within the document. Zoom in and out on an individual page by using your tablet's zoom feature.

Navigating via the table of contents: Touch the chapter title to go directly to that chapter.

Viewing term definitions: Glossary terms are bolded throughout the document. To see a definition of a bolded term, touch the term.

Table of Contents

Module Introduction

This module reviews the various sections in the FINTEPLA PI to help you gain confidence discussing FINTEPLA with healthcare professionals. The sections are presented in the order in which they appear within the PI. As you will see, each page of the PI is shown with corresponding numbered annotations that reinforce key information. Some of the annotations also provide additional background on disease state concepts and medical terminology.

How to Use This Module

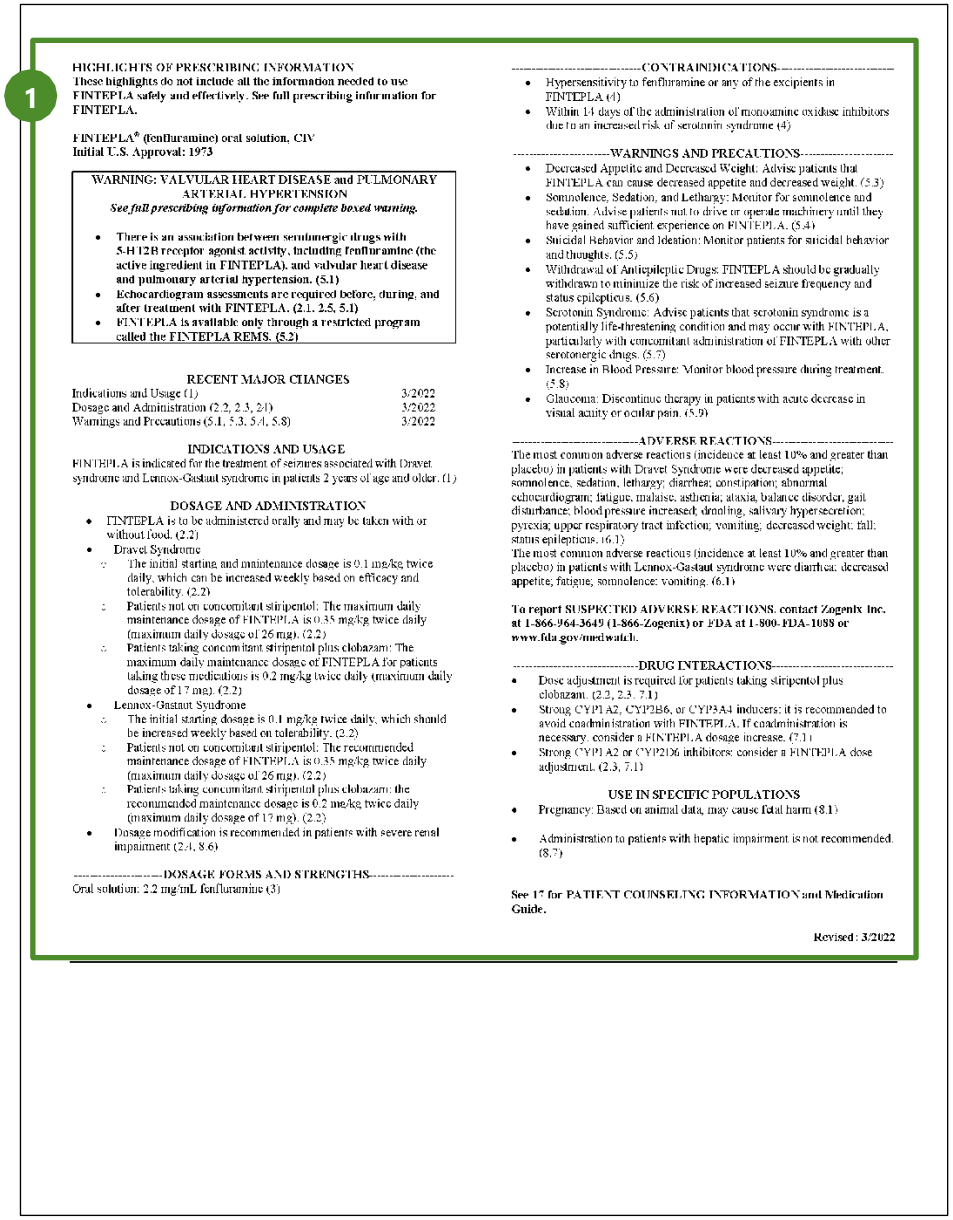
Each chapter within this module has its own Learning **Objectives**, **Take Home Points**, and **Knowledge Checks**. Take Home Points summarize the key points and will help you use the module as a quick reference source in the future. Throughout the module, key terms appear in boldface **green** and are defined in the **Glossary** at the end.

Chapter 1: Indications and Dosage and Administration

Learning Objectives

Upon completion of this chapter, you will be able to:

- Discuss the indications of FINTEPLA
- Describe the dosage and administration of FINTEPLA



HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use FINTEPLA safely and effectively. See full prescribing information for FINTEPLA.

FINTEPLA® (fenfluramine) oral solution, CIV
Initial U.S. Approval: 1973

WARNING: VALVULAR HEART DISEASE and PULMONARY ARTERIAL HYPERTENSION

See full prescribing information for complete boxed warning.

- There is an association between serotonergic drugs with 5-HT2B receptor agonist activity, including fenfluramine (the active ingredient in FINTEPLA), and valvular heart disease and pulmonary arterial hypertension. (5.1)
- Echocardiogram assessments are required before, during, and after treatment with FINTEPLA. (2.1, 2.5, 5.1)
- FINTEPLA is available only through a restricted program called the FINTEPLA REMS. (5.2)

RECENT MAJOR CHANGES

Indications and Usage (1)	3/2022
Dosage and Administration (2.2, 2.3, 2.4)	3/2022
Warnings and Precautions (5.1, 5.3, 5.4, 5.8)	3/2022

INDICATIONS AND USAGE

FINTEPLA is indicated for the treatment of seizures associated with Dravet syndrome and Lennox-Gastaut syndrome in patients 2 years of age and older. (1)

DOSAGE AND ADMINISTRATION

- FINTEPLA is to be administered orally and may be taken with or without food. (2.2)
- Dravet Syndrome
  - The initial starting and maintenance dosage is 0.1 mg/kg twice daily, which can be increased weekly based on efficacy and tolerability. (2.2)
  - Patients not on concomitant stiripentol: The maximum daily maintenance dosage of FINTEPLA is 0.35 mg/kg twice daily (maximum daily dosage of 26 mg). (2.2)
  - Patients taking concomitant stiripentol plus clobazam: The maximum daily maintenance dosage of FINTEPLA for patients taking these medications is 0.2 mg/kg twice daily (maximum daily dosage of 17 mg). (2.2)
- Lennox-Gastaut Syndrome
  - The initial starting dosage is 0.1 mg/kg twice daily, which should be increased weekly based on tolerability. (2.2)
  - Patients not on concomitant stiripentol: The recommended maintenance dosage of FINTEPLA is 0.35 mg/kg twice daily (maximum daily dosage of 26 mg). (2.2)
  - Patients taking concomitant stiripentol plus clobazam: the recommended maintenance dosage is 0.2 mg/kg twice daily (maximum daily dosage of 17 mg). (2.2)
- Dosage modification is recommended in patients with severe renal impairment (2.4, 8.6)

DOSAGE FORMS AND STRENGTHS

Oral solution: 2.2 mg/mL fenfluramine (3)

CONTRAINDICATIONS

- Hypersensitivity to fenfluramine or any of the excipients in FINTEPLA (4)
- Within 14 days of the administration of monoamine oxidase inhibitors due to an increased risk of serotonin syndrome (4)

WARNINGS AND PRECAUTIONS

- Decreased Appetite and Decreased Weight: Advise patients that FINTEPLA can cause decreased appetite and decreased weight. (5.3)
- Somnolence, Sedation, and Lethargy: Monitor for somnolence and sedation. Advise patients not to drive or operate machinery until they have gained sufficient experience on FINTEPLA. (5.4)
- Suicidal Behavior and Ideation: Monitor patients for suicidal behavior and thoughts. (5.5)
- Withdrawal of Antiepileptic Drugs: FINTEPLA should be gradually withdrawn to minimize the risk of increased seizure frequency and status epilepticus. (5.6)
- Serotonin Syndrome: Advise patients that serotonin syndrome is a potentially life-threatening condition and may occur with FINTEPLA, particularly with concomitant administration of FINTEPLA with other serotonergic drugs. (5.7)
- Increase in Blood Pressure: Monitor blood pressure during treatment. (5.8)
- Glaucoma: Discontinue therapy in patients with acute decrease in visual acuity or ocular pain. (5.9)

ADVERSE REACTIONS

The most common adverse reactions (incidence at least 10% and greater than placebo) in patients with Dravet Syndrome were decreased appetite; somnolence, sedation, lethargy; diarrhea; constipation; abnormal echocardiogram; fatigue, malaise, asthenia; ataxia; balance disorder, gait disturbance; blood pressure increased; drooling, salivary hypersecretion; pyrexia; upper respiratory tract infection; vomiting; decreased weight; fall; status epilepticus. (6.1)

The most common adverse reactions (incidence at least 10% and greater than placebo) in patients with Lennox-Gastaut syndrome were diarrhea; decreased appetite; fatigue; somnolence; vomiting. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Zogenix Inc. at 1-866-964-3649 (1-866-Zogenix) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- Dose adjustment is required for patients taking stiripentol plus clobazam. (2.2, 2.3, 7.1)
- Strong CYP1A2, CYP2B6, or CYP3A4 inducers: it is recommended to avoid coadministration with FINTEPLA. If coadministration is necessary, consider a FINTEPLA dosage increase. (7.1)
- Strong CYP1A2 or CYP2D6 inhibitors: consider a FINTEPLA dose adjustment. (2.3, 7.1)

USE IN SPECIFIC POPULATIONS

- Pregnancy: Based on animal data, may cause fetal harm (8.1)
- Administration to patients with hepatic impairment is not recommended. (8.7)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 3/2022

1 In June 2020, FINTEPLA was approved by the Food and Drug Administration (FDA) for the treatment of **seizures** associated with Dravet syndrome (DS) in patients 2 years of age and older. In March 2022, the indications for FINTEPLA were expanded to include patients with Lennox-Gastaut syndrome (LGS) 2 years of age and older.

As you have learned in other modules of this learning system, DS, which was previously known as severe myoclonic epilepsy in infancy (SMEI), is a severe and rare form of **developmental epileptic encephalopathy (DEE)** that typically presents during infancy and is commonly caused by a genetic variant of the *SCN1A* **gene**. With DS, seizures include generalized **tonic-clonic** and unilateral **clonic seizures** and are generally refractory to treatment with antiepileptic drugs (AEDs). Note that AEDs are also referred to as antiseizure medications (ASMs).

LGS is another severe and rare DEE with a peak onset between ages 3 to 5. It is characterized by multiple types of refractory seizures, most often **tonic** and **atypical** absence seizures. Other characteristics include abnormal electroencephalogram (EEG) patterns and cognitive impairment that is often accompanied by behavioral issues.

This highlights page provides an overview of the various sections of the FINTEPLA prescribing information (PI), which are described in more detail in subsequent pages.

1

FULL PRESCRIBING INFORMATION: CONTENTS*

WARNING: VALVULAR HEART DISEASE and PULMONARY ARTERIAL HYPERTENSION

*Sections or subsections omitted from the full prescribing information are not listed.

1 The FINTEPLA highlights continue onto the second page of the FINTEPLA PI and provide hyperlinks to the various sections.

FULL PRESCRIBING INFORMATION

1

WARNING: VALVULAR HEART DISEASE and PULMONARY ARTERIAL HYPERTENSION

There is an association between serotonergic drugs with 5–HT2B receptor agonist activity, including fenfluramine (the active ingredient in FINTEPLA), and valvular heart disease and pulmonary arterial hypertension *[see Warnings and Precautions (5.1)]*.

Echocardiogram assessments are required before, during, and after treatment with FINTEPLA. The benefits versus the risks of initiating or continuing FINTEPLA must be considered, based on echocardiogram findings *[see Dosage and Administration (2.1, 2.5) and Warnings and Precautions (5.1)]*.

Because of the risks of valvular heart disease and pulmonary arterial hypertension, FINTEPLA is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the FINTEPLA REMS *[see Warnings and Precautions (5.2)]*.

1 INDICATIONS AND USAGE

FINTEPLA is indicated for the treatment of seizures associated with Dravet syndrome (DS) and Lennox-Gastaut syndrome (LGS) in patients 2 years of age and older.

2 DOSAGE AND ADMINISTRATION

2.1 Assessments Prior to Initiating FINTEPLA

Prior to starting treatment with FINTEPLA, obtain an echocardiogram assessment to evaluate for valvular heart disease and pulmonary arterial hypertension *[see Dosage and Administration (2.5) and Warnings and Precautions (5.1)]*.

2.2 Dosing Information

FINTEPLA is to be administered orally and may be taken with or without food.

Dravet Syndrome

- The initial starting and maintenance dosage for patients with Dravet Syndrome is 0.1 mg/kg twice daily, which can be increased weekly based on efficacy and tolerability. Table 1 provides the recommended titration schedule, if needed.
- Patients with Dravet Syndrome not on concomitant stiripentol who are tolerating FINTEPLA at 0.1 mg/kg twice daily and require further reduction of seizures may benefit from a dosage increase up to a maximum recommended maintenance dosage of 0.35 mg/kg twice daily (maximum daily dosage of 26 mg).
- Patients with Dravet Syndrome taking concomitant stiripentol plus clobazam who are tolerating FINTEPLA at 0.1 mg/kg twice daily and require further reduction of seizures

1 The FINTEPLA PI contains a boxed warning regarding valvular heart disease and pulmonary arterial hypertension. It explains that echocardiogram assessments are required before, during, and after treatment with FINTEPLA. The boxed warning also explains that FINTEPLA is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the FINTEPLA REMS.

Echocardiography is a noninvasive test that uses ultrasound to visualize cardiac structures, and an echocardiogram is the graphic record produced by echocardiography. The heart contains four valves, including the:

- Aortic valve
- Pulmonary valve
- Mitral valve
- Tricuspid valve

These valves open to allow blood to flow through or out of the heart and close to keep blood from flowing backward. When these valves do not work properly, patients may have:

- Regurgitation, which refers to when blood leaks in the wrong direction back through the valve
- Mitral valve prolapse, which occurs when the flaps of the mitral valve do not close tightly; mitral valve prolapse may result in regurgitation
- Stenosis, which occurs when the valve is narrowed and does not open properly; the flaps of the valve may thicken, stiffen, or fuse together, prohibiting the valve from fully opening

Pulmonary arterial hypertension is a condition that occurs when small arteries throughout the lungs narrow and become thickened, resulting in increased blood pressure in the lung. It can also lead to the heart working harder and losing its ability to efficiently pump blood throughout the body.

FULL PRESCRIBING INFORMATION

WARNING: VALVULAR HEART DISEASE and PULMONARY ARTERIAL HYPERTENSION

There is an association between serotonergic drugs with 5–HT2B receptor agonist activity, including fenfluramine (the active ingredient in FINTEPLA), and valvular heart disease and pulmonary arterial hypertension *[see Warnings and Precautions (5.1)]*.

Echocardiogram assessments are required before, during, and after treatment with FINTEPLA. The benefits versus the risks of initiating or continuing FINTEPLA must be considered, based on echocardiogram findings *[see Dosage and Administration (2.1, 2.5) and Warnings and Precautions (5.1)]*.

Because of the risks of valvular heart disease and pulmonary arterial hypertension, FINTEPLA is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the FINTEPLA REMS *[see Warnings and Precautions (5.2)]*.

1

1 INDICATIONS AND USAGE

FINTEPLA is indicated for the treatment of seizures associated with Dravet syndrome (DS) and Lennox-Gastaut syndrome (LGS) in patients 2 years of age and older.

2

2 DOSAGE AND ADMINISTRATION

2.1 Assessments Prior to Initiating FINTEPLA

Prior to starting treatment with FINTEPLA, obtain an echocardiogram assessment to evaluate for valvular heart disease and pulmonary arterial hypertension *[see Dosage and Administration (2.5) and Warnings and Precautions (5.1)]*.

2.2 Dosing Information

FINTEPLA is to be administered orally and may be taken with or without food.

Dravet Syndrome

- The initial starting and maintenance dosage for patients with Dravet Syndrome is 0.1 mg/kg twice daily, which can be increased weekly based on efficacy and tolerability. Table 1 provides the recommended titration schedule, if needed.
- Patients with Dravet Syndrome not on concomitant stiripentol who are tolerating FINTEPLA at 0.1 mg/kg twice daily and require further reduction of seizures may benefit from a dosage increase up to a maximum recommended maintenance dosage of 0.35 mg/kg twice daily (maximum daily dosage of 26 mg).
- Patients with Dravet Syndrome taking concomitant stiripentol plus clobazam who are tolerating FINTEPLA at 0.1 mg/kg twice daily and require further reduction of seizures

1. Section 1 explains that FINTEPLA is indicated for the treatment of seizures associated with DS and LGS in patients 2 years of age and older.
2. Section 2 describes the dosage and administration of FINTEPLA. As discussed in Section 2.1, an echocardiogram assessment should be obtained before starting FINTEPLA treatment to evaluate for valvular heart disease and pulmonary arterial hypertension.

FULL PRESCRIBING INFORMATION

WARNING: VALVULAR HEART DISEASE and PULMONARY ARTERIAL HYPERTENSION

There is an association between serotonergic drugs with 5–HT2B receptor agonist activity, including fenfluramine (the active ingredient in FINTEPLA), and valvular heart disease and pulmonary arterial hypertension *[see Warnings and Precautions (5.1)]*.

Echocardiogram assessments are required before, during, and after treatment with FINTEPLA. The benefits versus the risks of initiating or continuing FINTEPLA must be considered, based on echocardiogram findings *[see Dosage and Administration (2.1, 2.5) and Warnings and Precautions (5.1)]*.

Because of the risks of valvular heart disease and pulmonary arterial hypertension, FINTEPLA is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the FINTEPLA REMS *[see Warnings and Precautions (5.2)]*.

1 INDICATIONS AND USAGE

FINTEPLA is indicated for the treatment of seizures associated with Dravet syndrome (DS) and Lennox-Gastaut syndrome (LGS) in patients 2 years of age and older.

2 DOSAGE AND ADMINISTRATION

2.1 Assessments Prior to Initiating FINTEPLA

Prior to starting treatment with FINTEPLA, obtain an echocardiogram assessment to evaluate for valvular heart disease and pulmonary arterial hypertension *[see Dosage and Administration (2.5) and Warnings and Precautions (5.1)]*.

1

2.2 Dosing Information

FINTEPLA is to be administered orally and may be taken with or without food.

Dravet Syndrome

- The initial starting and maintenance dosage for patients with Dravet Syndrome is 0.1 mg/kg twice daily, which can be increased weekly based on efficacy and tolerability. Table 1 provides the recommended titration schedule, if needed.
- Patients with Dravet Syndrome not on concomitant stiripentol who are tolerating FINTEPLA at 0.1 mg/kg twice daily and require further reduction of seizures may benefit from a dosage increase up to a maximum recommended maintenance dosage of 0.35 mg/kg twice daily (maximum daily dosage of 26 mg).
- Patients with Dravet Syndrome taking concomitant stiripentol plus clobazam who are tolerating FINTEPLA at 0.1 mg/kg twice daily and require further reduction of seizures

1 As described in Section 2.2, FINTEPLA is orally administered and may be taken with or without food. The initial starting dosage for patients with DS or LGS is 0.1 mg/kg twice daily.

Dravet Syndrome (DS)

- The initial maintenance dosage is also 0.1 mg/kg twice daily, which can be increased weekly based on efficacy and tolerability
- For patients who are tolerating FINTEPLA at 0.1 mg/kg twice daily and require further reduction of seizures:
  - Patients not on concomitant stiripentol may benefit from a dosage increase up to a maximum recommended maintenance dosage of 0.35 mg/kg twice daily (maximum daily dosage of 26 mg)
  - Patients taking concomitant stiripentol plus clobazam may benefit from a dosage increase up to a maximum recommended maintenance dosage of 0.2 mg/kg twice daily (maximum daily dosage of 17 mg)

Stiripentol (Diacomit®) is an AED indicated for the treatment of seizures associated with DS in patients 2 years of age and older taking clobazam.

Clobazam (Onfi®) is an AED indicated for the **adjunctive** treatment of seizures associated with LGS in patients 2 years of age or older.

may benefit from a dosage increase up to a maximum recommended maintenance dosage of 0.2 mg/kg twice daily (maximum daily dosage of 17 mg) *[see Drug Interactions (7.1)]*.

1

Lennox-Gastaut Syndrome

- The initial starting dosage for patients with Lennox-Gastaut syndrome is 0.1 mg/kg twice daily, which should be increased weekly based on tolerability. Table 1 provides the recommended titration schedule.
- Patients with Lennox-Gastaut syndrome not on concomitant stiripentol who are tolerating FINTEPLA should be titrated to the recommended maintenance dosage of 0.35 mg/kg twice daily (maximum daily dosage of 26 mg).
- Patients with Lennox-Gastaut syndrome taking concomitant stiripentol plus clobazam who are tolerating FINTEPLA should be titrated to the recommended maintenance dosage of 0.2 mg/kg twice daily (maximum daily dosage of 17 mg) *[see Drug Interactions (7.1)]*.

2

Table 1: FINTEPLA Recommended Titration Schedule*

	Without concomitant stiripentol*		With concomitant stiripentol plus clobazam	
	Weight-based Dosage	Maximum Total Daily Dosage±	Weight-based Dosage	Maximum Total Daily Dosage±
Initial Dosage+	0.1 mg/kg twice daily	26 mg	0.1 mg/kg twice daily	17 mg
Day 7	0.2 mg/kg twice daily	26 mg	0.15 mg/kg twice daily	17 mg
Day 14**	0.35 mg/kg twice daily	26 mg	0.2 mg/kg twice daily	17 mg

* *For patients not on concomitant stiripentol in whom a more rapid titration is warranted, the dose may be increased every 4 days.*
+ For patients with Dravet Syndrome, dosage may be increased based on clinical response to the maximum recommended dosage, as needed.
** For patients with Lennox-Gastaut syndrome, dosage should be increased as tolerated to the recommended maintenance dosage (i.e., Day 14).
± For maximum dosage with concomitant use of strong CYP1A2 or CYP2D6 inhibitors or in patients with severe renal impairment see Dosage and Administration 2.3, 2.4.

2.3 Dosage Modifications for Patients with Concomitant Use of Strong CYP1A2 or CYP2D6 Inhibitors (DS and LGS)

For patients with concomitant use of FINTEPLA with a strong CYP1A2 or CYP2D6 inhibitor, a maximum total daily dosage of 20 mg without concomitant stiripentol and 17 mg with concomitant stiripentol plus clobazam is recommended. *[see Drug Interactions (7.1)]*.

Lennox-Gastaut Syndrome (DS)

1 The initial starting dosage of 0.1 mg/kg twice daily should be increased weekly based on tolerability.

- For patients who are tolerating FINTEPLA at 0.1 mg/kg twice daily:
  - Patients not on concomitant stiripentol should be titrated to a maximum recommended maintenance dosage of 0.35 mg/kg twice daily (maximum daily dosage of 26 mg)
  - Patients taking concomitant stiripentol plus clobazam should be titrated to a dosage increase up to a maximum recommended maintenance dosage of 0.2 mg/kg twice daily (maximum daily dosage of 17 mg)

2 The recommended titration schedule for patients with either indication is summarized in Table 1. Footnotes below Table 1 provide further details for specific patient populations.

NOTE the difference in maintenance and titration recommendations for patients with DS versus those with LGS:

- For patients with DS, dosage *may be* increased based on clinical response to the maximum dosage, as needed
- For patients with LGS, dosage *should be* increased as tolerated to the recommended maintenance dosage (i.e., Day 14).

Recommendations are also provided for patients taking concomitant strong CYP1A2 or CYP2D6 inhibitors or in patients with severe renal impairment. These are discussed in Sections 2.3 and 2.4, respectively.

may benefit from a dosage increase up to a maximum recommended maintenance dosage of 0.2 mg/kg twice daily (maximum daily dosage of 17 mg) *[see Drug Interactions (7.1)]*.

Lennox-Gastaut Syndrome

- The initial starting dosage for patients with Lennox-Gastaut syndrome is 0.1 mg/kg twice daily, which should be increased weekly based on tolerability. Table 1 provides the recommended titration schedule.
- Patients with Lennox-Gastaut syndrome not on concomitant stiripentol who are tolerating FINTEPLA should be titrated to the recommended maintenance dosage of 0.35 mg/kg twice daily (maximum daily dosage of 26 mg).
- Patients with Lennox-Gastaut syndrome taking concomitant stiripentol plus clobazam who are tolerating FINTEPLA should be titrated to the recommended maintenance dosage of 0.2 mg/kg twice daily (maximum daily dosage of 17 mg) *[see Drug Interactions (7.1)]*.

Table 1: FINTEPLA Recommended Titration Schedule*

	Without concomitant stiripentol*		With concomitant stiripentol plus clobazam	
	Weight-based Dosage	Maximum Total Daily Dosage±	Weight-based Dosage	Maximum Total Daily Dosage±
Initial Dosage+	0.1 mg/kg twice daily	26 mg	0.1 mg/kg twice daily	17 mg
Day 7	0.2 mg/kg twice daily	26 mg	0.15 mg/kg twice daily	17 mg
Day 14**	0.35 mg/kg twice daily	26 mg	0.2 mg/kg twice daily	17 mg

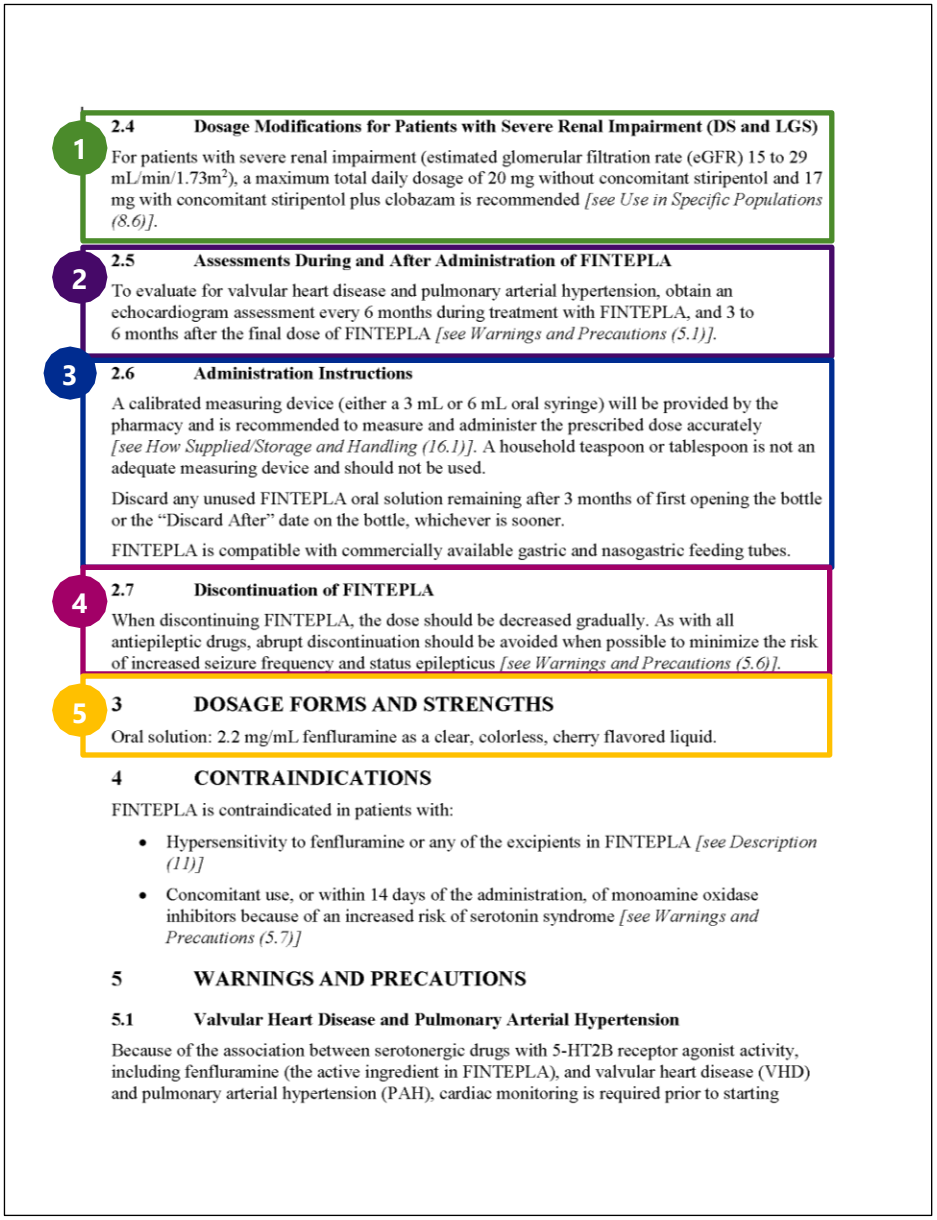
* *For patients not on concomitant stiripentol in whom a more rapid titration is warranted, the dose may be increased every 4 days.*
+ For patients with Dravet Syndrome, dosage may be increased based on clinical response to the maximum recommended dosage, as needed.
** For patients with Lennox-Gastaut syndrome, dosage should be increased as tolerated to the recommended maintenance dosage (i.e., Day 14).
± For maximum dosage with concomitant use of strong CYP1A2 or CYP2D6 inhibitors or in patients with severe renal impairment see Dosage and Administration 2.3, 2.4.

1

2.3 Dosage Modifications for Patients with Concomitant Use of Strong CYP1A2 or CYP2D6 Inhibitors (DS and LGS)

For patients with concomitant use of FINTEPLA with a strong CYP1A2 or CYP2D6 inhibitor, a maximum total daily dosage of 20 mg without concomitant stiripentol and 17 mg with concomitant stiripentol plus clobazam is recommended. *[see Drug Interactions (7.1)]*.

1 Section 2.3 describes dosage modifications needed in patients who are taking FINTEPLA concomitantly with drugs that are strong CYP1A2 or CYP2D6 inhibitors. In these patients, the recommended maximum total daily dosage is 20 mg without concomitant stiripentol and 17 mg with concomitant stiripentol plus clobazam.



2.4 Dosage Modifications for Patients with Severe Renal Impairment (DS and LGS)

For patients with severe renal impairment (estimated glomerular filtration rate (eGFR) 15 to 29 mL/min/1.73m^2), a maximum total daily dosage of 20 mg without concomitant stiripentol and 17 mg with concomitant stiripentol plus clobazam is recommended *[see Use in Specific Populations (8.6)]*.

2.5 Assessments During and After Administration of FINTEPLA

To evaluate for valvular heart disease and pulmonary arterial hypertension, obtain an echocardiogram assessment every 6 months during treatment with FINTEPLA, and 3 to 6 months after the final dose of FINTEPLA *[see Warnings and Precautions (5.1)]*.

2.6 Administration Instructions

A calibrated measuring device (either a 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 (16.1)]*. A household teaspoon or tablespoon is not an adequate measuring device and should not be used.

Discard any unused FINTEPLA oral solution remaining after 3 months of first opening the bottle or the "Discard After" date on the bottle, whichever is sooner.

FINTEPLA is compatible with commercially available gastric and nasogastric feeding tubes.

2.7 Discontinuation of FINTEPLA

When discontinuing FINTEPLA, the dose should be decreased gradually. As with all antiepileptic drugs, abrupt discontinuation should be avoided when possible to minimize the risk of increased seizure frequency and status epilepticus *[see Warnings and Precautions (5.6)]*.

3 DOSAGE FORMS AND STRENGTHS

Oral solution: 2.2 mg/mL fenfluramine as a clear, colorless, cherry flavored liquid.

4 CONTRAINDICATIONS

FINTEPLA is contraindicated in patients with:

- Hypersensitivity to fenfluramine or any of the excipients in FINTEPLA *[see Description (11)]*
- Concomitant use, or within 14 days of the administration, of monoamine oxidase inhibitors because of an increased risk of serotonin syndrome *[see Warnings and Precautions (5.7)]*

5 WARNINGS AND PRECAUTIONS

5.1 Valvular Heart Disease and Pulmonary Arterial Hypertension

Because of the association between serotonergic drugs with 5-HT2B receptor agonist activity, including fenfluramine (the active ingredient in FINTEPLA), and valvular heart disease (VHD) and pulmonary arterial hypertension (PAH), cardiac monitoring is required prior to starting

1. Section 2.4 states that the recommended maximum total daily dosage of FINTEPLA in patients with severe renal impairment (estimated glomerular filtration rate (eGFR) 15 to 29 mL/min/1.73m^2) is 20 mg without concomitant stiripentol and 17 mg with concomitant stiripentol plus clobazam.

2. Section 2.5 describes the assessments that are needed during and after the administration of FINTEPLA to evaluate for valvular heart disease and pulmonary arterial hypertension. Specifically, it explains that an echocardiogram assessment should be obtained:
   - Every 6 months during treatment with FINTEPLA
   - 3 to 6 months after the final dose of FINTEPLA

3. Section 2.6 of the FINTEPLA PI explains that a calibrated measuring device (either a 3 mL or 6 mL oral syringe) should be used to accurately measure and administer FINTEPLA. In addition, any unused FINTEPLA should be discarded if there is any remaining after 3 months of first opening the bottle or the "Discard After" date on the package and/or bottle has been reached, whichever is sooner. The labeling also states that FINTEPLA is compatible with commercially available gastric and nasogastric feeding tubes.

4. As explained in Section 2.7, abrupt discontinuation of AEDs should be avoided to minimize the risk of increased seizure frequency and **status epilepticus**. Therefore, the FINTEPLA dose should be gradually decreased when discontinuing its use.

5. Section 3 of the label states that FINTEPLA oral solution is available as a clear, colorless, cherry flavored liquid containing 2.2 mg/mL fenfluramine.

Take Home Points

- The FINTEPLA PI contains a boxed warning regarding valvular heart disease and pulmonary arterial hypertension; echocardiogram assessments are required before, during, and after treatment with FINTEPLA; FINTEPLA is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the FINTEPLA REMS
- FINTEPLA is indicated for the treatment of seizures associated with DS and LGS in patients 2 years of age and older
- Echocardiogram assessment should be obtained before starting FINTEPLA treatment to evaluate for valvular heart disease and pulmonary arterial hypertension
- FINTEPLA is orally administered and may be taken with or without food
- Dravet Syndrome
  - The initial starting and maintenance dosage is 0.1 mg/kg twice daily, which can be increased weekly based on efficacy and tolerability
  - Patients not on concomitant stiripentol who require further reduction of seizures may benefit from a dosage increase up to a maximum recommended maintenance dosage of 0.35 mg/kg twice daily (maximum daily dosage of 26 mg)
  - Patients taking concomitant stiripentol plus clobazam who require further reduction of seizures may benefit from a dosage increase up to a maximum recommended maintenance dosage of 0.2 mg/kg twice daily (maximum daily dosage of 17 mg)
- Lennox-Gastaut Syndrome
  - The initial starting dosage is 0.1 mg/kg twice daily, which should be increased weekly based on tolerability
  - Patients not on concomitant stiripentol who are tolerating FINTEPLA should be titrated to the recommended maintenance dosage of 0.35 mg/kg twice daily (maximum daily dosage of 26 mg)
  - Patients taking concomitant stiripentol plus clobazam who are tolerating FINTEPLA should be titrated to the recommended maintenance dosage of 0.2 mg/kg twice daily (maximum daily dosage of 17 mg)

Take Home Points (continued)

- FINTEPLA dosage modifications for patients with concomitant use of drugs that are strong CYP1A2 or CYP2D6 inhibitors:
  - Maximum total daily dosage: 20 mg without concomitant stiripentol
  - Maximum total daily dosage: 17 mg with concomitant stiripentol plus clobazam
- FINTEPLA dosage modifications for patients with severe renal impairment (eGFR 15 to 29 mL/min/1.73m^2):
  - Maximum total daily dosage: 20 mg without concomitant stiripentol
  - Maximum total daily dosage: 17 mg with concomitant stiripentol plus clobazam
- Echocardiogram assessment should be obtained every 6 months during treatment with FINTEPLA and 3 to 6 months after the final dose of FINTEPLA
- A calibrated measuring device (either a 3 mL or 6 mL oral syringe) should be used to accurately measure and administer FINTEPLA
- Any unused FINTEPLA should be discarded if there is any remaining after 3 months of first opening the bottle or the "Discard After" date on the package and/or bottle has been reached, whichever is sooner
- FINTEPLA dose should be gradually decreased when discontinuing its use
- FINTEPLA oral solution is available as a clear, colorless, cherry flavored liquid containing 2.2 mg/mL fenfluramine

Knowledge Check

FINTEPLA is indicated for the treatment of seizures associated with DS and LGS in patients _____ years of age and older.

- ☐ 2
- ☐ 4
- ☐ 10
- ☐ 12

SHOW ANSWER

Knowledge Check

FINTEPLA is indicated for the treatment of seizures associated with DS and LGS in patients _____ years of age and older.

- [x] **2**
- [ ] 4
- [ ] 10
- [ ] 12

NEXT QUESTION

Knowledge Check

Which of the following statements about the dosage and administration of FINTEPLA is true?

- [ ] FINTEPLA must be administered with food.
- [ ] The initial starting dosage is 0.35 mg/kg twice daily.
- [ ] An echocardiogram assessment should be obtained before starting FINTEPLA treatment to evaluate for valvular heart disease and pulmonary arterial hypertension.
- [ ] A teaspoon may be used to administer FINTEPLA.

SHOW ANSWER

Knowledge Check

Which of the following statements about the dosage and administration of FINTEPLA is true?

- ☐ FINTEPLA must be administered with food.
- ☐ The initial starting dosage is 0.35 mg/kg twice daily.
- ☑ **An echocardiogram assessment should be obtained before starting FINTEPLA treatment to evaluate for valvular heart disease and pulmonary arterial hypertension.**
- ☐ A teaspoon may be used to administer FINTEPLA.

NEXT PAGE

Chapter 2: Contraindications, Warnings and Precautions, Adverse Reactions

Learning Objectives

Upon completion of this chapter, you will be able to:

- Explain the contraindications of FINTEPLA
- Discuss the warnings and precautions associated with FINTEPLA
- Describe the adverse reactions observed in clinical trials of FINTEPLA

2.4 Dosage Modifications for Patients with Severe Renal Impairment (DS and LGS)

For patients with severe renal impairment (estimated glomerular filtration rate (eGFR) 15 to 29 mL/min/1.73m^2), a maximum total daily dosage of 20 mg without concomitant stiripentol and 17 mg with concomitant stiripentol plus clobazam is recommended *[see Use in Specific Populations (8.6)]*.

2.5 Assessments During and After Administration of FINTEPLA

To evaluate for valvular heart disease and pulmonary arterial hypertension, obtain an echocardiogram assessment every 6 months during treatment with FINTEPLA, and 3 to 6 months after the final dose of FINTEPLA *[see Warnings and Precautions (5.1)]*.

2.6 Administration Instructions

A calibrated measuring device (either a 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 (16.1)]*. A household teaspoon or tablespoon is not an adequate measuring device and should not be used.

Discard any unused FINTEPLA oral solution remaining after 3 months of first opening the bottle or the "Discard After" date on the bottle, whichever is sooner.

FINTEPLA is compatible with commercially available gastric and nasogastric feeding tubes.

2.7 Discontinuation of FINTEPLA

When discontinuing FINTEPLA, the dose should be decreased gradually. As with all antiepileptic drugs, abrupt discontinuation should be avoided when possible to minimize the risk of increased seizure frequency and status epilepticus *[see Warnings and Precautions (5.6)]*.

3 DOSAGE FORMS AND STRENGTHS

Oral solution: 2.2 mg/mL fenfluramine as a clear, colorless, cherry flavored liquid.

1

4 CONTRAINDICATIONS

FINTEPLA is contraindicated in patients with:

- Hypersensitivity to fenfluramine or any of the excipients in FINTEPLA *[see Description (11)]*
- Concomitant use, or within 14 days of the administration, of monoamine oxidase inhibitors because of an increased risk of serotonin syndrome *[see Warnings and Precautions (5.7)]*

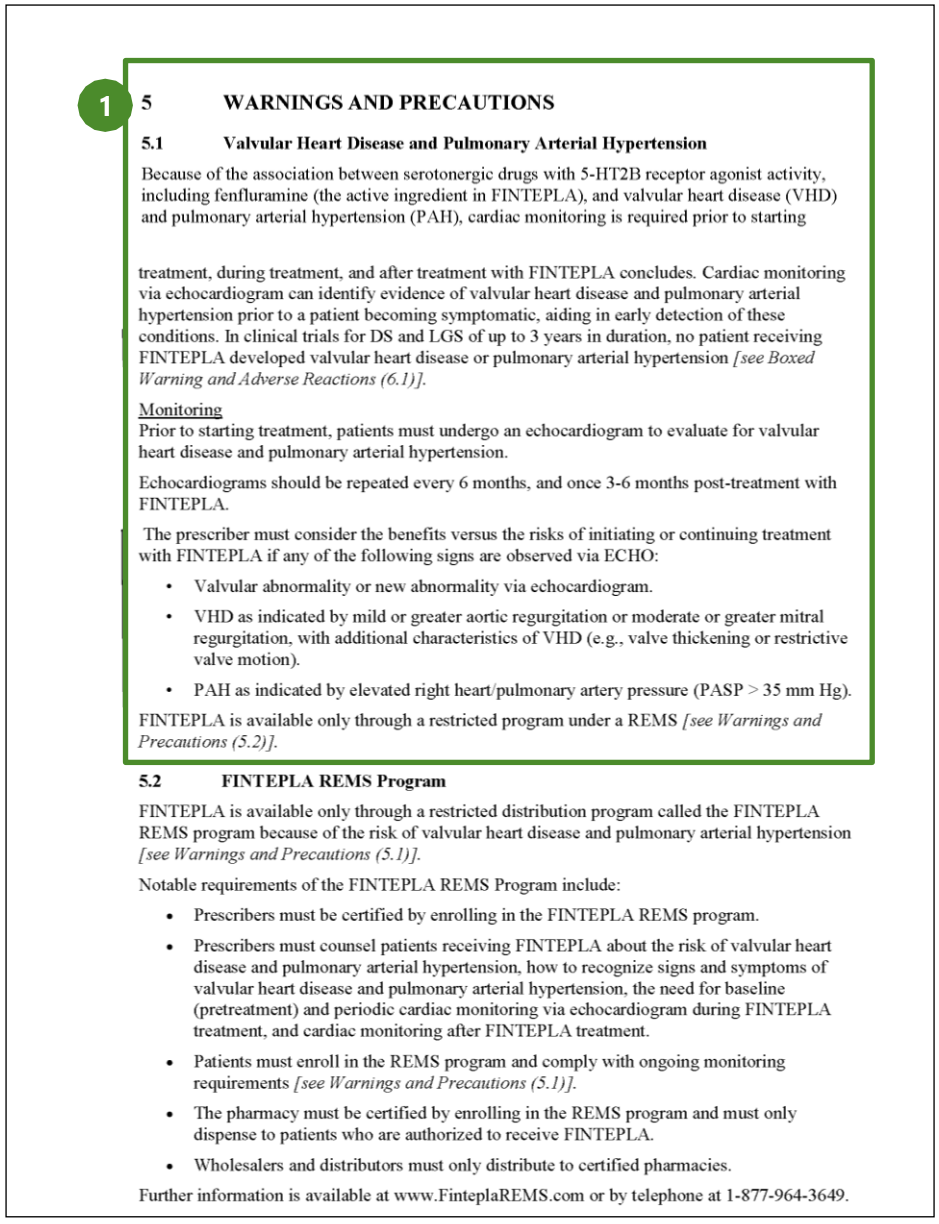
5 WARNINGS AND PRECAUTIONS

5.1 Valvular Heart Disease and Pulmonary Arterial Hypertension

Because of the association between serotonergic drugs with 5-HT2B receptor agonist activity, including fenfluramine (the active ingredient in FINTEPLA), and valvular heart disease (VHD) and pulmonary arterial hypertension (PAH), cardiac monitoring is required prior to starting

1 Section 4 of the FINTEPLA PI explains that FINTEPLA is contraindicated in patients with hypersensitivity to fenfluramine or any of the excipients in FINTEPLA.

FINTEPLA is also contraindicated in patients who are concomitantly using monoamine oxidase inhibitors (MAOIs) or have used an MAOI within 14 days because of an increased risk of **serotonin syndrome**.



1

5 WARNINGS AND PRECAUTIONS

5.1 Valvular Heart Disease and Pulmonary Arterial Hypertension

Because of the association between serotonergic drugs with 5-HT2B receptor agonist activity, including fenfluramine (the active ingredient in FINTEPLA), and valvular heart disease (VHD) and pulmonary arterial hypertension (PAH), cardiac monitoring is required prior to starting treatment, during treatment, and after treatment with FINTEPLA concludes. Cardiac monitoring via echocardiogram can identify evidence of valvular heart disease and pulmonary arterial hypertension prior to a patient becoming symptomatic, aiding in early detection of these conditions. In clinical trials for DS and LGS of up to 3 years in duration, no patient receiving FINTEPLA developed valvular heart disease or pulmonary arterial hypertension *[see Boxed Warning and Adverse Reactions (6.1)]*.

Monitoring

Prior to starting treatment, patients must undergo an echocardiogram to evaluate for valvular heart disease and pulmonary arterial hypertension.

Echocardiograms should be repeated every 6 months, and once 3-6 months post-treatment with FINTEPLA.

The prescriber must consider the benefits versus the risks of initiating or continuing treatment with FINTEPLA if any of the following signs are observed via ECHO:

- Valvular abnormality or new abnormality via echocardiogram.
- VHD as indicated by mild or greater aortic regurgitation or moderate or greater mitral regurgitation, with additional characteristics of VHD (e.g., valve thickening or restrictive valve motion).
- PAH as indicated by elevated right heart/pulmonary artery pressure (PASP > 35 mm Hg).

FINTEPLA is available only through a restricted program under a REMS *[see Warnings and Precautions (5.2)]*.

5.2 FINTEPLA REMS Program

FINTEPLA is available only through a restricted distribution program called the FINTEPLA REMS program because of the risk of valvular heart disease and pulmonary arterial hypertension *[see Warnings and Precautions (5.1)]*.

Notable requirements of the FINTEPLA REMS Program include:

- Prescribers must be certified by enrolling in the FINTEPLA REMS program.
- Prescribers must counsel patients receiving FINTEPLA about the risk of valvular heart disease and pulmonary arterial hypertension, how to recognize signs and symptoms of valvular heart disease and pulmonary arterial hypertension, the need for baseline (pretreatment) and periodic cardiac monitoring via echocardiogram during FINTEPLA treatment, and cardiac monitoring after FINTEPLA treatment.
- Patients must enroll in the REMS program and comply with ongoing monitoring requirements *[see Warnings and Precautions (5.1)]*.
- The pharmacy must be certified by enrolling in the REMS program and must only dispense to patients who are authorized to receive FINTEPLA.
- Wholesalers and distributors must only distribute to certified pharmacies.

Further information is available at www.FinteplaREMS.com or by telephone at 1-877-964-3649.

1 Section 5 of the FINTEPLA PI discusses its warnings and precautions, beginning with valvular heart disease (VHD) and pulmonary arterial hypertension (PAH).

Section 5.1 explains that cardiac monitoring with an echocardiogram before, during, and after treatment with FINTEPLA must be performed because of the association between serotonergic drugs with 5-HT2B receptor agonist activity and VHD and PAH. Monitoring patients with echocardiogram can provide evidence of VHD and PAH before a patient becomes symptomatic and aids in the early detection of these conditions. The FINTEPLA labeling notes that in clinical trials of up to 3 years duration, no patient treated with FINTEPLA developed VHD or PAH.

This section explains that echocardiograms should be obtained as follows:

- Before beginning FINTEPLA
- Every 6 months during FINTEPLA treatment
- 3 to 6 months after FINTEPLA treatment ends

Physicians must consider the benefits versus the risks of initiating or continuing FINTEPLA if any of the following signs are observed on an echocardiogram:

- Valvular abnormality or new abnormality
- VHD, as indicated by mild or greater aortic regurgitation or moderate or greater mitral regurgitation, with additional characteristics of VHD (e.g., valve thickening or restrictive valve motion)
- PAH, as indicated by elevated right heart/pulmonary artery pressure (pulmonary artery systolic pressure [PASP] >35 mmHg)

treatment, during treatment, and after treatment with FINTEPLA concludes. Cardiac monitoring via echocardiogram can identify evidence of valvular heart disease and pulmonary arterial hypertension prior to a patient becoming symptomatic, aiding in early detection of these conditions. In clinical trials for DS and LGS of up to 3 years in duration, no patient receiving FINTEPLA developed valvular heart disease or pulmonary arterial hypertension *[see Boxed Warning and Adverse Reactions (6.1)]*.

Monitoring

Prior to starting treatment, patients must undergo an echocardiogram to evaluate for valvular heart disease and pulmonary arterial hypertension.

Echocardiograms should be repeated every 6 months, and once 3-6 months post-treatment with FINTEPLA.

The prescriber must consider the benefits versus the risks of initiating or continuing treatment with FINTEPLA if any of the following signs are observed via ECHO:

- Valvular abnormality or new abnormality via echocardiogram.
- VHD as indicated by mild or greater aortic regurgitation or moderate or greater mitral regurgitation, with additional characteristics of VHD (e.g., valve thickening or restrictive valve motion).
- PAH as indicated by elevated right heart/pulmonary artery pressure (PASP > 35 mm Hg).

FINTEPLA is available only through a restricted program under a REMS *[see Warnings and Precautions (5.2)]*.

1

5.2 FINTEPLA REMS Program

FINTEPLA is available only through a restricted distribution program called the FINTEPLA REMS program because of the risk of valvular heart disease and pulmonary arterial hypertension *[see Warnings and Precautions (5.1)]*.

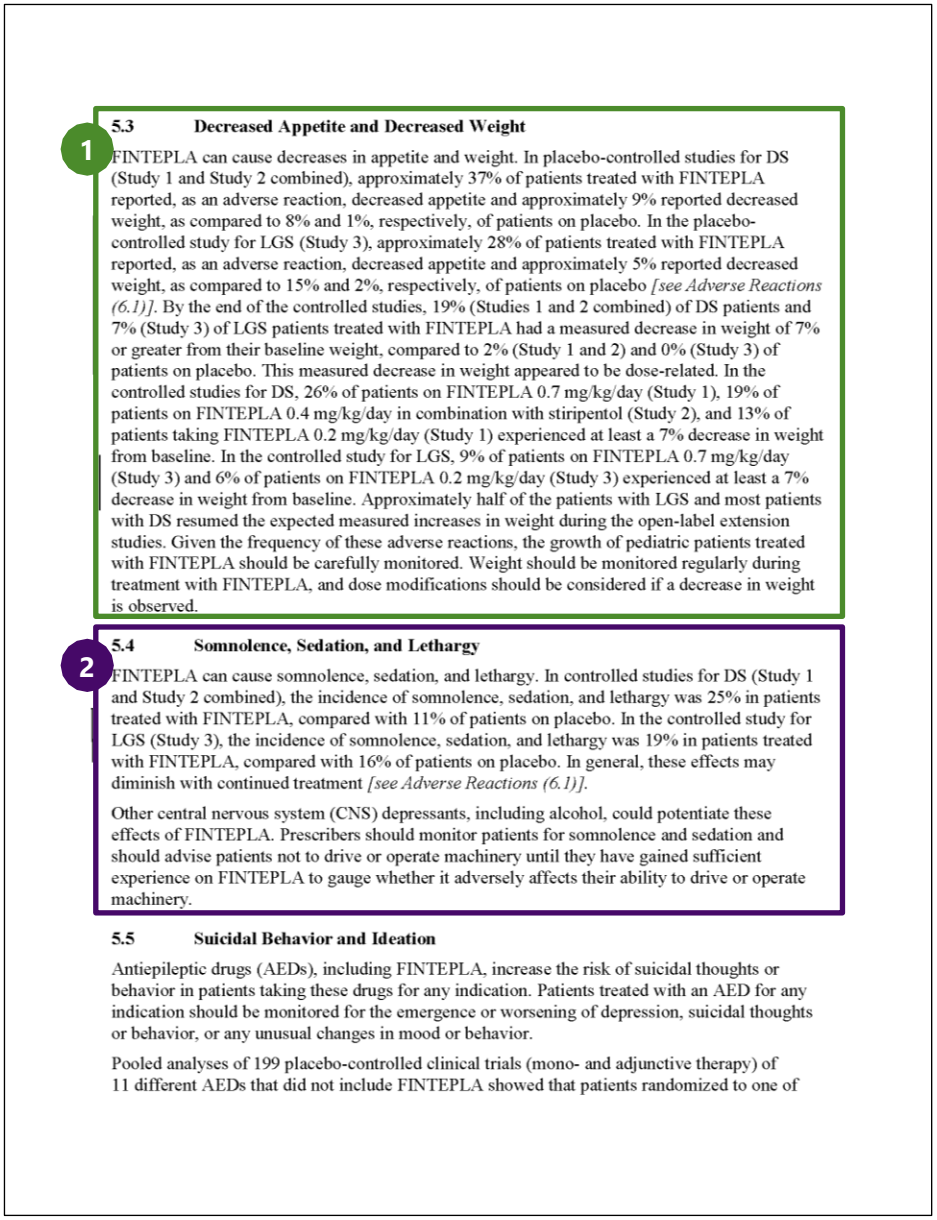
Notable requirements of the FINTEPLA REMS Program include:

- Prescribers must be certified by enrolling in the FINTEPLA REMS program.
- Prescribers must counsel patients receiving FINTEPLA about the risk of valvular heart disease and pulmonary arterial hypertension, how to recognize signs and symptoms of valvular heart disease and pulmonary arterial hypertension, the need for baseline (pretreatment) and periodic cardiac monitoring via echocardiogram during FINTEPLA treatment, and cardiac monitoring after FINTEPLA treatment.
- Patients must enroll in the REMS program and comply with ongoing monitoring requirements *[see Warnings and Precautions (5.1)]*.
- The pharmacy must be certified by enrolling in the REMS program and must only dispense to patients who are authorized to receive FINTEPLA.
- Wholesalers and distributors must only distribute to certified pharmacies.

Further information is available at www.FinteplaREMS.com or by telephone at 1-877-964-3649.

1 Section 5.2 of the PI explains that FINTEPLA is only available through the FINTEPLA REMS Program, which is a restricted distribution program, because of the potential risk of valvular heart disease and pulmonary arterial hypertension.

More information about this program is available online at www.FinteplaREMS.com or by telephone at 1-877-964-3649.



5.3 Decreased Appetite and Decreased Weight

FINTEPLA can cause decreases in appetite and weight. In placebo-controlled studies for DS (Study 1 and Study 2 combined), approximately 37% of patients treated with FINTEPLA reported, as an adverse reaction, decreased appetite and approximately 9% reported decreased weight, as compared to 8% and 1%, respectively, of patients on placebo. In the placebo-controlled study for LGS (Study 3), approximately 28% of patients treated with FINTEPLA reported, as an adverse reaction, decreased appetite and approximately 5% reported decreased weight, as compared to 15% and 2%, respectively, of patients on placebo *[see Adverse Reactions (6.1)]*. By the end of the controlled studies, 19% (Studies 1 and 2 combined) of DS patients and 7% (Study 3) of LGS patients treated with FINTEPLA had a measured decrease in weight of 7% or greater from their baseline weight, compared to 2% (Study 1 and 2) and 0% (Study 3) of patients on placebo. This measured decrease in weight appeared to be dose-related. In the controlled studies for DS, 26% of patients on FINTEPLA 0.7 mg/kg/day (Study 1), 19% of patients on FINTEPLA 0.4 mg/kg/day in combination with stiripentol (Study 2), and 13% of patients taking FINTEPLA 0.2 mg/kg/day (Study 1) experienced at least a 7% decrease in weight from baseline. In the controlled study for LGS, 9% of patients on FINTEPLA 0.7 mg/kg/day (Study 3) and 6% of patients on FINTEPLA 0.2 mg/kg/day (Study 3) experienced at least a 7% decrease in weight from baseline. Approximately half of the patients with LGS and most patients with DS resumed the expected measured increases in weight during the open-label extension studies. Given the frequency of these adverse reactions, the growth of pediatric patients treated with FINTEPLA should be carefully monitored. Weight should be monitored regularly during treatment with FINTEPLA, and dose modifications should be considered if a decrease in weight is observed.

5.4 Somnolence, Sedation, and Lethargy

FINTEPLA can cause somnolence, sedation, and lethargy. In controlled studies for DS (Study 1 and Study 2 combined), the incidence of somnolence, sedation, and lethargy was 25% in patients treated with FINTEPLA, compared with 11% of patients on placebo. In the controlled study for LGS (Study 3), the incidence of somnolence, sedation, and lethargy was 19% in patients treated with FINTEPLA, compared with 16% of patients on placebo. In general, these effects may diminish with continued treatment *[see Adverse Reactions (6.1)]*.

Other central nervous system (CNS) depressants, including alcohol, could potentiate these effects of FINTEPLA. Prescribers should monitor patients for somnolence and sedation and should advise patients not to drive or operate machinery until they have gained sufficient experience on FINTEPLA to gauge whether it adversely affects their ability to drive or operate machinery.

5.5 Suicidal Behavior and Ideation

Antiepileptic drugs (AEDs), including FINTEPLA, increase the risk of suicidal thoughts or behavior in patients taking these drugs for any indication. Patients treated with an AED for any indication should be monitored for the emergence or worsening of depression, suicidal thoughts or behavior, or any unusual changes in mood or behavior.

Pooled analyses of 199 placebo-controlled clinical trials (mono- and adjunctive therapy) of 11 different AEDs that did not include FINTEPLA showed that patients randomized to one of

1. The third warning and precaution in the FINTEPLA PI states FINTEPLA can cause decreases in appetite and weight as demonstrated in clinical trials. It is explained that measured weight decreases appeared to be dose-related and that approximately half of the patients with LGS and most patients with DS resumed the expected measured increases in weight during the open-label extension studies. It is explained that the growth of pediatric patients treated with FINTEPLA should be carefully monitored. During treatment with FINTEPLA, weight should be monitored regularly, and dose modifications should be considered if a decrease in weight is observed.

2. Section 5.4 of the PI explains that in controlled studies for DS (Studies 1 and 2 combined), the incidence of **somnolence**, **sedation**, and **lethargy** was as follows:
   - Patients treated with FINTEPLA: 25%
   - Patients treated with placebo: 11%

   In the controlled study for LGS (Study 3), the incidence of somnolence, sedation, and lethargy was as follows:
   - Patients treated with FINTEPLA: 19%
   - Patients treated with placebo: 16%

   The PI explains that, in general, these effects may diminish with continued treatment.

   It should be noted that other central nervous system (CNS) depressants (e.g., alcohol) could potentiate these effects of FINTEPLA. Patients should be monitored for somnolence and sedation. Furthermore, patients should be advised to not drive or operate machinery until they have gained sufficient experience on FINTEPLA.

5.3 Decreased Appetite and Decreased Weight

FINTEPLA can cause decreases in appetite and weight. In placebo-controlled studies for DS (Study 1 and Study 2 combined), approximately 37% of patients treated with FINTEPLA reported, as an adverse reaction, decreased appetite and approximately 9% reported decreased weight, as compared to 8% and 1%, respectively, of patients on placebo. In the placebo-controlled study for LGS (Study 3), approximately 28% of patients treated with FINTEPLA reported, as an adverse reaction, decreased appetite and approximately 5% reported decreased weight, as compared to 15% and 2%, respectively, of patients on placebo *[see Adverse Reactions (6.1)]*. By the end of the controlled studies, 19% (Studies 1 and 2 combined) of DS patients and 7% (Study 3) of LGS patients treated with FINTEPLA had a measured decrease in weight of 7% or greater from their baseline weight, compared to 2% (Study 1 and 2) and 0% (Study 3) of patients on placebo. This measured decrease in weight appeared to be dose-related. In the controlled studies for DS, 26% of patients on FINTEPLA 0.7 mg/kg/day (Study 1), 19% of patients on FINTEPLA 0.4 mg/kg/day in combination with stiripentol (Study 2), and 13% of patients taking FINTEPLA 0.2 mg/kg/day (Study 1) experienced at least a 7% decrease in weight from baseline. In the controlled study for LGS, 9% of patients on FINTEPLA 0.7 mg/kg/day (Study 3) and 6% of patients on FINTEPLA 0.2 mg/kg/day (Study 3) experienced at least a 7% decrease in weight from baseline. Approximately half of the patients with LGS and most patients with DS resumed the expected measured increases in weight during the open-label extension studies. Given the frequency of these adverse reactions, the growth of pediatric patients treated with FINTEPLA should be carefully monitored. Weight should be monitored regularly during treatment with FINTEPLA, and dose modifications should be considered if a decrease in weight is observed.

5.4 Somnolence, Sedation, and Lethargy

FINTEPLA can cause somnolence, sedation, and lethargy. In controlled studies for DS (Study 1 and Study 2 combined), the incidence of somnolence, sedation, and lethargy was 25% in patients treated with FINTEPLA, compared with 11% of patients on placebo. In the controlled study for LGS (Study 3), the incidence of somnolence, sedation, and lethargy was 19% in patients treated with FINTEPLA, compared with 16% of patients on placebo. In general, these effects may diminish with continued treatment *[see Adverse Reactions (6.1)]*.

Other central nervous system (CNS) depressants, including alcohol, could potentiate these effects of FINTEPLA. Prescribers should monitor patients for somnolence and sedation and should advise patients not to drive or operate machinery until they have gained sufficient experience on FINTEPLA to gauge whether it adversely affects their ability to drive or operate machinery.

1 **5.5 Suicidal Behavior and Ideation**

Antiepileptic drugs (AEDs), including FINTEPLA, increase the risk of suicidal thoughts or behavior in patients taking these drugs for any indication. Patients treated with an AED for any indication should be monitored for the emergence or worsening of depression, suicidal thoughts or behavior, or any unusual changes in mood or behavior.

Pooled analyses of 199 placebo-controlled clinical trials (mono- and adjunctive therapy) of 11 different AEDs that did not include FINTEPLA showed that patients randomized to one of

1 The fifth warning and precaution of the FINTEPLA PI explains that there is an increased risk of suicidal thoughts or behavior in patients taking AEDs for any indication and patients should be monitored for:

- Emergence or worsening of depression
- Suicidal thoughts or behavior
- Any unusual changes in mood or behavior

Data from a pooled analysis of 199 **placebo-controlled** clinical trials of 11 different AEDs (not including FINTEPLA) for monotherapy or adjunctive therapy are presented.

Results are presented on the next screen.

1 the AEDs had approximately twice the risk (adjusted Relative Risk 1.8, 95% CI:1.2, 2.7) of suicidal thinking or behavior compared to patients randomized to placebo. In these trials, which had a median treatment duration of 12 weeks, the estimated incidence rate of suicidal behavior or ideation among 27,863 AED-treated patients was 0.43%, compared to 0.24% among 16,029 placebo-treated patients, representing an increase of approximately one case of suicidal thinking or behavior for every 530 patients treated. There were four suicides in drug-treated patients in the trials and none in placebo-treated patients, but the number is too small to allow any conclusion about drug effect on suicide.

The increased risk of suicidal thoughts or behavior with AEDs was observed as early as 1 week after starting drug treatment with AEDs and persisted for the duration of treatment assessed. Because most trials included in the analysis did not extend beyond 24 weeks, the risk of suicidal thoughts or behavior beyond 24 weeks could not be assessed.

The risk of suicidal thoughts or behavior was generally consistent among drugs in the data analyzed. The finding of increased risk with AEDs of varying mechanisms of action and across a range of indications suggests that the risk applies to all AEDs used for any indication. The risk did not vary substantially by age (5-100 years) in the clinical trials analyzed. Table 2 shows absolute and relative risk by indication for all evaluated AEDs.

Table 2: Risk of Suicidal Thoughts or Behaviors by Indication for Antiepileptic Drugs in the Pooled Analysis

Indication	Placebo Patients with Events per 1000 Patients	Drug Patients with Events per 1000 Patients	Relative Risk: Incidence of Events in Drug Patients/ Incidence in Placebo Patients	Risk Difference: Additional Drug Patients with Events per 1000 Patients
Epilepsy	1.0	3.4	3.5	2.4
Psychiatric	5.7	8.5	1.5	2.9
Other	1.0	1.8	1.9	0.9
Total	2.4	4.3	1.8	1.9

The relative risk for suicidal thoughts or behavior was higher in clinical trials in patients with epilepsy than in clinical trials in patients with psychiatric or other conditions, but the absolute risk differences were similar for the epilepsy and psychiatric indications.

Anyone considering prescribing FINTEPLA or any other AED must balance the risk of suicidal thoughts or behaviors with the risk of untreated illness. Epilepsy and many other illnesses for which AEDs are prescribed are themselves associated with morbidity and mortality and an increased risk of suicidal thoughts and behavior. Should suicidal thoughts and behavior emerge during treatment, consider whether the emergence of these symptoms in any given patient may be related to the illness being treated.

2 **5.6 Withdrawal of Antiepileptic Drugs**

As with most AEDs, FINTEPLA should generally be withdrawn gradually because of the risk of increased seizure frequency and status epilepticus. If withdrawal is needed because of a serious adverse reaction, rapid discontinuation can be considered.

1 Section 5.5 Suicidal Behavior and Ideation (continued)

Results showed that patients treated with an AED had about twice the risk of suicidal thinking or behavior compared to patients treated with placebo. In addition, the risk of suicidal thoughts or behavior was generally consistent among the drugs in the data analyzed.

Healthcare professionals must balance the risk of suicidal thoughts or behaviors with the risk of untreated illness when prescribing FINTEPLA to patients.

2 Section 5.6 explains that FINTEPLA should generally be withdrawn gradually because of the risk of increased seizure frequency and status epilepticus. Rapid discontinuation can be considered due to a serious adverse reaction.

Recall that discontinuation of FINTEPLA was also discussed in Section 2.7 of the PI.

1

5.7 Serotonin Syndrome

Serotonin syndrome, a potentially life-threatening condition, may occur with FINTEPLA, particularly with concomitant administration of FINTEPLA with other serotonergic drugs, including, but not limited to, selective serotonin-norepinephrine reuptake inhibitors (SNRIs), selective serotonin reuptake inhibitors (SSRIs), tricyclic antidepressants (TCAs), bupropion, triptans, dietary supplements (e.g., St. John's Wort, tryptophan), drugs that impair metabolism of serotonin (including monoamine oxidase inhibitors [MAOIs], which are contraindicated with FINTEPLA *[see Contraindications (4)]*, dextromethorphan, lithium, tramadol, and antipsychotics with serotonergic agonist activity. Patients should be monitored for the emergence of signs and symptoms of serotonin syndrome, which include mental status changes (e.g., agitation, hallucinations, coma), autonomic instability (e.g., tachycardia, labile blood pressure, hyperthermia), neuromuscular signs (e.g., hyperreflexia, incoordination), and/or gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea). If serotonin syndrome is suspected, treatment with FINTEPLA should be stopped immediately and symptomatic treatment should be started.

5.8 Increase in Blood Pressure

FINTEPLA can cause an increase in blood pressure *[see Adverse Reactions (6.1)]*. Rare cases of significant elevation in blood pressure, including hypertensive crisis, has been reported in adult patients treated with fenfluramine, including patients without a history of hypertension. In clinical trials of up to 3 years in duration, no pediatric or adult patient receiving FINTEPLA developed a hypertensive crisis. Monitor blood pressure in patients treated with FINTEPLA.

5.9 Glaucoma

Fenfluramine can cause mydriasis and can precipitate angle closure glaucoma. Consider discontinuing treatment with FINTEPLA in patients with acute decreases in visual acuity or ocular pain.

6 ADVERSE REACTIONS

The following clinically significant adverse reactions are described elsewhere in labeling:

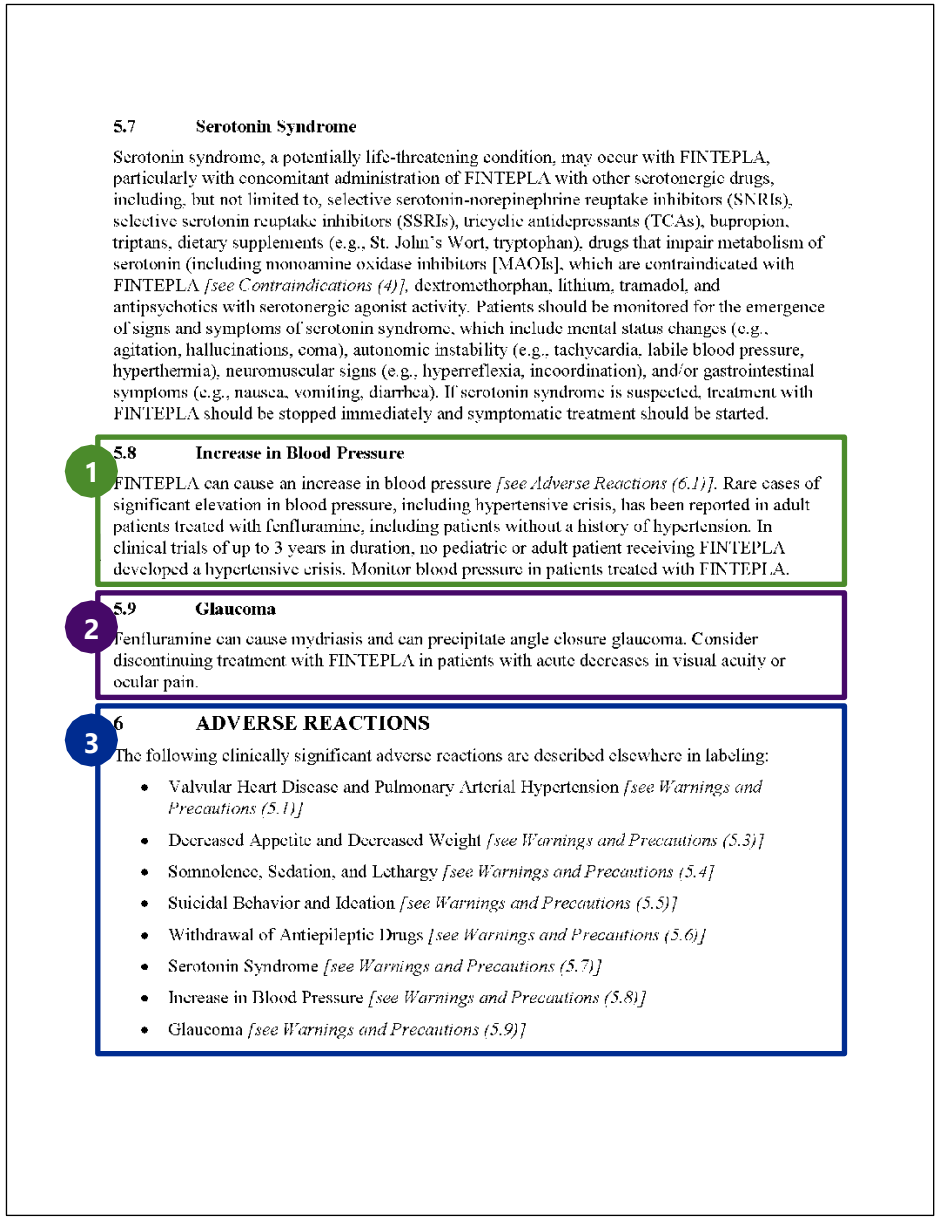
- Valvular Heart Disease and Pulmonary Arterial Hypertension *[see Warnings and Precautions (5.1)]*
- Decreased Appetite and Decreased Weight *[see Warnings and Precautions (5.3)]*
- Somnolence, Sedation, and Lethargy *[see Warnings and Precautions (5.4]*
- Suicidal Behavior and Ideation *[see Warnings and Precautions (5.5)]*
- Withdrawal of Antiepileptic Drugs *[see Warnings and Precautions (5.6)]*
- Serotonin Syndrome *[see Warnings and Precautions (5.7)]*
- Increase in Blood Pressure *[see Warnings and Precautions (5.8)]*
- Glaucoma *[see Warnings and Precautions (5.9)]*

1 The seventh warning and precaution of the FINTEPLA PI explains that serotonin syndrome may occur with FINTEPLA, particularly with concomitant administration of FINTEPLA with other serotonergic drugs, such as:

- Selective serotonin-norepinephrine reuptake inhibitors (SNRIs)
- Selective serotonin reuptake inhibitors (SSRIs)
- Tricyclic antidepressants (TCAs)
- Bupropion
- Triptans
- Dietary supplements (e.g., St. John's Wort, tryptophan)
- Drugs that impair metabolism of serotonin (i.e., MAOIs)
- Dextromethorphan
- Lithium
- Tramadol
- Antipsychotics with serotonergic agonist activity

Patients should be monitored for the emergence of signs and symptoms and treatment with FINTEPLA should be stopped if serotonin syndrome is suspected.

Remember that Section 4 states that FINTEPLA is contraindicated in patients who are concomitantly using MAOIs or have used an MAOI within 14 days due to an increased risk of serotonin syndrome.



5.7 Serotonin Syndrome

Serotonin syndrome, a potentially life-threatening condition, may occur with FINTEPLA, particularly with concomitant administration of FINTEPLA with other serotonergic drugs, including, but not limited to, selective serotonin-norepinephrine reuptake inhibitors (SNRIs), selective serotonin reuptake inhibitors (SSRIs), tricyclic antidepressants (TCAs), bupropion, triptans, dietary supplements (e.g., St. John's Wort, tryptophan), drugs that impair metabolism of serotonin (including monoamine oxidase inhibitors [MAOIs], which are contraindicated with FINTEPLA *[see Contraindications (4)]*, dextromethorphan, lithium, tramadol, and antipsychotics with serotonergic agonist activity. Patients should be monitored for the emergence of signs and symptoms of serotonin syndrome, which include mental status changes (e.g., agitation, hallucinations, coma), autonomic instability (e.g., tachycardia, labile blood pressure, hyperthermia), neuromuscular signs (e.g., hyperreflexia, incoordination), and/or gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea). If serotonin syndrome is suspected, treatment with FINTEPLA should be stopped immediately and symptomatic treatment should be started.

1

5.8 Increase in Blood Pressure

FINTEPLA can cause an increase in blood pressure *[see Adverse Reactions (6.1)]*. Rare cases of significant elevation in blood pressure, including hypertensive crisis, has been reported in adult patients treated with fenfluramine, including patients without a history of hypertension. In clinical trials of up to 3 years in duration, no pediatric or adult patient receiving FINTEPLA developed a hypertensive crisis. Monitor blood pressure in patients treated with FINTEPLA.

2

5.9 Glaucoma

Fenfluramine can cause mydriasis and can precipitate angle closure glaucoma. Consider discontinuing treatment with FINTEPLA in patients with acute decreases in visual acuity or ocular pain.

3

6 ADVERSE REACTIONS

The following clinically significant adverse reactions are described elsewhere in labeling:

- Valvular Heart Disease and Pulmonary Arterial Hypertension *[see Warnings and Precautions (5.1)]*
- Decreased Appetite and Decreased Weight *[see Warnings and Precautions (5.3)]*
- Somnolence, Sedation, and Lethargy *[see Warnings and Precautions (5.4]*
- Suicidal Behavior and Ideation *[see Warnings and Precautions (5.5)]*
- Withdrawal of Antiepileptic Drugs *[see Warnings and Precautions (5.6)]*
- Serotonin Syndrome *[see Warnings and Precautions (5.7)]*
- Increase in Blood Pressure *[see Warnings and Precautions (5.8)]*
- Glaucoma *[see Warnings and Precautions (5.9)]*

1. Section 5.8 of the FINTEPLA PI explains that FINTEPLA can cause an increase in blood pressure. However, in clinical trials of up to 3 years in duration, no patient (pediatric or adult) receiving FINTEPLA developed a hypertensive crisis. Patients treated with FINTEPLA should have their blood pressure monitored.

2. The final warning and precaution of the FINTEPLA PI explains that fenfluramine can cause mydriasis, which is dilation of the pupil, and can lead to the development of angle closure glaucoma.

   Angle-closure glaucoma, which is also referred to as narrow-angle glaucoma, is a sudden rise in eye pressure due to blocked drainage canals. Symptoms include headaches, eye pain, nausea, rainbows around lights at night, and very blurred vision.

   Discontinuation of FINTEPLA should be considered in patients with acute decreases in visual acuity or ocular pain.

3. Section 6 of the PI describes the adverse reactions associated with FINTEPLA. It begins by explaining that several important adverse reactions are described in more detail in the various warnings and precautions sections of the FINTEPLA PI.

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

In controlled and uncontrolled trials in patients with Dravet syndrome (DS), 341 patients were treated with FINTEPLA, including 312 patients treated for more than 6 months, 284 patients treated for more than 1 year, and 138 patients treated for more than 2 years.

In controlled and uncontrolled trials in patients with Lennox-Gastaut syndrome (LGS), 262 patients were treated with FINTEPLA, including 219 patients treated for more than 6 months, 172 patients treated for more than 1 year, and 127 patients treated for more than 2 years.

Dravet Syndrome

In placebo-controlled trials of patients with DS taking concomitant standard of care AEDs, 122 patients were treated with FINTEPLA and 84 patients received placebo *[see Clinical Studies (14.1)]*. The duration of treatment in these trials was 16 weeks (Study 1) or 17 weeks (Study 2). In Study 1 and Study 2, the mean age was 9 years (range 2 to 19 years) and approximately 46% of patients were female and 74% were White. All patients were receiving at least one other AED.

In Study 1 and Study 2, the rates of discontinuation as a result of any adverse reaction were 13%, 0%, and 7% for patients treated with FINTEPLA 0.7 mg/kg/day, 0.2 mg/kg/day, and 0.4 mg/kg/day in combination with stiripentol, respectively, compared to 6% for patients on placebo. The most frequent adverse reaction leading to discontinuation in the patients treated with any dose of FINTEPLA was somnolence (3%).

The most common adverse reactions that occurred in patients treated with FINTEPLA (incidence at least 10% and greater than placebo) were decreased appetite; somnolence, sedation, lethargy; diarrhea; constipation; abnormal echocardiogram; fatigue, malaise, asthenia; ataxia, balance disorder, gait disturbance; blood pressure increased; drooling, salivary hypersecretion; pyrexia; upper respiratory tract infection; vomiting; decreased weight; fall; status epilepticus.

Table 3 lists the adverse reactions that were reported in 5% or more of patients treated with FINTEPLA and at a rate greater than those on placebo during the titration and maintenance phases of Study 1 and Study 2.

Table 2: Adverse Reactions in 5% or More of Patients Treated with FINTEPLA and Greater Than Placebo in Placebo-Controlled Trials for Dravet Syndrome (Study 1 and 2)

	FINTEPLA Dose Group			Combined Placebo Group[2]
	Study 1		Study 2	
	0.2 mg/kg/day	0.7 mg/kg/day	0.4 mg/kg/day[1]	
Adverse Reaction	N=39 %	N=40 %	N=43 %	N=84 %
Decreased appetite	23	38	49	8
Somnolence, sedation, lethargy	26	25	23	11
Abnormal echocardiogram[3]	18	23	9	6
Diarrhea	31	15	23	6
Constipation	3	10	7	0

1. A total of 341 patients with DS were treated with FINTEPLA in controlled and uncontrolled trials and included:
   - 312 patients treated with FINTEPLA for >6 months
   - 284 patients treated with FINTEPLA for >1 year
   - 138 patients treated with FINTEPLA for >2 years

   A total of 262 patients with LGS were treated with FINTEPLA in controlled and uncontrolled trials. This included:
   - 219 patients treated with FINTEPLA for >6 months
   - 172 patients treated with FINTEPLA for >1 year
   - 127 patients treated with FINTEPLA for >2 years

2. **Dravet Syndrome**

   In placebo-controlled trials, 122 patients with DS who were taking concomitant standard of care AEDs were treated with FINTEPLA. The duration of treatment with FINTEPLA was 16 weeks in Study 1 and 17 weeks in Study 2. All patients in the studies were receiving ≥1 other AED.

Studies 1 and 2 Discontinuation Rates Due to Adverse Reactions	
Treatment	**Discontinuation Rate**
FINTEPLA 0.7 mg/kg/day	13%
FINTEPLA 0.4 mg/kg/day in combination with stiripentol	7%
FINTEPLA 0.2 mg/kg/day	0%
Placebo	6%

The PI explains that somnolence was the most frequent adverse reaction leading to discontinuation in patients treated with any dose of FINTEPLA.

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

In controlled and uncontrolled trials in patients with Dravet syndrome (DS), 341 patients were treated with FINTEPLA, including 312 patients treated for more than 6 months, 284 patients treated for more than 1 year, and 138 patients treated for more than 2 years.

In controlled and uncontrolled trials in patients with Lennox-Gastaut syndrome (LGS), 262 patients were treated with FINTEPLA, including 219 patients treated for more than 6 months, 172 patients treated for more than 1 year, and 127 patients treated for more than 2 years.

Dravet Syndrome

In placebo-controlled trials of patients with DS taking concomitant standard of care AEDs, 122 patients were treated with FINTEPLA and 84 patients received placebo *[see Clinical Studies (14.1)]*. The duration of treatment in these trials was 16 weeks (Study 1) or 17 weeks (Study 2). In Study 1 and Study 2, the mean age was 9 years (range 2 to 19 years) and approximately 46% of patients were female and 74% were White. All patients were receiving at least one other AED.

In Study 1 and Study 2, the rates of discontinuation as a result of any adverse reaction were 13%, 0%, and 7% for patients treated with FINTEPLA 0.7 mg/kg/day, 0.2 mg/kg/day, and 0.4 mg/kg/day in combination with stiripentol, respectively, compared to 6% for patients on placebo. The most frequent adverse reaction leading to discontinuation in the patients treated with any dose of FINTEPLA was somnolence (3%).

1 The most common adverse reactions that occurred in patients treated with FINTEPLA (incidence at least 10% and greater than placebo) were decreased appetite; somnolence, sedation, lethargy; diarrhea; constipation; abnormal echocardiogram; fatigue, malaise, asthenia; ataxia, balance disorder, gait disturbance; blood pressure increased; drooling, salivary hypersecretion; pyrexia; upper respiratory tract infection; vomiting; decreased weight; fall; status epilepticus.

2 Table 3 lists the adverse reactions that were reported in 5% or more of patients treated with FINTEPLA and at a rate greater than those on placebo during the titration and maintenance phases of Study 1 and Study 2.

Table 2: Adverse Reactions in 5% or More of Patients Treated with FINTEPLA and Greater Than Placebo in Placebo-Controlled Trials for Dravet Syndrome (Study 1 and 2)

	FINTEPLA Dose Group			Combined Placebo Group[2]
	Study 1		Study 2	
	0.2 mg/kg/day	0.7 mg/kg/day	0.4 mg/kg/day[1]	
Adverse Reaction	N=39 %	N=40 %	N=43 %	N=84 %
Decreased appetite	23	38	49	8
Somnolence, sedation, lethargy	26	25	23	11
Abnormal echocardiogram[3]	18	23	9	6
Diarrhea	31	15	23	6
Constipation	3	10	7	0

1 **Dravet Syndrome (continued)**

The most common adverse reactions that occurred in patients treated with FINTEPLA (≥10% and greater than placebo) were:

- Decreased appetite
- Somnolence, sedation, lethargy
- Diarrhea
- Constipation
- Abnormal echocardiogram
- Fatigue, malaise, asthenia
- **Ataxia**, balance disorder, gait disturbance
- Blood pressure increased
- Drooling, salivary hypersecretion
- **Pyrexia**
- Upper respiratory tract infection
- Vomiting
- Decreased weight
- Fall
- Status epilepticus

2 Table 3 presents the adverse reactions that occurred in ≥5% of patients treated with FINTEPLA and a rate greater than those on placebo during the titration and maintenance phases of Study 1 and Study 2. Table 3 continues onto the next page.

As shown in the table, the most common adverse reactions among patients treated with FINTEPLA were decreased appetite and diarrhea.

1

Adverse Reaction	FINTEPLA Dose Group			Combined Placebo Group[2]
	Study 1		Study 2	
	0.2 mg/kg/day	0.7 mg/kg/day	0.4 mg/kg/day[1]	
	N=39 %	N=40 %	N=43 %	N=84 %
Fatigue, malaise, asthenia	15	10	30	5
Ataxia, balance disorder, gait disturbance	10	10	7	1
Abnormal behavior	0	8	9	0
Blood pressure increased	13	8	0	5
Drooling, salivary hypersecretion	13	8	2	0
Hypotonia	0	8	0	0
Rash	8	8	5	4
Blood prolactin increased	0	5	0	0
Chills	0	5	2	0
Decreased activity	0	5	0	1
Dehydration	0	5	0	0
Insomnia	0	5	5	2
Pyrexia	15	5	21	14
Stereotypy	0	5	0	0
Upper respiratory tract infection	21	5	7	10
Vomiting	10	5	5	8
Weight decreased	13	5	7	1
Croup	5	3	0	1
Ear infection	8	3	9	5
Gastroenteritis	8	3	2	0
Increased heart rate	5	3	0	2
Irritability	0	3	9	2
Rhinitis	8	3	7	2
Tremor	3	3	9	0
Urinary incontinence	5	3	0	0
Decreased blood glucose	0	0	9	1
Bronchitis	3	0	9	1
Contusion	5	0	0	0
Eczema	0	0	5	0
Enuresis	5	0	0	0
Fall	10	0	0	4
Headache	8	0	0	2
Laryngitis	0	0	5	0
Negativism	5	0	0	0
Status epilepticus	3	0	12	2
Urinary tract infection	5	0	5	0
Viral infection	0	0	5	1

(1) 0.4 mg/kg/day was not an intermediate dose. Patients on the 0.4 mg/kg/day dose were also taking concomitant stiripentol plus clobazam, which increases exposure of FINTEPLA.
(2) Patients in placebo groups from Studies 1 and 2 were pooled.
(3) Consisted of trace and mild mitral regurgitation, and trace aortic regurgitation, which are considered physiologic.

1 Table 3 Adverse Reactions in ≥5% of Patients Treated With FINTEPLA and Greater Than Placebo in Studies 1 and 2 in Dravet Syndrome (continued)

Lennox-Gastaut Syndrome

1 In the placebo-controlled trial of patients with LGS taking concomitant standard of care AEDs (Study 3), 176 patients were treated with FINTEPLA and 87 patients received placebo *[see Clinical Studies (14.2)]*. The duration of treatment in this trial was 16 weeks. The mean age was 13.7 years (range 2 to 35 years) and 29% of patients were at least 18 years of age, 45% of patients were female, and 79% were White. All patients were receiving at least one other AED.

2 The rates of discontinuation as a result of any adverse reaction were 6% and 5% for patients treated with FINTEPLA 0.7 mg/kg/day and 0.2 mg/kg/day, respectively, compared to 1% for patients on placebo. The most frequent adverse reactions leading to discontinuation in the patients treated with any dose of FINTEPLA were seizure (2%) and somnolence (2%).

The common adverse reactions that occurred in patients treated with FINTEPLA (incidence at least 10% and greater than placebo) were diarrhea; decreased appetite; fatigue; somnolence; vomiting.

Table 4 lists the adverse reactions that were reported in 5% or more of patients treated with FINTEPLA and at a rate greater than those on placebo during the titration and maintenance phases of Study 3.

Table 3: Adverse Reactions in 5% or More of Patients Treated with FINTEPLA and Greater Than Placebo in the Placebo-Controlled Trial for Lennox Gastaut Syndrome (Study 3)

Adverse Reaction	FINTEPLA Dose Group		
	Study 3		
	0.2 mg/kg/day	0.7mg/kg/day	Placebo Group
	N=89 %	N=87 %	N=87 %
Decreased appetite	20	36	12
Fatigue, malaise, asthenia	14	24	16
Somnolence, sedation, lethargy	12	22	16
Diarrhea	11	13	5
Constipation	6	9	6
Vomiting	14	8	6
Weight decreased	2	8	2
Upper respiratory tract infection	8	7	3
Seizure	9	5	7
Irritability	8	3	6

Echocardiographic Safety Assessments of Valvular Heart Disease and Pulmonary Arterial Hypertension

Valvular heart disease and pulmonary arterial hypertension were evaluated in the placebo-controlled and open-label extension studies via echocardiography for up to 3 years in duration for 341 DS patients and 263 LGS patients *[see Warnings and Precautions (5.1)]*. Screening for valvular heart disease assessed for mild or greater aortic regurgitation or moderate or greater

1 Lennox-Gastaut Syndrome

Study 3 was a placebo-controlled trial that included patients with LGS who were taking concomitant standard of care AEDs. In this trial, 176 patients were treated with FINTEPLA and 87 patients were treated with placebo. Baseline demographic information was as follows:

- Mean age: 13.7 years (range 2 to 35 years)
- Patients ≥18 years of age: 29%
- Female patients: 45%
- White patients: 79%

The duration of treatment with FINTEPLA was 16 weeks. All patients were receiving ≥1 other AED.

2 The rates of discontinuation in each treatment group due to adverse reactions are summarized in the table below. Seizure and somnolence were the most frequent adverse reactions leading to discontinuation in patients treated with any dose of FINTEPLA.

Study 3 Discontinuation Rates Due to Adverse Reactions

Treatment	Discontinuation Rate
FINTEPLA 0.7 mg/kg/day	6%
FINTEPLA 0.2 mg/kg/day	5%
Placebo	1%

Lennox-Gastaut Syndrome

In the placebo-controlled trial of patients with LGS taking concomitant standard of care AEDs (Study 3), 176 patients were treated with FINTEPLA and 87 patients received placebo *[see Clinical Studies (14.2)]*. The duration of treatment in this trial was 16 weeks. The mean age was 13.7 years (range 2 to 35 years) and 29% of patients were at least 18 years of age, 45% of patients were female, and 79% were White. All patients were receiving at least one other AED.

The rates of discontinuation as a result of any adverse reaction were 6% and 5% for patients treated with FINTEPLA 0.7 mg/kg/day and 0.2 mg/kg/day, respectively, compared to 1% for patients on placebo. The most frequent adverse reactions leading to discontinuation in the patients treated with any dose of FINTEPLA were seizure (2%) and somnolence (2%).

1 The common adverse reactions that occurred in patients treated with FINTEPLA (incidence at least 10% and greater than placebo) were diarrhea; decreased appetite; fatigue; somnolence; vomiting.

2 Table 4 lists the adverse reactions that were reported in 5% or more of patients treated with FINTEPLA and at a rate greater than those on placebo during the titration and maintenance phases of Study 3.

Table 3: Adverse Reactions in 5% or More of Patients Treated with FINTEPLA and Greater Than Placebo in the Placebo-Controlled Trial for Lennox Gastaut Syndrome (Study 3)

Adverse Reaction	FINTEPLA Dose Group		
	Study 3		
	0.2 mg/kg/day	0.7mg/kg/day	Placebo Group
	N=89 %	N=87 %	N=87 %
Decreased appetite	20	36	12
Fatigue, malaise, asthenia	14	24	16
Somnolence, sedation, lethargy	12	22	16
Diarrhea	11	13	5
Constipation	6	9	6
Vomiting	14	8	6
Weight decreased	2	8	2
Upper respiratory tract infection	8	7	3
Seizure	9	5	7
Irritability	8	3	6

Echocardiographic Safety Assessments of Valvular Heart Disease and Pulmonary Arterial Hypertension

Valvular heart disease and pulmonary arterial hypertension were evaluated in the placebo-controlled and open-label extension studies via echocardiography for up to 3 years in duration for 341 DS patients and 263 LGS patients *[see Warnings and Precautions (5.1)]*. Screening for valvular heart disease assessed for mild or greater aortic regurgitation or moderate or greater

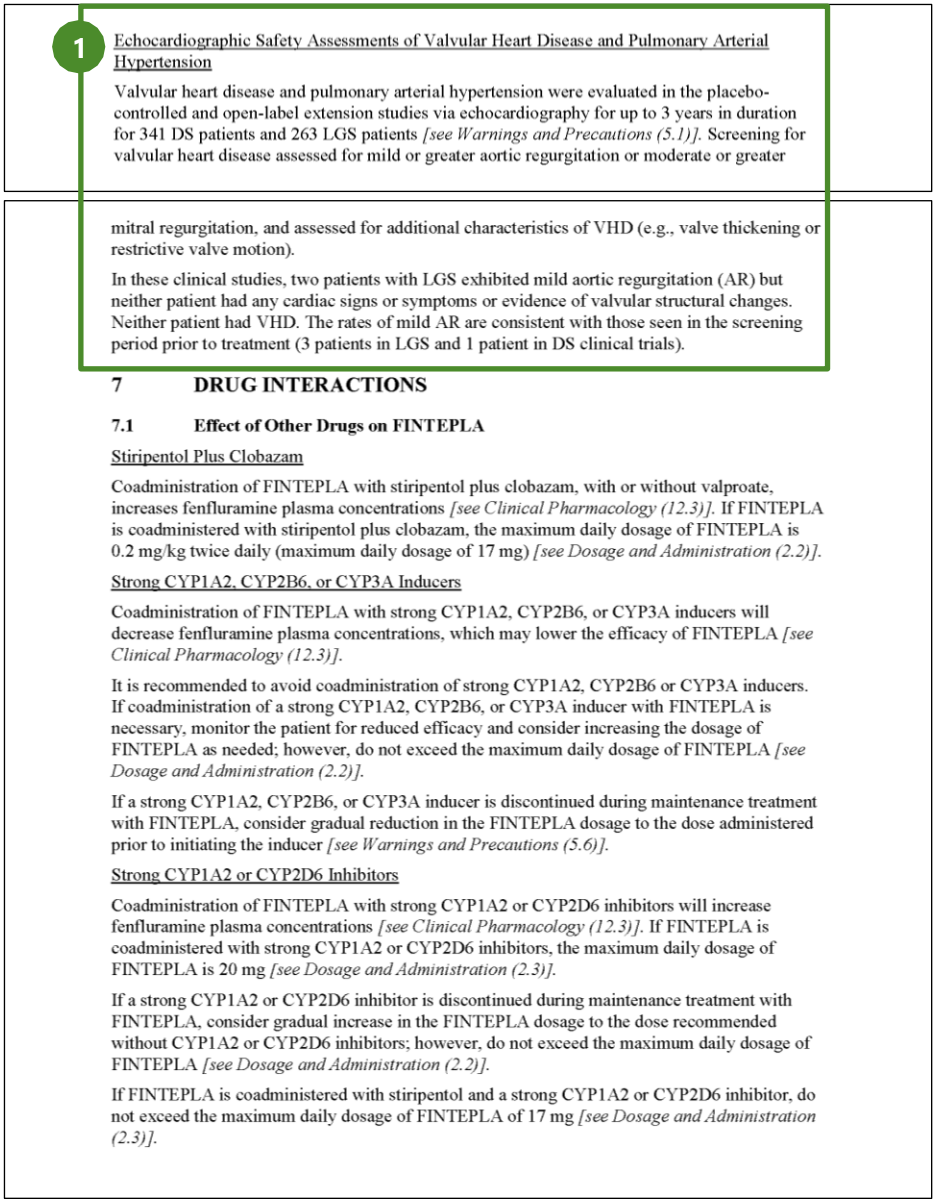
1 Lennox-Gastaut Syndrome (continued)

The most common adverse reactions that occurred in patients treated with FINTEPLA (≥10% and greater than placebo) were:

- Diarrhea
- Decreased appetite
- Fatigue
- Somnolence
- Vomiting

2 Table 4 presents adverse reactions that occurred in ≥5% of patients treated with FINTEPLA and a rate greater than those on placebo during the titration and maintenance phases of Study 3. As shown in the table:

- In patients taking FINTEPLA 0.7 mg/kg/day, the most common adverse reactions were decreased appetite, fatigue, somnolence, and diarrhea
- In patients taking FINTEPLA 0.2 mg/kg/day, the most common adverse reactions were decreased appetite, fatigue, somnolence, and vomiting



1 Echocardiographic Safety Assessments of Valvular Heart Disease and Pulmonary Arterial Hypertension

Valvular heart disease and pulmonary arterial hypertension were evaluated in the placebo-controlled and open-label extension studies via echocardiography for up to 3 years in duration for 341 DS patients and 263 LGS patients *[see Warnings and Precautions (5.1)]*. Screening for valvular heart disease assessed for mild or greater aortic regurgitation or moderate or greater mitral regurgitation, and assessed for additional characteristics of VHD (e.g., valve thickening or restrictive valve motion).

In these clinical studies, two patients with LGS exhibited mild aortic regurgitation (AR) but neither patient had any cardiac signs or symptoms or evidence of valvular structural changes. Neither patient had VHD. The rates of mild AR are consistent with those seen in the screening period prior to treatment (3 patients in LGS and 1 patient in DS clinical trials).

7 DRUG INTERACTIONS

7.1 Effect of Other Drugs on FINTEPLA

Stiripentol Plus Clobazam

Coadministration of FINTEPLA with stiripentol plus clobazam, with or without valproate, increases fenfluramine plasma concentrations *[see Clinical Pharmacology (12.3)]*. If FINTEPLA is coadministered with stiripentol plus clobazam, the maximum daily dosage of FINTEPLA is 0.2 mg/kg twice daily (maximum daily dosage of 17 mg) *[see Dosage and Administration (2.2)]*.

Strong CYP1A2, CYP2B6, or CYP3A Inducers

Coadministration of FINTEPLA with strong CYP1A2, CYP2B6, or CYP3A inducers will decrease fenfluramine plasma concentrations, which may lower the efficacy of FINTEPLA *[see Clinical Pharmacology (12.3)]*.

It is recommended to avoid coadministration of strong CYP1A2, CYP2B6 or CYP3A inducers. If coadministration of a strong CYP1A2, CYP2B6, or CYP3A inducer with FINTEPLA is necessary, monitor the patient for reduced efficacy and consider increasing the dosage of FINTEPLA as needed; however, do not exceed the maximum daily dosage of FINTEPLA *[see Dosage and Administration (2.2)]*.

If a strong CYP1A2, CYP2B6, or CYP3A inducer is discontinued during maintenance treatment with FINTEPLA, consider gradual reduction in the FINTEPLA dosage to the dose administered prior to initiating the inducer *[see Warnings and Precautions (5.6)]*.

Strong CYP1A2 or CYP2D6 Inhibitors

Coadministration of FINTEPLA with strong CYP1A2 or CYP2D6 inhibitors will increase fenfluramine plasma concentrations *[see Clinical Pharmacology (12.3)]*. If FINTEPLA is coadministered with strong CYP1A2 or CYP2D6 inhibitors, the maximum daily dosage of FINTEPLA is 20 mg *[see Dosage and Administration (2.3)]*.

If a strong CYP1A2 or CYP2D6 inhibitor is discontinued during maintenance treatment with FINTEPLA, consider gradual increase in the FINTEPLA dosage to the dose recommended without CYP1A2 or CYP2D6 inhibitors; however, do not exceed the maximum daily dosage of FINTEPLA *[see Dosage and Administration (2.2)]*.

If FINTEPLA is coadministered with stiripentol and a strong CYP1A2 or CYP2D6 inhibitor, do not exceed the maximum daily dosage of FINTEPLA of 17 mg *[see Dosage and Administration (2.3)]*.

1 As you know, the FINTEPLA PI contains a boxed warning regarding valvular heart disease (VHD) and pulmonary arterial hypertension (PAH). You may recall that echocardiography is a noninvasive test that uses ultrasound to visualize the structure of the heart.

In FINTEPLA clinical trials, echocardiography was used to evaluate the safety of FINTEPLA in relation to VHD and PAH. Assessments were performed during placebo-controlled and open-label extension studies of up to 3 years in duration for 341 patients with DS and 263 patients with LGS. Screening for VHD assessed for mild or greater aortic regurgitation or moderate or greater mitral regurgitation, and assessed for additional characteristics of VHD (e.g., valve thickening or restrictive valve motion).

The FINTEPLA PI explains that no patients developed echocardiographic findings consistent with either VHD or PAH in the placebo-controlled studies or during the open-label extension study of up to 3 years in duration.

Two patients with LGS exhibited mild **aortic regurgitation (AR)**. However, neither patient had any cardiac signs or symptoms, nor evidence of valvular structural changes. In addition, neither patient developed VHD. Zero patients with Dravet syndrome exhibited mild AR.

The rates of mild AR are consistent with those seen in the screening period prior to treatment (3 patients in LGS clinical trials and 1 patient in DS clinical trials).

Take Home Points

- FINTEPLA is contraindicated in patients with hypersensitivity to fenfluramine or any of the excipients in FINTEPLA; FINTEPLA is also contraindicated in patients who are concomitantly using monoamine oxidase inhibitors (MAOIs) or have used an MAOI within 14 days because of an increased risk of serotonin syndrome
- Warnings and precautions associated with FINTEPLA include:
  - Valvular heart disease and pulmonary arterial hypertension
  - FINTEPLA REMS Program
  - Decreased appetite and decreased weight
  - Somnolence, sedation, and lethargy
  - Suicidal behavior and ideation
  - Withdrawal of antiepileptic drugs
  - Serotonin syndrome
  - Increase in blood pressure
  - Glaucoma
- In Studies 1 and 2, discontinuation rates due to adverse reactions were as follows: FINTEPLA 0.7 mg/kg/day: 13%; FINTEPLA 0.4 mg/kg/day in combination with stiripentol: 7%; FINTEPLA 0.2 mg/kg/day: 0%; Placebo: 6%
- In Study 3, discontinuation rates due to adverse reactions were as follows: FINTEPLA 0.7 mg/kg/day: 6%; FINTEPLA 0.2 mg/kg/day: 5%; Placebo: 1%
- During the titration and maintenance phases of Studies 1 and 2, the most common adverse reactions occurring in ≥5% of patients treated with FINTEPLA and at a rate greater than those on placebo were decreased appetite and diarrhea
- During the titration and maintenance phases of Study 3, the most common adverse reactions occurring in ≥5% of patients treated with FINTEPLA 0.7 mg/kg/day and at a rate greater than those on placebo were decreased appetite, fatigue, somnolence, and diarrhea. In patients taking FINTEPLA 0.2 mg/kg/day, the most common adverse reactions were decreased appetite, fatigue, somnolence, and vomiting
- No patients developed echocardiographic findings consistent with either valvular heart disease or pulmonary arterial hypertension in placebo-controlled studies or during the open-label extension study of up to 3 years in duration
- Two patients with LGS exhibited mild aortic regurgitation (AR). However, neither patient had any cardiac signs or symptoms, nor evidence of valvular structural changes. In addition, neither patient developed VHD

Knowledge Check

FINTEPLA is contraindicated in patients who are concomitantly using monoamine oxidase inhibitors (MAOIs) or have used an MAOI within _____ days because of an increased risk of serotonin syndrome.

- ☐ 7
- ☐ 14
- ☐ 21
- ☐ 28

SHOW ANSWER

Knowledge Check

FINTEPLA is contraindicated in patients who are concomitantly using monoamine oxidase inhibitors (MAOIs) or have used an MAOI within _____ days because of an increased risk of serotonin syndrome.

- [ ] 7
- [x] **14**
- [ ] 21
- [ ] 28

NEXT QUESTION

Knowledge Check

In Studies 1 and 2, the most common adverse reactions among patients treated with FINTEPLA (≥10% and greater than placebo) were:

- ☐ Rash and pruritus
- ☐ Hypotension and weakness
- ☐ Breathlessness and myalgia
- ☐ Decreased appetite and diarrhea

SHOW ANSWER

Knowledge Check

In Studies 1 and 2, the most common adverse reactions among patients treated with FINTEPLA (≥10% and greater than placebo) were:

- ☐ Rash and pruritus
- ☐ Hypotension and weakness
- ☐ Breathlessness and myalgia
- ☑ **Decreased appetite and diarrhea**

NEXT QUESTION

Knowledge Check

In clinical trials of up to 3 years in duration in DS and LGS, no patients developed valvular heart disease or pulmonary arterial hypertension.

- ☐ True
- ☐ False

SHOW ANSWER

Knowledge Check

In clinical trials of up to 3 years in duration in DS and LGS, no patients developed valvular heart disease or pulmonary arterial hypertension.

- [x] **True**
- [ ] False

NEXT PAGE

Chapter 3: Drug Interactions, Use in Specific Populations, Drug Abuse and Dependence, and Overdosage

Learning Objectives

Upon completion of this chapter, you will be able to:

- Discuss the drug interactions associated with FINTEPLA
- Explain the use of FINTEPLA in specific populations
- Describe how FINTEPLA is classified as a controlled substance
- Discuss overdosage information associated with FINTEPLA

mitral regurgitation, and assessed for additional characteristics of VHD (e.g., valve thickening or restrictive valve motion).

In these clinical studies, two patients with LGS exhibited mild aortic regurgitation (AR) but neither patient had any cardiac signs or symptoms or evidence of valvular structural changes. Neither patient had VHD. The rates of mild AR are consistent with those seen in the screening period prior to treatment (3 patients in LGS and 1 patient in DS clinical trials).

7 DRUG INTERACTIONS

7.1 Effect of Other Drugs on FINTEPLA

Stiripentol Plus Clobazam

Coadministration of FINTEPLA with stiripentol plus clobazam, with or without valproate, increases fenfluramine plasma concentrations *[see Clinical Pharmacology (12.3)]*. If FINTEPLA is coadministered with stiripentol plus clobazam, the maximum daily dosage of FINTEPLA is 0.2 mg/kg twice daily (maximum daily dosage of 17 mg) *[see Dosage and Administration (2.2)]*.

Strong CYP1A2, CYP2B6, or CYP3A Inducers

Coadministration of FINTEPLA with strong CYP1A2, CYP2B6, or CYP3A inducers will decrease fenfluramine plasma concentrations, which may lower the efficacy of FINTEPLA *[see Clinical Pharmacology (12.3)]*.

It is recommended to avoid coadministration of strong CYP1A2, CYP2B6 or CYP3A inducers. If coadministration of a strong CYP1A2, CYP2B6, or CYP3A inducer with FINTEPLA is necessary, monitor the patient for reduced efficacy and consider increasing the dosage of FINTEPLA as needed; however, do not exceed the maximum daily dosage of FINTEPLA *[see Dosage and Administration (2.2)]*.

If a strong CYP1A2, CYP2B6, or CYP3A inducer is discontinued during maintenance treatment with FINTEPLA, consider gradual reduction in the FINTEPLA dosage to the dose administered prior to initiating the inducer *[see Warnings and Precautions (5.6)]*.

Strong CYP1A2 or CYP2D6 Inhibitors

Coadministration of FINTEPLA with strong CYP1A2 or CYP2D6 inhibitors will increase fenfluramine plasma concentrations *[see Clinical Pharmacology (12.3)]*. If FINTEPLA is coadministered with strong CYP1A2 or CYP2D6 inhibitors, the maximum daily dosage of FINTEPLA is 20 mg *[see Dosage and Administration (2.3)]*.

If a strong CYP1A2 or CYP2D6 inhibitor is discontinued during maintenance treatment with FINTEPLA, consider gradual increase in the FINTEPLA dosage to the dose recommended without CYP1A2 or CYP2D6 inhibitors; however, do not exceed the maximum daily dosage of FINTEPLA *[see Dosage and Administration (2.2)]*.

If FINTEPLA is coadministered with stiripentol and a strong CYP1A2 or CYP2D6 inhibitor, do not exceed the maximum daily dosage of FINTEPLA of 17 mg *[see Dosage and Administration (2.3)]*.

1

1 In Section 7.1, the effects of other drugs on FINTEPLA are presented.

Stiripentol Plus Clobazam

If FINTEPLA is coadministered with stiripentol plus clobazam, the maximum daily dosage of FINTEPLA is 0.2 mg/kg twice daily, with a maximum total daily dosage of 17 mg. This information was also presented in Section 2.2 of the FINTEPLA PI.

Strong CYP1A2, CYP2B6, or CYP3A Inducers

Coadministration of FINTEPLA with strong CYP1A2, CYP2B6, or CYP3A inducers will decrease fenfluramine plasma concentrations, which may lower the efficacy of FINTEPLA. As a result, coadministration of FINTEPLA with these types of drugs should be avoided. However, if coadministration of FINTEPLA with a strong CYP1A2, CYP2B6, or CYP3A inducer is necessary, the patient should be monitored for reduced efficacy. An increase in FINTEPLA dosage may be considered if needed, but the maximum daily dosage of FINTEPLA should not be exceeded. (See Section 2.3 Dosage and Administration for more information.)

Strong CYP1A2 or CYP2D6 Inhibitors

Coadministration of FINTEPLA with strong CYP1A2 or CYP2D6 inhibitors will increase fenfluramine plasma concentrations. If FINTEPLA is coadministered with these types of drugs, the maximum daily dosage of FINTEPLA is 20 mg. If FINTEPLA is coadministered with stiripentol and a strong CYP1A2 or CYP2D6 inhibitor, the maximum daily dosage of FINTEPLA is 17 mg.

If treatment with any of the CYPs mentioned above is discontinued, gradual adjustments in the dosage of FINTEPLA should be considered.

7.2 Effects of Serotonin Receptor Antagonists

Cyproheptadine and potent 5-HT1A, 5-HT1D, 5-HT2A, and 5-HT2C serotonin receptor antagonists may decrease the efficacy of FINTEPLA. If cyproheptadine or potent 5--HT1A, 5--HT1D, 5-HT2A, or 5-HT2C serotonin receptor antagonists are coadministered with FINTEPLA, patients should be monitored appropriately.

7.3 Serotonergic Drugs

Concomitant administration of FINTEPLA and drugs (e.g., SSRIs, SNRIs, TCAs, MAO inhibitors, trazodone, etc.), over-the-counter medications (e.g., dextromethorphan), or herbal supplements (e.g., St. John's Wort) that increase serotonin may increase the risk of serotonin syndrome *[see Warnings and Precautions (5.7)]*. Concomitant use of FINTEPLA is contraindicated within 14 days of taking MAOIs. Use FINTEPLA with caution in patients taking other medications that increase serotonin.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Exposure Registry

There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to antiepileptic drugs (AEDs), such as FINTEPLA, during pregnancy. Encourage women who are taking FINTEPLA during pregnancy to enroll in the North American Antiepileptic Drug (NAAED) Pregnancy Registry by calling the toll-free number 1-888-233-2334 or visiting http://www.aedpregnancyregistry.org.

Risk Summary

There are no data on FINTEPLA use in pregnant women. Available data from epidemiologic studies with fenfluramine or dexfenfluramine are insufficient to evaluate for a drug-associated risk of major birth defects, miscarriage, or other adverse maternal or fetal outcomes. FINTEPLA can cause decreased appetite and decreased weight *[see Warnings and Precautions (5.3)]*; monitor for adequate weight gain during pregnancy. In animal studies, administration of fenfluramine throughout organogenesis (rat and rabbit) or throughout gestation and lactation (rat) resulted in adverse effects on development (fetal malformations, embryofetal and offspring mortality and growth impairment) in the presence of maternal toxicity at clinically relevant maternal plasma levels of fenfluramine and its major active metabolite *(see Data)*.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

Data

Animal Data

Oral administration of fenfluramine (0, 5, 10, or 40 mg/kg/day) to pregnant rats during organogenesis resulted in decreased fetal body weights and marked increases in fetal

1 Section 7.2 explains that patients should be monitored if **cyproheptadine** or potent 5-HT1A, 5-HT1D, 5-HT2A, or 5-HT2C serotonin receptor antagonists are coadministered with FINTEPLA.

Remember, the **neurotransmitter** serotonin (5-HT) is a vasoconstrictor found in platelets, the gastrointestinal mucosa, mast cells, carcinoid tumors, and the central nervous system (CNS) and works as a vasoconstrictor.

Serotonin, through its action on cellular receptors, plays important roles in intestinal motility, nausea and vomiting, sleep-wake cycles, obsessive-compulsive behaviors, depression, and eating.

2 Section 7.3 explains that there may be an increased risk of serotonin syndrome with the concomitant administration of FINTEPLA and agents that increase serotonin, including:

- Drugs, such as SSRIs, SNRIs, TCAs, MAOIs, trazodone, etc.
- Over-the-counter medications, such as dextromethorphan
- Herbal supplements, such as St. John's Wort

As discussed earlier in Section 4 of the PI, FINTEPLA is contraindicated in patients who are concomitantly using MAOIs or have used an MAOI within 14 days. In addition, FINTEPLA should be used with caution in patients taking other medications that increase serotonin.

7.2 Effects of Serotonin Receptor Antagonists

Cyproheptadine and potent 5-HT1A, 5-HT1D, 5-HT2A, and 5-HT2C serotonin receptor antagonists may decrease the efficacy of FINTEPLA. If cyproheptadine or potent 5--HT1A, 5--HT1D, 5-HT2A, or 5-HT2C serotonin receptor antagonists are coadministered with FINTEPLA, patients should be monitored appropriately.

7.3 Serotonergic Drugs

Concomitant administration of FINTEPLA and drugs (e.g., SSRIs, SNRIs, TCAs, MAO inhibitors, trazodone, etc.), over-the-counter medications (e.g., dextromethorphan), or herbal supplements (e.g., St. John's Wort) that increase serotonin may increase the risk of serotonin syndrome *[see Warnings and Precautions (5.7)]*. Concomitant use of FINTEPLA is contraindicated within 14 days of taking MAOIs. Use FINTEPLA with caution in patients taking other medications that increase serotonin.

1

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Exposure Registry

There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to antiepileptic drugs (AEDs), such as FINTEPLA, during pregnancy. Encourage women who are taking FINTEPLA during pregnancy to enroll in the North American Antiepileptic Drug (NAAED) Pregnancy Registry by calling the toll-free number 1-888-233-2334 or visiting http://www.aedpregnancyregistry.org.

2

Risk Summary

There are no data on FINTEPLA use in pregnant women. Available data from epidemiologic studies with fenfluramine or dexfenfluramine are insufficient to evaluate for a drug-associated risk of major birth defects, miscarriage, or other adverse maternal or fetal outcomes. FINTEPLA can cause decreased appetite and decreased weight *[see Warnings and Precautions (5.3)]*; monitor for adequate weight gain during pregnancy. In animal studies, administration of fenfluramine throughout organogenesis (rat and rabbit) or throughout gestation and lactation (rat) resulted in adverse effects on development (fetal malformations, embryofetal and offspring mortality and growth impairment) in the presence of maternal toxicity at clinically relevant maternal plasma levels of fenfluramine and its major active metabolite *(see Data)*.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

Data

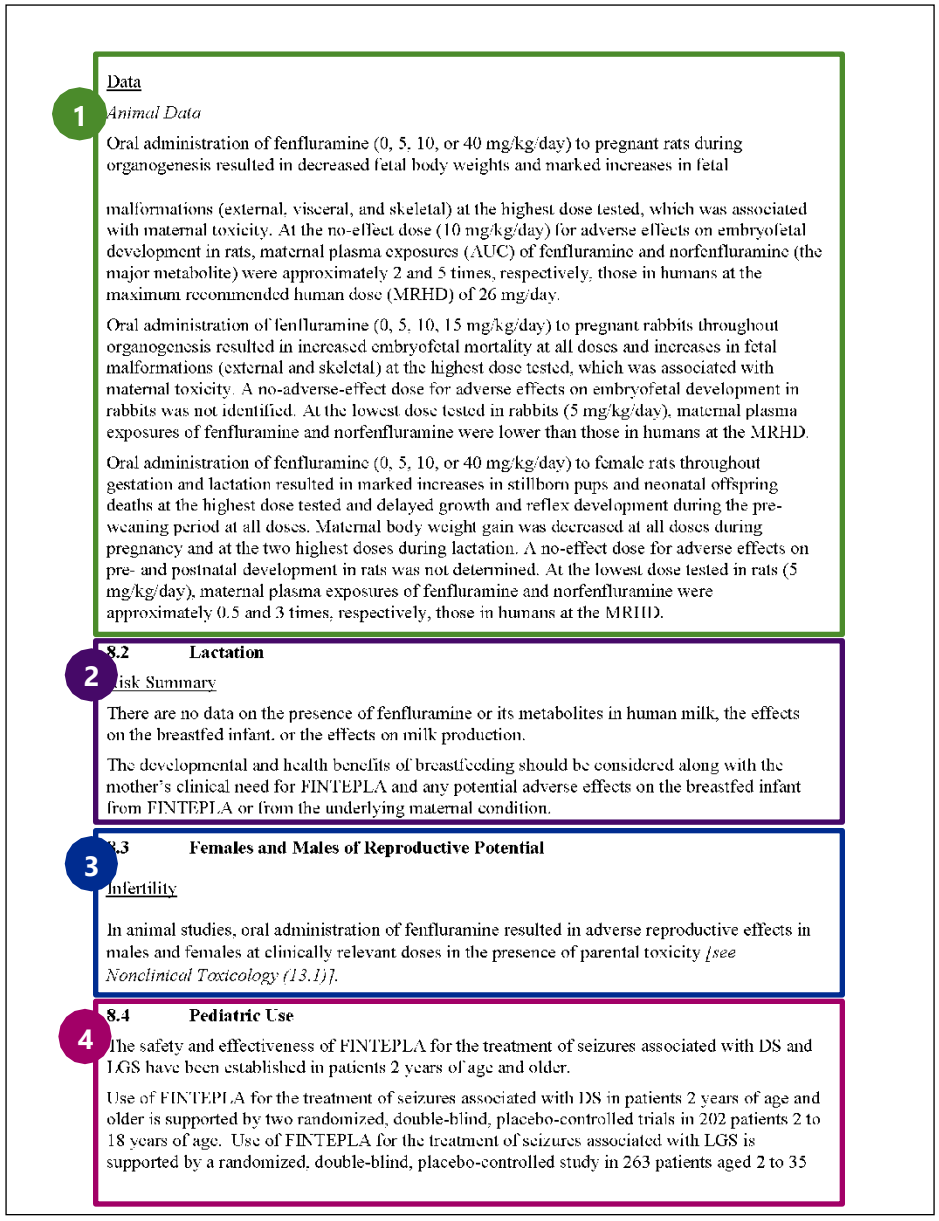
Animal Data

Oral administration of fenfluramine (0, 5, 10, or 40 mg/kg/day) to pregnant rats during organogenesis resulted in decreased fetal body weights and marked increases in fetal

1. Section 8 describes the use of FINTEPLA in specific populations. As described in Section 8.1, female patients taking FINTEPLA are encouraged to enroll in the North American Antiepileptic Drug (NAAED) Pregnancy Registry, which monitors pregnancy outcomes in women exposed to AEDs.

2. No studies of FINTEPLA in pregnant women have been conducted by Zogenix. Available data from epidemiologic studies with fenfluramine or **dexfenfluramine** are insufficient to evaluate for a drug-associated risk of major birth defects, miscarriage, or other adverse maternal or fetal outcomes.

   The FINTEPLA PI states that the estimated background risk of major birth defects and miscarriage for the indicated population is unknown. However, all pregnancies have a background risk of birth defect, loss, or other adverse outcome. In the US general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and15% to 20%, respectively.



Data

Animal Data

Oral administration of fenfluramine (0, 5, 10, or 40 mg/kg/day) to pregnant rats during organogenesis resulted in decreased fetal body weights and marked increases in fetal malformations (external, visceral, and skeletal) at the highest dose tested, which was associated with maternal toxicity. At the no-effect dose (10 mg/kg/day) for adverse effects on embryofetal development in rats, maternal plasma exposures (AUC) of fenfluramine and norfenfluramine (the major metabolite) were approximately 2 and 5 times, respectively, those in humans at the maximum recommended human dose (MRHD) of 26 mg/day.

Oral administration of fenfluramine (0, 5, 10, 15 mg/kg/day) to pregnant rabbits throughout organogenesis resulted in increased embryofetal mortality at all doses and increases in fetal malformations (external and skeletal) at the highest dose tested, which was associated with maternal toxicity. A no-adverse-effect dose for adverse effects on embryofetal development in rabbits was not identified. At the lowest dose tested in rabbits (5 mg/kg/day), maternal plasma exposures of fenfluramine and norfenfluramine were lower than those in humans at the MRHD.

Oral administration of fenfluramine (0, 5, 10, or 40 mg/kg/day) to female rats throughout gestation and lactation resulted in marked increases in stillborn pups and neonatal offspring deaths at the highest dose tested and delayed growth and reflex development during the pre-weaning period at all doses. Maternal body weight gain was decreased at all doses during pregnancy and at the two highest doses during lactation. A no-effect dose for adverse effects on pre- and postnatal development in rats was not determined. At the lowest dose tested in rats (5 mg/kg/day), maternal plasma exposures of fenfluramine and norfenfluramine were approximately 0.5 and 3 times, respectively, those in humans at the MRHD.

8.2 Lactation

Risk Summary

There are no data on the presence of fenfluramine or its metabolites in human milk, the effects on the breastfed infant, or the effects on milk production.

The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for FINTEPLA and any potential adverse effects on the breastfed infant from FINTEPLA or from the underlying maternal condition.

8.3 Females and Males of Reproductive Potential

Infertility

In animal studies, oral administration of fenfluramine resulted in adverse reproductive effects in males and females at clinically relevant doses in the presence of parental toxicity *[see Nonclinical Toxicology (13.1)]*.

8.4 Pediatric Use

The safety and effectiveness of FINTEPLA for the treatment of seizures associated with DS and LGS have been established in patients 2 years of age and older.

Use of FINTEPLA for the treatment of seizures associated with DS in patients 2 years of age and older is supported by two randomized, double-blind, placebo-controlled trials in 202 patients 2 to 18 years of age. Use of FINTEPLA for the treatment of seizures associated with LGS is supported by a randomized, double-blind, placebo-controlled study in 263 patients aged 2 to 35

1. The FINTEPLA PI summarizes data from animal studies in rats and rabbits evaluating developmental risks associated with the use of fenfluramine at dose levels ranging from 0 to 40 mg/kg/day. Adverse effects were found in developing fetuses and lactating offspring.

2. Section 8.2 discusses the use of FINTEPLA in women who are breastfeeding. There are no data regarding the effects of fenfluramine in women who are breastfeeding and their breastfed infants. The benefits and risks of using FINTEPLA in a woman who is breastfeeding and the potential adverse effects on the breastfed infant should be considered.

3. Section 8.3 discusses the use of FINTEPLA in women and men with reproductive potential. However, only animal fertility data is available. In animal studies, oral administration of fenfluramine at clinically relevant doses resulted in adverse reproductive effects in males and females.

4. The pediatric use of FINTEPLA is described in Section 8.4 of the PI. The safety and effectiveness of FINTEPLA for the treatment of seizures associated with DS and LGS have been established in patients age ≥2 years in randomized, double-blind, placebo-controlled trials:
   - Patients with DS: Two trials in 202 patients 2 to 18 years of age
   - Patients with LGS: One trial in 263 patients aged 2 to 35 years, including 187 patients <18 years of age

1 years, including 187 patients less than 18 years *[see Boxed Warning, Warnings and Precautions (5), Adverse Reaction (6.1), and Clinical Studies (14)]*.

FINTEPLA can cause decreases in appetite and weight. The growth of pediatric patients treated with FINTEPLA should be carefully monitored.

Safety and effectiveness in patients less than 2 years of age have not been established.

Juvenile Animal Data

Oral administration of fenfluramine (0, 3.5, 9, or 20 mg/kg/day) to young rats for 10 weeks starting on postnatal day 7 resulted in reduced body weight and neurobehavioral changes (decreased locomotor activity and learning and memory deficits) at all doses tested. Neurobehavioral effects persisted after dosing was discontinued. Bone size was decreased at the mid and high doses; brain size was decreased at the highest dose. Partial or complete recovery was seen for these endpoints. A no-effect dose for postnatal developmental toxicity was not identified. The lowest dose tested (3.5 mg/kg/day) was associated with plasma fenfluramine exposures (AUC) less than that in humans at the maximum recommended human dose (MRHD of 26 mg/day) and norfenfluramine (metabolite) exposures (AUC) approximately 2 times that in humans at the MRHD.

2 **8.5 Geriatric Use**

Clinical studies of FINTEPLA for the treatment of DS or LGS did not include patients 65 years of age and over to determine whether they respond differently from younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

3 **8.6 Renal Impairment**

In patients with estimated glomerular filtration rate (eGFR) 15 to 29 mL/min/1.73m^2, do not exceed the maximum daily dosage of FINTEPLA of 20 mg. In patients with eGFR 15 to 29 ml/min/1.73m^2 and concomitant stiripentol use, do not exceed the maximum daily dosage of FINTEPLA of 17 mg *[see Dosage and Administration (2.2) and Clinical Pharmacology (12.3)]*. FINTEPLA has not been studied in patients with eGFR < 15 mL/min/1.73m^2.

8.7 Hepatic Impairment

Administration of FINTEPLA to patients with hepatic impairment is not recommended *[see Clinical Pharmacology (12.3)]*.

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

FINTEPLA contains fenfluramine, a Schedule IV controlled substance.

10 OVERDOSAGE

Overdose has not been observed in the FINTEPLA clinical trial program. However, overdose of fenfluramine, the active ingredient in FINTEPLA, has been reported at higher doses than those

1 **Section 8.4 Pediatric Use** (continued)

FINTEPLA can cause decreases in appetite and weight. The growth of pediatric patients treated with FINTEPLA should be carefully monitored.

The safety and effectiveness of FINTEPLA in patients less than 2 years of age have not been established.

2 Section 8.5 addresses the use of FINTEPLA in patients ≥65 years of age to determine whether they respond differently than younger patients. However, this patient population was not included in FINTEPLA clinical studies.

In general, dose selection in patients ≥65 years of age should start at a lower dosage due to the potential for decreased hepatic, renal, or cardiac function and of concomitant disease or other drug therapy among these patients.

3 Section 8.6 addresses the use of FINTEPLA in patients with renal impairment. Severe renal impairment is defined as an eGFR of 15 to 29 mL/min/1.73m^2. In FINTEPLA patients with severe renal impairment:

- Without concomitant stiripentol: The maximum total daily dosage of FINTEPLA should not exceed 20 mg
- With concomitant stiripentol plus clobazam: The maximum total daily dosage of FINTEPLA should not exceed 17 mg

The use of FINTEPLA in patients with severe renal impairment is further discussed in Sections 2.4 and 12.3.

years, including 187 patients less than 18 years *[see Boxed Warning, Warnings and Precautions (5), Adverse Reaction (6.1), and Clinical Studies (14)]*.

FINTEPLA can cause decreases in appetite and weight. The growth of pediatric patients treated with FINTEPLA should be carefully monitored.

Safety and effectiveness in patients less than 2 years of age have not been established.

Juvenile Animal Data

Oral administration of fenfluramine (0, 3.5, 9, or 20 mg/kg/day) to young rats for 10 weeks starting on postnatal day 7 resulted in reduced body weight and neurobehavioral changes (decreased locomotor activity and learning and memory deficits) at all doses tested. Neurobehavioral effects persisted after dosing was discontinued. Bone size was decreased at the mid and high doses; brain size was decreased at the highest dose. Partial or complete recovery was seen for these endpoints. A no-effect dose for postnatal developmental toxicity was not identified. The lowest dose tested (3.5 mg/kg/day) was associated with plasma fenfluramine exposures (AUC) less than that in humans at the maximum recommended human dose (MRHD of 26 mg/day) and norfenfluramine (metabolite) exposures (AUC) approximately 2 times that in humans at the MRHD.

8.5 Geriatric Use

Clinical studies of FINTEPLA for the treatment of DS or LGS did not include patients 65 years of age and over to determine whether they respond differently from younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

8.6 Renal Impairment

In patients with estimated glomerular filtration rate (eGFR) 15 to 29 mL/min/1.73m^2, do not exceed the maximum daily dosage of FINTEPLA of 20 mg. In patients with eGFR 15 to 29 ml/min/1.73m^2 and concomitant stiripentol use, do not exceed the maximum daily dosage of FINTEPLA of 17 mg *[see Dosage and Administration (2.2) and Clinical Pharmacology (12.3)]*. FINTEPLA has not been studied in patients with eGFR < 15 mL/min/1.73m^2.

1

8.7 Hepatic Impairment

Administration of FINTEPLA to patients with hepatic impairment is not recommended *[see Clinical Pharmacology (12.3)]*.

2

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

FINTEPLA contains fenfluramine, a Schedule IV controlled substance.

10 OVERDOSAGE

Overdose has not been observed in the FINTEPLA clinical trial program. However, overdose of fenfluramine, the active ingredient in FINTEPLA, has been reported at higher doses than those

1 The use of FINTEPLA in patients with hepatic impairment is described in Section 8.7. The administration of FINTEPLA is not recommended in patients with hepatic impairment.

2 Section 9 of the FINTEPLA PI describes drug abuse and dependence. Section 9.1 states that FINTEPLA contains fenfluramine, a Schedule IV controlled substance.

In the US, drugs are classified into five schedules based on the acceptable medical use of the agent and its potential for abuse and dependence.

- Schedule I drugs have the highest potential for abuse
- Schedule V drugs have the lowest potential for abuse
- Schedule IV drugs, like FINTEPLA, are those with a low potential for abuse and a low risk of dependence

1

10 OVERDOSAGE

Overdose has not been observed in the FINTEPLA clinical trial program. However, overdose of fenfluramine, the active ingredient in FINTEPLA, has been reported at higher doses than those included in the clinical trial program. Some of the cases were fatal. Events reported after overdose include mydriasis, tachycardia, flushing, tremors/twitching/muscle spasms, agitation/restlessness/anxiety, increased muscle tone/rigor/opisthotonos, respiratory distress or failure, and seizure. Seizure, coma, and cardiorespiratory arrest were reported in most of the fatal overdoses.

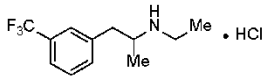
There is no available specific antidote to the overdose reactions of FINTEPLA. In the event of overdose, standard medical practice for the management of drug overdosage should be used. An adequate airway, oxygenation, and ventilation should be ensured; monitoring of cardiac rhythm and vital sign measurement is recommended. A certified poison control center should be contacted for updated information on the management of overdose with FINTEPLA.

11 DESCRIPTION

FINTEPLA oral solution contains 2.2 mg/mL fenfluramine, equivalent to 2.5 mg/mL of the hydrochloride salt.

The active ingredient, fenfluramine hydrochloride, is designated chemically as N-ethyl-α-methyl-3-(trifluoromethyl)phenethylamine hydrochloride.

The structural formula is:



Fenfluramine hydrochloride is a white to off-white crystalline solid. The pKa of fenfluramine is 10.2.

FINTEPLA is a clear, colorless solution, pH 5.

FINTEPLA contains the following inactive ingredients: cherry flavor, citric acid, ethylparaben hydroxyethylcellulose, methylparaben, potassium citrate, sucralose, and water.

FINTEPLA contains no ingredient made from gluten-containing grain (wheat, barley, or rye), and contains not more than 0.1% of carbohydrates, which is solely derived from the cherry flavor.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The precise mechanism by which fenfluramine exerts its therapeutic effects in the treatment of seizures associated with Dravet syndrome and Lennox-Gastaut syndrome is unknown. Fenfluramine and the metabolite, norfenfluramine, exhibit agonist activity at serotonin 5-HT2 receptors. There is an association between serotonergic drugs with 5-HT2B receptor agonist activity, including fenfluramine and norfenfluramine, and valvular heart disease and pulmonary arterial hypertension.

1 Section 10 explains that overdosage has not been observed in the FINTEPLA clinical trial program. However, overdose of fenfluramine, the active ingredient in FINTEPLA, has been reported at higher doses than those included in the clinical trial program, with some cases being fatal.

There is no available specific antidote to overdose reactions from FINTEPLA. Standard medical practice for the management of drug overdosage should be used in the event of FINTEPLA overdose. This includes ensuring an adequate airway, oxygenation, and ventilation. In addition, monitoring of cardiac rhythm and vital sign measurement is recommended.

For updated information on the management of FINTEPLA overdose, a certified poison control center should be contacted.

Take Home Points

- If FINTEPLA is coadministered with stiripentol plus clobazam, the maximum daily dosage of FINTEPLA is 0.2 mg/kg twice daily, with a maximum total daily dosage of 17 mg
- Coadministration of FINTEPLA with a strong CYP1A2, CYP2B6, or CYP3A inducer should be avoided. Patients requiring concomitant use of these drugs should be monitored for reduced efficacy. An increase in FINTEPLA dosage may be considered but the maximum daily dosage should not be exceeded (See Section 2.3)
- Coadministration of FINTEPLA with strong CYP1A2 or CYP2D6 inhibitors will increase fenfluramine plasma concentrations; in these cases, the maximum daily dosage of FINTEPLA is 20 mg
- There may be an increased risk of serotonin syndrome with the concomitant administration of FINTEPLA and agents that increase serotonin, including drugs (e.g., SSRIs, SNRIs, TCAs, MAOIs, trazodone, etc.), over-the-counter medications (e.g., dextromethorphan), and herbal supplements (e.g., St. John's Wort)
- FINTEPLA use in specific populations:
  - No studies of FINTEPLA in pregnant women have been conducted by Zogenix.
  - There are no data regarding the effects of fenfluramine in women who are breastfeeding and their breastfed infants
  - The safety and effectiveness of FINTEPLA for the treatment of seizures associated with DS and LGS have been established in patients age ≥2 years
  - FINTEPLA can cause decreases in appetite and weight; the growth of pediatric patients treated with FINTEPLA should be carefully monitored
  - Patients ≥65 years were not included in clinical studies of FINTEPLA for the treatment of DS or LGS to determine whether they respond differently from younger patients; dosing range should usually start on the low end
  - FINTEPLA dosage modifications for patients with severe renal impairment (eGFR 15 to 29 mL/min/1.73m^2):
    - Maximum total daily dosage: 20 mg without concomitant stiripentol
    - Maximum total daily dosage: 17 mg with concomitant stiripentol plus clobazam
  - In patients with hepatic impairment, the administration of FINTEPLA is not recommended
- FINTEPLA contains fenfluramine, a Schedule IV controlled substance
- Overdosage has not been observed in the FINTEPLA clinical trial program; however, overdose of fenfluramine, the active ingredient in FINTEPLA, has been reported at higher doses than those included in the clinical trial program, with some cases being fatal

Knowledge Check

If FINTEPLA is coadministered with stiripentol plus clobazam, the maximum daily dosage of FINTEPLA is 0.2 mg/kg twice daily, with a maximum total daily dosage of _____ .

- ☐ 9 mg
- ☐ 17 mg
- ☐ 24 mg
- ☐ 30 mg

SHOW ANSWER

Knowledge Check

If FINTEPLA is coadministered with stiripentol plus clobazam, the maximum daily dosage of FINTEPLA is 0.2 mg/kg twice daily, with a maximum total daily dosage of _____ .

- [ ] 9 mg
- [x] **17 mg**
- [ ] 24 mg
- [ ] 30 mg

NEXT QUESTION

Knowledge Check

Which of the following statements about FINTEPLA use in specific populations is true? (Select all that apply.)

- ☐ Patients ≥65 years were included in clinical studies of FINTEPLA for the treatment of DS and LGS.
- ☐ No dose adjustment of FINTEPLA is required in patients with impaired renal function.
- ☐ FINTEPLA is not recommended in patients with hepatic impairment.
- ☐ The safety and effectiveness of FINTEPLA has been established in women who are breastfeeding.

SHOW ANSWER

Knowledge Check

Which of the following statements about FINTEPLA use in specific populations is true? (Select all that apply.)

- ☐ Patients ≥65 years were included in clinical studies of FINTEPLA for the treatment of DS and LGS.
- ☐ No dose adjustment of FINTEPLA is required in patients with impaired renal function.
- ☑ **FINTEPLA is not recommended in patients with hepatic impairment.**
- ☐ The safety and effectiveness of FINTEPLA has been established in women who are breastfeeding.

NEXT QUESTION

Knowledge Check

FINTEPLA contains fenfluramine, a Schedule ___ controlled substance.

- ☐ I
- ☐ II
- ☐ III
- ☐ IV

SHOW ANSWER

Knowledge Check

FINTEPLA contains fenfluramine, a Schedule ____ controlled substance.

- ☐ I
- ☐ II
- ☐ III
- ☑ **IV**

NEXT QUESTION

Knowledge Check

Overdosage has not been observed in the FINTEPLA clinical trial program; however, overdose of fenfluramine, the active ingredient in FINTEPLA, has been reported at higher doses than those included in the clinical trial program.

- ☐ True
- ☐ False

SHOW ANSWER

Knowledge Check

Overdosage has not been observed in the FINTEPLA clinical trial program; however, overdose of fenfluramine, the active ingredient in FINTEPLA, has been reported at higher doses than those included in the clinical trial program.

- [x] **True**
- [ ] False

NEXT PAGE

Chapter 4: Description, Clinical Pharmacology, and Nonclinical Toxicology

Learning Objectives

Upon completion of this chapter, you will be able to:

- Describe the contents of FINTEPLA
- Discuss the clinical pharmacology of fenfluramine, including its mechanism of action, pharmacodynamics, and pharmacokinetics
- Explain the nonclinical toxicology associated with fenfluramine, including its carcinogenesis, mutagenesis, and impairment of fertility, as well as animal toxicology and pharmacology

included in the clinical trial program. Some of the cases were fatal. Events reported after overdose include mydriasis, tachycardia, flushing, tremors/twitching/muscle spasms, agitation/restlessness/anxiety, increased muscle tone/rigor/opisthotonos, respiratory distress or failure, and seizure. Seizure, coma, and cardiorespiratory arrest were reported in most of the fatal overdoses.

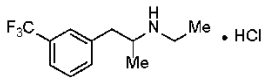
There is no available specific antidote to the overdose reactions of FINTEPLA. In the event of overdose, standard medical practice for the management of drug overdosage should be used. An adequate airway, oxygenation, and ventilation should be ensured; monitoring of cardiac rhythm and vital sign measurement is recommended. A certified poison control center should be contacted for updated information on the management of overdose with FINTEPLA.

11 DESCRIPTION

FINTEPLA oral solution contains 2.2 mg/mL fenfluramine, equivalent to 2.5 mg/mL of the hydrochloride salt.

The active ingredient, fenfluramine hydrochloride, is designated chemically as N-ethyl-α-methyl-3-(trifluoromethyl)phenethylamine hydrochloride.

The structural formula is:



Fenfluramine hydrochloride is a white to off-white crystalline solid. The pKa of fenfluramine is 10.2.

FINTEPLA is a clear, colorless solution, pH 5.

FINTEPLA contains the following inactive ingredients: cherry flavor, citric acid, ethylparaben hydroxyethylcellulose, methylparaben, potassium citrate, sucralose, and water.

FINTEPLA contains no ingredient made from gluten-containing grain (wheat, barley, or rye), and contains not more than 0.1% of carbohydrates, which is solely derived from the cherry flavor.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The precise mechanism by which fenfluramine exerts its therapeutic effects in the treatment of seizures associated with Dravet syndrome and Lennox-Gastaut syndrome is unknown. Fenfluramine and the metabolite, norfenfluramine, exhibit agonist activity at serotonin 5-HT2 receptors. There is an association between serotonergic drugs with 5-HT2B receptor agonist activity, including fenfluramine and norfenfluramine, and valvular heart disease and pulmonary arterial hypertension.

1 Section 11 describes FINTEPLA oral solution, which explains that it that contains 2.2 mg/mL of fenfluramine, equivalent to 2.5 mg/mL of the hydrochloride salt.

FINTEPLA is a clear, colorless solution with a pH of 5. FINTEPLA contains the following inactive ingredients:

- Cherry flavor
- Citric acid
- Ethylparaben hydroxyethylcellulose
- Methylparaben
- Potassium citrate
- Sucralose
- Water

FINTEPLA does not contain any ingredients made from gluten-containing grains (wheat, barley, or rye) and not more than 0.1% of carbohydrates, derived solely from the cherry flavor.

2 Section 12 discusses the clinical pharmacology of fenfluramine. It begins by describing its mechanism of action in Section 12.1. The precise mechanism by which fenfluramine exerts its therapeutic effects in the treatment of seizures associated with DS and LGS is unknown. Fenfluramine, and the metabolite norfenfluramine, exhibit agonist activity at serotonin 5-HT2 receptors. There is an association between serotonergic drugs with 5-HT2B receptor agonist activity, including fenfluramine and norfenfluramine, and valvular heart disease and pulmonary arterial hypertension.

The mechanism of action (MOA) of FINTEPLA is different from that of other available AEDs. This may be a key consideration for health care providers who often try to combine AEDs with multiple MOAs to improve efficacy in treatment-resistant patients with LGS.

12.2 Pharmacodynamics

Cardiac Electrophysiology

At a dose 4 times the maximum recommended dose, FINTEPLA did not prolong the QT interval when tested in an adult population.

12.3 Pharmacokinetics

The pharmacokinetics of fenfluramine and norfenfluramine were studied in healthy subjects, in pediatric patients with DS, and in pediatric and adult patients with LGS. The steady-state systemic exposure (Cmax and AUC) of fenfluramine was slightly greater than dose proportional over the dose range of 13 to 51.8 mg twice-daily fenfluramine (i.e., 1 to 4 times the maximum recommended dose). In pediatric patients with DS who received FINTEPLA 0.7 mg/kg/day, up to a total daily dose of 26 mg fenfluramine, the geometric mean steady-state fenfluramine (coefficient of variation) C_{max} was 68.0 (41%) ng/mL and $AUC_{0\text{-}24h}$ was 1390 (44%) ng*h/mL.

Absorption

Fenfluramine has a time to maximum plasma concentration (T_{max}) of 3 to 5 hours at steady state. The absolute bioavailability of fenfluramine is approximately 68-74%. There was no effect of food on the pharmacokinetics of fenfluramine or norfenfluramine.

Distribution

The geometric mean (CV%) apparent volume of distribution (Vz/F) of fenfluramine is 11.9 (16.5%) L/kg following oral administration of FINTEPLA in healthy subjects. Fenfluramine is 50% bound to human plasma proteins in vitro and binding is independent of drug concentrations.

Elimination

The elimination half-life of fenfluramine was 20 hours and the geometric mean (CV%) clearance (CL/F) was 24.8 (29%) L/h, following oral administration of FINTEPLA in healthy subjects.

Metabolism

Over 75% of fenfluramine is metabolized to norfenfluramine prior to elimination, primarily by CYP1A2, CYP2B6, and CYP2D6. Other CYP enzymes involved to a minor extent are CYP2C9, CYP2C19, and CYP3A4/5. Norfenfluramine is then deaminated and oxidized to form inactive metabolites.

Excretion

Most of an orally administered dose of fenfluramine (greater than 90%) is excreted in the urine as fenfluramine, norfenfluramine, or other metabolites with fenfluramine and norfenfluramine accounting for less than 25% of the total; less than 5% is found in feces.

Specific Populations

The effect of age (range: 2 to 50 years), sex, and race had no clinically meaningful effect on the pharmacokinetics of fenfluramine.

Renal Impairment

In a dedicated clinical study comparing the pharmacokinetics of a single dose of 0.4 mg/kg FINTEPLA in subjects with severe renal impairment (eGFR < 30 mL/min/1.73m^2 determined by

1. Section 12.2 explains that FINTEPLA did not prolong the **QT interval** when given at 4 times the maximum recommended dose in an adult population.

2. As described in Section 12.3, the pharmacokinetics of fenfluramine and norfenfluramine were studied in healthy individuals, pediatric patients with DS, and in pediatric and adult patients with LGS. Both the **C_{max}** and **area under the curve (AUC)** of fenfluramine were slightly greater than the proportional dose when given 1 to 4 times the maximum recommended dose (13 mg to 51.8 mg twice-daily).

   This section continues by discussing the pharmacokinetics of fenfluramine in pediatric patients with DS treated with FINTEPLA 0.7 mg/kg/day, up to a total daily dose of 26 mg, the following was observed:

   - Geometric mean steady-state fenfluramine C_{max}: 68.0 (41%) ng/mL
   - $AUC_{0\text{-}24h}$: 1390 (44%) ng*h/mL

3. Section 12.3 continues by explaining that the **time to maximum plasma concentration (T_{max})** for fenfluramine is 3 to 5 hours at steady state. The absolute **bioavailability** of fenfluramine is approximately 68% to 74%. Food does not affect the pharmacokinetics of fenfluramine or norfenfluramine.

4. In healthy individuals, the elimination half-life of fenfluramine was 20 hours following oral administration.

   Prior to elimination, >75% of fenfluramine is metabolized to norfenfluramine mostly by CYP1A2, CYP2B6, and CYP2D6. Other CYP enzymes involved to a minor extent are CYP2C9, CYP2C19, and CYP3A4/5.

   Over 90% of the orally administered fenfluramine dose is excreted in the urine. Less than 5% is excreted in the feces.

1

Specific Populations

The effect of age (range: 2 to 50 years), sex, and race had no clinically meaningful effect on the pharmacokinetics of fenfluramine.

Renal Impairment

In a dedicated clinical study comparing the pharmacokinetics of a single dose of 0.4 mg/kg FINTEPLA in subjects with severe renal impairment (eGFR < 30 mL/min/1.73m^2 determined by

MDRD) and matched healthy volunteers, C_{max} and $AUC_{0\text{-}inf}$ of fenfluramine increased by 20% and 88%, respectively, and C_{max} and $AUC_{0\text{-}inf}$ of norfenfluramine increased by 13% and 21%, respectively in subjects with severe renal impairment *[see Use in Specific Populations (8.6)]*. FINTEPLA has not been studied in patients with eGFR < 15 mL/min/1.73m^2 (determined by MDRD). It is not known if fenfluramine or norfenfluramine is dialyzable.

2

Drug Interaction Studies

Clinical Studies

Effect of a single dose of stiripentol, clobazam, and valproic acid combination:

Coadministration of a single 0.7 mg/kg dose of FINTEPLA, with a single dose of a stiripentol, clobazam, and valproic acid combination in healthy volunteers, increased the $AUC_{0\text{-}INF}$ of fenfluramine by 69% and the Cmax by 18%, and decreased the $AUC_{0\text{-}72\ hours}$ of norfenfluramine by 41% and the Cmax by 42%, as compared to FINTEPLA administered alone.

Effect of steady state stiripentol plus clobazam, with or without valproate:

Fenfluramine pharmacokinetic data were collected from patients after receiving multiple fenfluramine administrations in Study 1 as well as Study 2. Population pharmacokinetic modeling and simulation were used to assess the effect of stiripentol plus clobazam with or without valproate on fenfluramine pharmacokinetics. The effect of stiripentol plus clobazam, with or without valproate, on fenfluramine pharmacokinetics is greater when FINTEPLA is at steady-state than for the first dose of FINTEPLA. At steady state in the patient population, the coadministration of 0.1 mg/kg twice daily (0.2 mg/kg/day), maximum 17 mg/day, of FINTEPLA with stiripentol plus clobazam with or without valproate, is expected to result in a 166% increase in fenfluramine $AUC_{0\text{-}24}$ and a 38% decrease in norfenfluramine $AUC_{0\text{-}24}$, as compared to 0.2 mg/kg/day, maximum 26 mg/day, FINTEPLA dose administered alone *[see Dosage and Administration (2.1, 2.2) and Drug Interactions (7.1)]*.

1 Section 12.3 continues by explaining that the effect of age, sex, race, and body weight had no clinically meaningful effect on fenfluramine pharmacokinetics (PK).

The pharmacokinetics of FINTEPLA in patients with severe renal impairment was assessed by comparing the C_{max} and $AUC_{0\text{-}t}$ of fenfluramine in this patient population with matched healthy volunteers after administration of a single dose of 0.4 mg/kg FINTEPLA. Results for fenfluramine showed:

- C_{max} increased by 20%
- $AUC_{0\text{-}t}$ increased by 88%

It is not known if fenfluramine or norfenfluramine is dialyzable.

2 The FINTEPLA PI also presents results from drug interaction studies. These included:

- Effect of a single dose of stiripentol, clobazam, and valproic acid combination on FINTEPLA
- Effect of steady state stiripentol plus clobazam, with or without valproate on FINTEPLA
- Effect of steady state **cannabidiol** on FINTEPLA
- Effect of strong CYP1A2 or CYP2D6 inhibitors
- Effect of strong CYP1A2, CYP2B6 or CYP3A inducers
- Effect of FINTEPLA on other drugs, including a single dose of stiripentol, clobazam, and valproic acid combination, as well as cannabidiol

Effect of steady state cannabidiol:

Coadministration of a single 0.35 mg/kg dose of FINTEPLA with repeated doses of cannabidiol increased the $AUC_{0\text{-}INF}$ of fenfluramine by 59% and the C_{max} by 10%, and decreased the $AUC_{0\text{-}INF}$ of norfenfluramine by 22% and the C_{max} by 33%, as compared to FINTEPLA administered alone. This interaction is not expected to be clinically significant.

1 Effect of strong CYP1A2 or CYP2D6 inhibitors:

Coadministration of a single 0.4 mg/kg dose of FINTEPLA with fluvoxamine (a strong CYP1A2 inhibitor) at steady state (50 mg once daily) in healthy volunteers increased the $AUC_{0\text{-}inf}$ of fenfluramine by 102% and the C_{max} by 22%, and decreased the $AUC_{0\text{-}inf}$ of norfenfluramine by 22% and the C_{max} by 44%, as compared to FINTEPLA administered alone *[see Drug Interactions (7.1)]*.

Coadministration of a single 0.4 mg/kg dose of FINTEPLA with paroxetine (a strong CYP2D6 inhibitor) at steady state (30 mg once daily) in healthy volunteers increased the $AUC_{0\text{-}inf}$ of fenfluramine by 81% and the C_{max} by 13%, and decreased the $AUC_{0\text{-}inf}$ of norfenfluramine by 13% and the C_{max} by 29%, as compared to FINTEPLA administered alone *[see Drug Interactions (7.1)]*.

2 Effect of strong CYP1A2, CYP2B6 or CYP3A inducers:

Coadministration of a single 0.4 mg/kg dose of FINTEPLA with rifampin (a CYP1A2, CYP2B6, and CYP3A inducer) at steady state (600 mg once daily) in healthy volunteers decreased the $AUC_{0\text{-}inf}$ of fenfluramine by 58% and the C_{max} by 40%, and decreased the $AUC_{0\text{-}inf}$ of norfenfluramine by 50%, and increased the C_{max} of norfenfluramine by 13%, as compared to FINTEPLA administered alone *[see Drug Interactions (7.1)]*.

Effect of FINTEPLA on other drugs:

Coadministration of a single 0.7 mg/kg dose of FINTEPLA, with a single dose of a stiripentol, clobazam, and valproic acid combination, did not affect the pharmacokinetics of stiripentol, nor the pharmacokinetics of clobazam or its N-desmethyl-metabolite norclobazam, nor the pharmacokinetics of valproic acid, as compared to the stiripentol, clobazam, and valproic acid combination alone. Coadministration of a single 0.35 mg/kg dose of FINTEPLA, with repeated doses of cannabidiol, did not affect the pharmacokinetics of cannabidiol, as compared to cannabidiol alone.

3 *In Vitro Studies*

Fenfluramine is primarily metabolized by CYP1A2, CYP2B6, and CYP2D6 in vitro. Other CYP enzymes involved to a minor extent are CYP2C9, CYP2C19, and CYP3A4/5.

Effect of fenfluramine and norfenfluramine on CYP Substrates: fenfluramine and norfenfluramine are not inhibitors or inducers of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, or CYP3A4 at clinically relevant concentrations.

Effect of transporters on fenfluramine and norfenfluramine: fenfluramine and norfenfluramine are not substrates of the P-g, BCRP, OAT1, OAT3, OCT2, MATE1, or MATE2-K transporters.

Effect of FINTEPLA on Transporters: fenfluramine and norfenfluramine are not inhibitors of P-gp, BCRP, OAT1B1, OATP1B3, OAT1, OAT3, OCT2, MATE1, or MATE2-K transporters.

1 The FINTEPLA PI provides information about the coadministration of FINTEPLA with strong CYP1A2 or CYP2D6 inhibitors, such as **fluvoxamine** and **paroxetine**. Increases in the $AUC_{0\text{-}t}$ and C_{max} of fenfluramine and decreases in the $AUC_{0\text{-}t}$ and C_{max} of norfenfluramine were observed.

2 Results of pharmacokinetic studies of FINTEPLA in conjunction with strong CYP1A2, CYP2B6, or CYP3A inducers such as rifampin showed decreases in the $AUC_{0\text{-}inf}$ and C_{max} of fenfluramine, decreases in the $AUC_{0\text{-}inf}$ of norfenfluramine, and increases in the C_{max} of norfenfluramine, as compared to FINTEPLA administered alone. An increase in FINTEPLA dose may be necessary when coadministered with such products.

3 The FINTEPLA PI explains that fenfluramine is primarily metabolized by CYP1A2, CYP2B6, and CYP2D6 in vitro. Other CYP enzymes involved to a minor extent are CYP2C9, CYP2C19, and CYP3A4/5.

1

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Studies to assess the carcinogenic potential of fenfluramine have not been conducted.

Mutagenesis

Fenfluramine was negative in an in vitro bacterial mutation (Ames) assay and an in vivo micronucleus and comet assay in rats.

Impairment of Fertility

Oral administration of fenfluramine (0, 3.5, 8, or 20 mg/kg/day) to male and female rats prior to and throughout mating and continuing in females to day 7 of gestation resulted in a decrease in fertility and increases in abnormal sperm and epithelial vacuolation of the epididymis at the highest dose tested and altered estrous cyclicity, decreased corpora lutea and implantations, and increased embryolethality at the mid and high dose. These doses were associated with parental toxicity. The no-effect doses for adverse effects on fertility and reproductive performance in rats (8 and 3.5 mg/kg/day in males and females, respectively) were associated with plasma fenfluramine exposures (AUC) approximately 3 and 0.6 times, respectively, and norfenfluramine exposures approximately 5 and 3 times, respectively, those in humans at the maximum recommended human dose of 26 mg/kg.

14 CLINICAL STUDIES

14.1 Dravet Syndrome

The effectiveness of FINTEPLA for the treatment of seizures associated with DS in patients 2 years of age and older was established in two randomized, double-blind, placebo-controlled trials in patients 2 to 18 years of age.

Study 1 (N=117) compared a 0.7 mg/kg/day and a 0.2 mg/kg/day dose of FINTEPLA with placebo in patients who were not receiving stiripentol (NCT02682927 and NCT02826863). Study 2 (N=85) compared a 0.4 mg/kg/day dose of FINTEPLA with placebo in patients who were receiving stiripentol and either clobazam, valproate, or both (NCT02926898). In both studies, patients had a clinical diagnosis of DS and were inadequately controlled on at least one AED or other antiseizure treatment including vagal nerve stimulation or a ketogenic diet. Both trials had a 6-week baseline period, during which patients were required to have a minimum of 6 convulsive seizures while on stable AED therapy. Convulsive seizures included tonic, clonic, generalized tonic-clonic, tonic-atonic, secondarily generalized tonic-clonic, hemiclonic, and focal with observable motor signs. The baseline period was followed by randomization into a 2-week (Study 1) or 3-week (Study 2) titration period and a subsequent 12-week maintenance period, where the dose of FINTEPLA remained stable.

In Study 1, 98% of patients were taking between 1 and 4 concomitant AEDs. The most frequently used concomitant AEDs (in at least 25% of patients), were valproate (61%), clobazam (59%), and topiramate (25%). In Study 2, 100% of patients were taking between 2 and 4 concomitant AEDs. The most frequently used concomitant AEDs (in at least 25% of patients), were stiripentol (100%), clobazam (94%), and valproate (89%).

1 Section 13 of the FINTEPLA PI describes the results of nonclinical toxicology studies designed to assess the potential for **carcinogenesis, mutagenesis,** or impairment of fertility with fenfluramine. No studies have been conducted to assess the carcinogenic potential of fenfluramine. Fertility studies in rats revealed a decrease in fertility at a fenfluramine dose of 20 mg/kg/day.

Take Home Points

- FINTEPLA is an oral solution that contains 2.2 mg/mL of fenfluramine, equivalent to 2.5 mg/mL of the hydrochloride salt
- The precise mechanism by which fenfluramine exerts its therapeutic effects in the treatment of seizures associated with DS and LGS are unknown; fenfluramine and the metabolite, norfenfluramine, exhibit agonist activity at serotonin 5HT-2 receptors
- FINTEPLA did not prolong the QT interval when given at 4 times the maximum recommended dose in an adult population
- The time to maximum plasma concentration (T_{max}) for fenfluramine is 3 to 5 hours at steady state
- The absolute bioavailability of fenfluramine is approximately 68% to 74%
- Food does not affect the pharmacokinetics of fenfluramine or norfenfluramine
- In healthy individuals, the elimination half-life of fenfluramine was 20 hours following oral administration
- Over 90% of the orally administered fenfluramine dose is excreted in the urine; less than 5% is excreted in the feces
- The effect of age, sex, race, and body weight had no clinically meaningful effect on fenfluramine pharmacokinetics
- Fenfluramine is primarily metabolized by CYP1A2, CYP2B6, and CYP2D6 in vitro; other CYP enzymes involved to a minor extent are CYP2C9, CYP2C19, and CYP3A4/5
- An increase in the dose of FINTEPLA may be necessary when coadministered with strong CYP1A2, CYP2B6, or CYP3A inducers such as rifampin

Knowledge Check

FINTEPLA contains _____ of fenfluramine.

- ☐ 1.5 mg/mL
- ☐ 2.2 mg/mL
- ☐ 3.8 mg/mL
- ☐ 4.7 mg/mL

SHOW ANSWER

Knowledge Check

FINTEPLA contains _____ of fenfluramine.

- [ ] 1.5 mg/mL
- [x] **2.2 mg/mL**
- [ ] 3.8 mg/mL
- [ ] 4.7 mg/mL

NEXT QUESTION

Knowledge Check

Fenfluramine and the metabolite, norfenfluramine, exhibit agonist activity at serotonin 5HT-2 receptors.

- ☐ True
- ☐ False

SHOW ANSWER

Knowledge Check

Fenfluramine and the metabolite, norfenfluramine, exhibit agonist activity at serotonin 5HT-2 receptors.

- [x] **True**
- [ ] False

NEXT QUESTION

Knowledge Check

Which of the following statements about fenfluramine is true?

- [ ] Food affects the pharmacokinetics of fenfluramine or norfenfluramine.
- [ ] In healthy individuals, the half-life of fenfluramine is 4 hours following oral administration.
- [ ] The effect of age, sex, race, and body weight had no clinically meaningful effect on fenfluramine pharmacokinetics.
- [ ] Over 90% of the orally administered fenfluramine dose is excreted in the feces.

SHOW ANSWER

Knowledge Check

Which of the following statements about fenfluramine is true?

- ☐ Food affects the pharmacokinetics of fenfluramine or norfenfluramine.
- ☐ In healthy individuals, the half-life of fenfluramine is 4 hours following oral administration.
- ☑ **The effect of age, sex, race, and body weight had no clinically meaningful effect on fenfluramine pharmacokinetics.**
- ☐ Over 90% of the orally administered fenfluramine dose is excreted in the feces.

NEXT PAGE

Chapter 5: Clinical Studies

Learning Objectives

Upon completion of this chapter, you will be able to:

- Describe the clinical studies that evaluated FINTEPLA for the treatment of DS and LGS in patients age ≥2 years

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Studies to assess the carcinogenic potential of fenfluramine have not been conducted.

Mutagenesis

Fenfluramine was negative in an in vitro bacterial mutation (Ames) assay and an in vivo micronucleus and comet assay in rats.

Impairment of Fertility

Oral administration of fenfluramine (0, 3.5, 8, or 20 mg/kg/day) to male and female rats prior to and throughout mating and continuing in females to day 7 of gestation resulted in a decrease in fertility and increases in abnormal sperm and epithelial vacuolation of the epididymis at the highest dose tested and altered estrous cyclicity, decreased corpora lutea and implantations, and increased embryolethality at the mid and high dose. These doses were associated with parental toxicity. The no-effect doses for adverse effects on fertility and reproductive performance in rats (8 and 3.5 mg/kg/day in males and females, respectively) were associated with plasma fenfluramine exposures (AUC) approximately 3 and 0.6 times, respectively, and norfenfluramine exposures approximately 5 and 3 times, respectively, those in humans at the maximum recommended human dose of 26 mg/kg.

14 CLINICAL STUDIES

14.1 Dravet Syndrome

The effectiveness of FINTEPLA for the treatment of seizures associated with DS in patients 2 years of age and older was established in two randomized, double-blind, placebo-controlled trials in patients 2 to 18 years of age.

Study 1 (N=117) compared a 0.7 mg/kg/day and a 0.2 mg/kg/day dose of FINTEPLA with placebo in patients who were not receiving stiripentol (NCT02682927 and NCT02826863). Study 2 (N=85) compared a 0.4 mg/kg/day dose of FINTEPLA with placebo in patients who were receiving stiripentol and either clobazam, valproate, or both (NCT02926898). In both studies, patients had a clinical diagnosis of DS and were inadequately controlled on at least one AED or other antiseizure treatment including vagal nerve stimulation or a ketogenic diet. Both trials had a 6-week baseline period, during which patients were required to have a minimum of 6 convulsive seizures while on stable AED therapy. Convulsive seizures included tonic, clonic, generalized tonic-clonic, tonic-atonic, secondarily generalized tonic-clonic, hemiclonic, and focal with observable motor signs. The baseline period was followed by randomization into a 2-week (Study 1) or 3-week (Study 2) titration period and a subsequent 12-week maintenance period, where the dose of FINTEPLA remained stable.

In Study 1, 98% of patients were taking between 1 and 4 concomitant AEDs. The most frequently used concomitant AEDs (in at least 25% of patients), were valproate (61%), clobazam (59%), and topiramate (25%). In Study 2, 100% of patients were taking between 2 and 4 concomitant AEDs. The most frequently used concomitant AEDs (in at least 25% of patients), were stiripentol (100%), clobazam (94%), and valproate (89%).

1 Section 14 describes the clinical studies that evaluated FINTEPLA for the treatment of seizures associated with DS and LGS in patients ≥2 years. These included:

- Studies 1 and 2 in patients with DS
- Study 3 in patients with LGS

Dravet Syndrome

Studies 1 and 2 were **randomized**, **double-blind**, placebo-controlled trials in patients 2 to 18 years of age with DS:

- Study 1 involved 117 patients and compared two doses of FINTEPLA (0.7 mg/kg/day and 0.2 mg/kg/day) with placebo in patients who were not receiving stiripentol
- Study 2 involved 85 patients and compared a FINTEPLA 0.4 mg/kg/day dose with placebo in patients who were receiving stiripentol and either clobazam, valproate, or both

Patients in these studies had a clinical diagnosis of DS and were inadequately controlled on ≥1 AED or other antiseizure treatment **including vagal nerve stimulation** or a **ketogenic diet**.

The section continues by describing the study design of Studies 1 and 2, which was as follows:

- Baseline period: 6 weeks in which patients were required to have ≥6 convulsive seizures while on stable AED therapy
- Titration period:
  - 2 weeks for Study 1
  - 3 weeks for Study 2
- Maintenance period: 12 weeks with a stable FINTEPLA dose

1 In Study 1, 98% of patients were taking between 1 and 4 concomitant AEDs. The most frequently used concomitant AEDs (in at least 25% of patients), were valproate (61%), clobazam (59%), and topiramate (25%). In Study 2, 100% of patients were taking between 2 and 4 concomitant AEDs. The most frequently used concomitant AEDs (in at least 25% of patients), were stiripentol (100%), clobazam (94%), and valproate (89%).

2 The primary efficacy endpoint in both studies was the change from baseline in the frequency of convulsive seizures per 28 days during the combined 14-week (Study 1) or 15-week (Study 2) titration and maintenance periods (i.e., treatment period). The median longest interval between convulsive seizures was also assessed.

In Study 1 and Study 2, the reduction in convulsive seizure frequency per 28 days was statistically significantly greater for all dose groups of FINTEPLA compared to placebo (Table 5). A reduction in convulsive seizures was observed within 3 to 4 weeks of starting FINTEPLA, and the effect remained generally consistent over the 14- or 15-week treatment period.

Table 4: Change in Convulsive Seizure Frequency During the Treatment Period in Patients with Dravet Syndrome (Study 1 and Study 2)

Convulsive Seizure Frequency (per 28 days)	Placebo	FINTEPLA 0.2 mg/kg/day	FINTEPLA 0.7 mg/kg/day	FINTEPLA 0.4 mg/kg/day
Study 1	**N=39**	**N=38**	**N=40**	**NA**
Baseline Period Median	29.4	18.1	18.7	NA
% Difference Relative to Placebo*		-31.7%	-70.0%	NA
p-value compared to placebo		0.043	<0.001	
Study 2	**N=42**	**NA**	**NA**	**N=43**
Baseline Period Median	11.5	NA	NA	15.0
% Difference Relative to Placebo*		NA	NA	-59.5%
p-value compared to placebo				<0.001

*Derived from the primary analysis model
±All 0.4 mg/kg/day patients were also taking concomitant stiripentol, which increases the exposure of FINTEPLA.

Figure 1 and Figure 2 display the percentage of patients by category of seizure response from baseline in convulsive seizure frequency (per 28 days) during the treatment period in Study 1 and Study 2, respectively.

1 The percentage of patients taking concomitant AEDs in the clinical trials is shown in the following table.

Concomitant AEDs	
Study 1	• 98% of patients were taking between 1 and 4 concomitant AEDs • The most frequently used (≥25% of patients) were: – Valproate: 61% – Clobazam: 59% – Topiramate: 25%
Study 2	• 100% of patients were taking between 2 and 4 concomitant AEDs • The most frequently used (≥25% of patients) were: – Stiripentol: 100% – Clobazam: 94% – Valproate: 89%

2 The primary efficacy endpoint in both studies was the change from baseline in the frequency of convulsive seizures per 28 days during the combined 14-week (Study 1) or 15-week (Study 2) titration and maintenance periods (i.e., treatment period). The median longest interval between convulsive seizures was also assessed.

In Study 1, 98% of patients were taking between 1 and 4 concomitant AEDs. The most frequently used concomitant AEDs (in at least 25% of patients), were valproate (61%), clobazam (59%), and topiramate (25%). In Study 2, 100% of patients were taking between 2 and 4 concomitant AEDs. The most frequently used concomitant AEDs (in at least 25% of patients), were stiripentol (100%), clobazam (94%), and valproate (89%).

The primary efficacy endpoint in both studies was the change from baseline in the frequency of convulsive seizures per 28 days during the combined 14-week (Study 1) or 15-week (Study 2) titration and maintenance periods (i.e., treatment period). The median longest interval between convulsive seizures was also assessed.

1 In Study 1 and Study 2, the reduction in convulsive seizure frequency per 28 days was statistically significantly greater for all dose groups of FINTEPLA compared to placebo (Table 5). A reduction in convulsive seizures was observed within 3 to 4 weeks of starting FINTEPLA, and the effect remained generally consistent over the 14- or 15-week treatment period.

2 **Table 4: Change in Convulsive Seizure Frequency During the Treatment Period in Patients with Dravet Syndrome (Study 1 and Study 2)**

Convulsive Seizure Frequency (per 28 days)	Placebo	FINTEPLA 0.2 mg/kg/day	FINTEPLA 0.7 mg/kg/day	FINTEPLA 0.4 mg/kg/day
Study 1	**N=39**	**N=38**	**N=40**	**NA**
Baseline Period Median	29.4	18.1	18.7	NA
% Difference Relative to Placebo*		-31.7%	-70.0%	NA
p-value compared to placebo		0.043	<0.001	
Study 2	**N=42**	**NA**	**NA**	**N=43**
Baseline Period Median	11.5	NA	NA	15.0
% Difference Relative to Placebo*		NA	NA	-59.5%
p-value compared to placebo				<0.001

*Derived from the primary analysis model
±All 0.4 mg/kg/day patients were also taking concomitant stiripentol, which increases the exposure of FINTEPLA.

Figure 1 and Figure 2 display the percentage of patients by category of seizure response from baseline in convulsive seizure frequency (per 28 days) during the treatment period in Study 1 and Study 2, respectively.

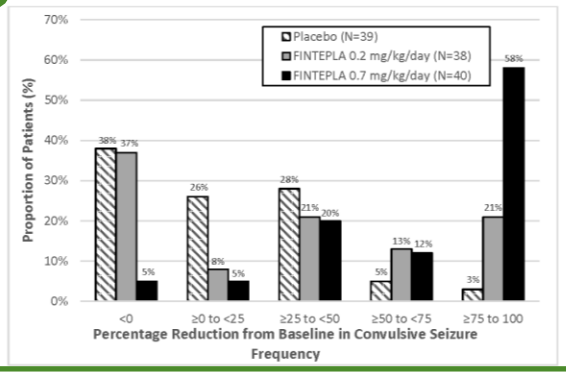
1 Results from Study 1 and Study 2 showed that the reduction in convulsive seizure frequency per 28 days (the primary endpoint) was statistically significantly greater for all dose groups of FINTEPLA (0.2 mg/kg/day and 0.7 mg/kg/day in Study 1 and FINTEPLA 0.4 mg/kg/day in Study 2) compared to placebo.

Within 3 to 4 weeks of starting FINTEPLA, a reduction in convulsive seizures was observed. This effect remained generally consistent over the entire 14-week (Study 1) or 15-week (Study 2) treatment period.

2 Table 5 presents the change in convulsive seizure frequency during the treatment period in both Study 1 and Study 2. As mentioned earlier, results were statistically significantly greater for all FINTEPLA dose groups compared to placebo. Note that results are considered statistically significant if the *P*-value is <0.05.

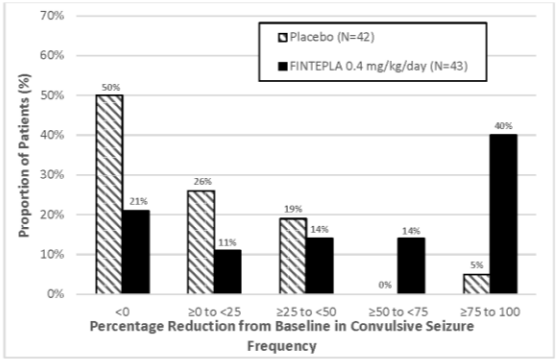
1

Figure 1: Proportion of Patients by Category of Seizure Response for FINTEPLA and Placebo in Patients with Dravet Syndrome (Study 1)



2

Figure 2: Proportion of Patients by Category of Seizure Response for FINTEPLA and Placebo in Patients with Dravet Syndrome (Study 2)



1 Figure 1 presents results from Study 1. Specifically, it shows the proportion of patients by category of seizure response from baseline in convulsive seizure frequency (per 28 days) for patients treated with either FINTEPLA 0.2 mg/kg/day, FINTEPLA 0.7 mg/kg/day, or placebo.

The five categories of seizure response were defined as the percentage reduction from baseline in convulsive seizure frequency, including:

- <0%
- ≥0% to <25%
- ≥25% to <50%
- ≥50% to <75%
- ≥75% to 100%

As shown in the figure, FINTEPLA 0.7 mg/kg/day led to a ≥75% to 100% reduction from baseline in convulsive seizure frequency in >50% of patients.

2 Figure 2 presents results from Study 2. Specifically, it shows the proportion of patients by category of seizure response from baseline in convulsive seizure frequency (per 28 days) for patients treated with either FINTEPLA 0.4 mg/kg/day or placebo. Study 2 had the same five categories of seizure response as Study 1. As shown in the figure, FINTEPLA 0.4 mg/kg/day led to a ≥75% to 100% reduction from baseline in convulsive seizure frequency in 40% of patients.

1 In Study 1, 3 of 40 (8%) patients in the FINTEPLA 0.7 mg/kg/day group and 3 of 38 (8%) patients in the FINTEPLA 0.2 mg/kg/day group reported no convulsive seizures during the 14-week treatment period, compared to 0 patients in the placebo group. In Study 2, 1 of 43 (2%) patients in the FINTEPLA 0.4 mg/kg/day group reported no convulsive seizures during the 15-week treatment period, compared to 0 patients in the placebo group.

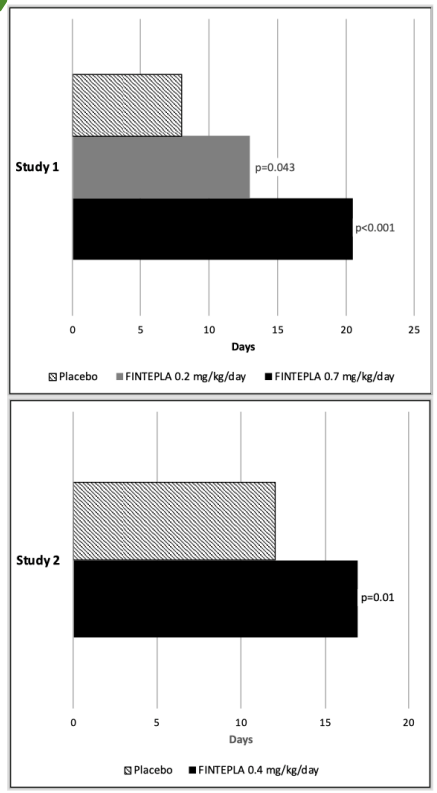
In Study 1 and Study 2, FINTEPLA was associated with a statistically significant longer interval between convulsive seizures compared to placebo (Figure 3).

1 Section 14 continues by discussing the proportion of patients who reported no convulsive seizures during the treatment periods of Study 1 and Study 2. These results are summarized in the following table.

Patients Reporting No Convulsive Seizures During the Treatment Periods of Study 1 (14 Weeks) and Study 2 (15 weeks)			
	FINTEPLA 0.7 mg/kg/day	**FINTEPLA 0.2 mg/kg/day**	**Placebo**
Number of patients (percentage)	3 of 40 (8%)	3 of 38 (8%)	0
Study 2	**FINTEPLA 0.4 mg/kg/day**		**Placebo**
Number of patients (percentage)	1 of 43 (2%)		0

In Study 1 and Study 2, FINTEPLA was associated with a statistically significant longer interval between convulsive seizures compared to placebo (Figure 3).

Figure 3: Median Longest Interval Between Convulsive Seizures in Patients with Dravet Syndrome (Study 1 and Study 2)



14.2 Lennox-Gastaut Syndrome

The effectiveness of FINTEPLA for the treatment of seizures associated with LGS in patients 2 years of age and older was established in a randomized, double-blind, placebo-controlled study in 263 patients 2 to 35 years of age (Study 3; NCT03355209).

1 The FINTEPLA PI also explains that FINTEPLA was associated with a statistically significant longer interval between convulsive seizures compared to placebo in both Study 1 and Study 2.

Figure 3 presents the median longest seizure-free interval among patients in Study 1 and Study 2. As shown in the figure, results were statistically significantly greater for all FINTEPLA dose groups compared to placebo.

1

14.2 Lennox-Gastaut Syndrome

The effectiveness of FINTEPLA for the treatment of seizures associated with LGS in patients 2 years of age and older was established in a randomized, double-blind, placebo-controlled study in 263 patients 2 to 35 years of age (Study 3; NCT03355209).

Study 3 compared a 0.7 mg/kg/day and a 0.2 mg/kg/day dose of FINTEPLA with placebo. Patients had a diagnosis of LGS and were inadequately controlled on at least one AED, with or without vagal nerve stimulation and/or ketogenic diet. The study had a 4-week baseline period, during which patients were required to have a minimum of 8 drop seizures while on stable AED therapy. Drop seizures were generalized tonic-clonic, secondarily generalized tonic-clonic, tonic, atonic, or tonic-atonic seizures that were confirmed to result in drops. The baseline period was followed by randomization into a 2-week titration period and a subsequent 12-week maintenance period, where the dose of FINTEPLA remained stable.

In Study 3, 99% of patients were taking between 1 and 4 concomitant AEDs. The most frequently used concomitant AEDs (in at least 25% of patients) were clobazam (45%), lamotrigine (34%), and valproate (56%).

The primary efficacy endpoint in Study 3 was the median percent change from baseline in the frequency of drop seizures per 28 days during the combined 14-week titration and maintenance periods (i.e., treatment period). The proportion of patients who achieve improvement (minimally, much, or very much improved) in the Clinical Global Impression of Change (CGI-I) as assessed by Principal Investigator was a secondary endpoint.

In Study 3, the median percent change from baseline (reduction) in the frequency of drop seizures per 28 days was significantly greater for the 0.7 mg/kg/day dose group of FINTEPLA compared with placebo (Table 6). A reduction in drop seizures was observed within 2 weeks of initiating treatment with FINTEPLA, and the effect remained generally consistent over the 14-week treatment period.

The median percent reduction from baseline in drop seizure frequency per 28 days for the lower dose of FINTEPLA (0.2 mg/kg/day) did not reach statistical significance compared to placebo (Table 6).

Table 5: Change in Drop Seizure Frequency during the Treatment Period in Patients with Lennox-Gastaut Syndrome (Study 3)

Drop Seizure Frequency (per 28 days)	Placebo	FINTEPLA 0.2 mg/kg/day	FINTEPLA 0.7 mg/kg/day
Study 3	N=85*	N=86*	N=83*
Baseline Period Median Seizure Frequency	55.0	77.8	80.0
Median Percentage Change from Baseline During Treatment	-8.7%	-13.2%	-23.7%
p-value compared to placebo		0.1917#	0.0037

*The total number of patients upon which the efficacy analysis was based is less than the total number randomized in the double-blind, placebo-controlled study because patients with missing data were excluded from the efficacy analysis.
Not statistically significant

Figure 4 displays the percentage of patients by category of reduction from baseline in drop seizure frequency per 28 days during the treatment period in Study 3.

1

Lennox-Gastaut Syndrome

FINTEPLA Study 3 was a randomized, double-blind, placebo-controlled trial comparing 2 doses of FINTEPLA to placebo: 0.7 mg/kg/day and 0.2 mg/kg/day. A total of 263 patients 2 to 35 years of age participated in Study 3.

Patients had a diagnosis of LGS and were inadequately controlled on ≥1 AED or other antiseizure treatment, including vagal nerve stimulation and/or ketogenic diet. Prior to enrolling in Study 3, patients had tried between 1 and 20 AEDs, with a median of 7 prior AED failures.

The design of Study 3 included a:

- 4-week baseline period
- 2-week titration period
- 12-week maintenance period

→ 14-week treatment period

During the 4-week baseline period, patients were required to have ≥8 drop seizures while on stable AED therapy. Drop seizures included generalized tonic-clonic (GTC) seizures, secondarily generalized tonic-clonic (SGTC) seizures, tonic seizures, atonic seizures, and tonic-atonic seizures that were confirmed to result in drops by the Epilepsy Study Consortium (ESC).

The most common types of drop seizures that occurred across all treatment groups during the 4-week baseline period were:

- Tonic seizures: 77%
- GTCs: 45%
- Atonic seizures: 38%

Note that during the baseline period and throughout Study 3, patients were on a regimen of concomitant AEDs (median: 3). See next page for details.

14.2 Lennox-Gastaut Syndrome

The effectiveness of FINTEPLA for the treatment of seizures associated with LGS in patients 2 years of age and older was established in a randomized, double-blind, placebo-controlled study in 263 patients 2 to 35 years of age (Study 3; NCT03355209).

Study 3 compared a 0.7 mg/kg/day and a 0.2 mg/kg/day dose of FINTEPLA with placebo. Patients had a diagnosis of LGS and were inadequately controlled on at least one AED, with or without vagal nerve stimulation and/or ketogenic diet. The study had a 4-week baseline period, during which patients were required to have a minimum of 8 drop seizures while on stable AED therapy. Drop seizures were generalized tonic-clonic, secondarily generalized tonic-clonic, tonic, atonic, or tonic-atonic seizures that were confirmed to result in drops. The baseline period was followed by randomization into a 2-week titration period and a subsequent 12-week maintenance period, where the dose of FINTEPLA remained stable.

1 In Study 3, 99% of patients were taking between 1 and 4 concomitant AEDs. The most frequently used concomitant AEDs (in at least 25% of patients) were clobazam (45%), lamotrigine (34%), and valproate (56%).

2 The primary efficacy endpoint in Study 3 was the median percent change from baseline in the frequency of drop seizures per 28 days during the combined 14-week titration and maintenance periods (i.e., treatment period). The proportion of patients who achieve improvement (minimally, much, or very much improved) in the Clinical Global Impression of Change (CGI-I) as assessed by Principal Investigator was a secondary endpoint.

In Study 3, the median percent change from baseline (reduction) in the frequency of drop seizures per 28 days was significantly greater for the 0.7 mg/kg/day dose group of FINTEPLA compared with placebo (Table 6). A reduction in drop seizures was observed within 2 weeks of initiating treatment with FINTEPLA, and the effect remained generally consistent over the 14-week treatment period.

The median percent reduction from baseline in drop seizure frequency per 28 days for the lower dose of FINTEPLA (0.2 mg/kg/day) did not reach statistical significance compared to placebo (Table 6).

Table 5: Change in Drop Seizure Frequency during the Treatment Period in Patients with Lennox-Gastaut Syndrome (Study 3)

Drop Seizure Frequency (per 28 days)	Placebo	FINTEPLA 0.2 mg/kg/day	FINTEPLA 0.7 mg/kg/day
Study 3	N=85*	N=86*	N=83*
Baseline Period Median Seizure Frequency	55.0	77.8	80.0
Median Percentage Change from Baseline During Treatment	-8.7%	-13.2%	-23.7%
p-value compared to placebo		0.1917#	0.0037

*The total number of patients upon which the efficacy analysis was based is less than the total number randomized in the double-blind, placebo-controlled study because patients with missing data were excluded from the efficacy analysis.
Not statistically significant

Figure 4 displays the percentage of patients by category of reduction from baseline in drop seizure frequency per 28 days during the treatment period in Study 3.

1 In Study 3, 99% of patients were taking between 1 and 4 concomitant AEDs (median 3). The most frequently used concomitant AEDs (in at least 25% of patients) were:

- Valproate (55.9%)
- Clobazam (45.2%)
- Lamotrigine (33.5%)

2 The primary efficacy endpoint of Study 3 was the change in drop seizure frequency (DSF) per 28 days between baseline and the 14-week treatment period with FINTEPLA 0.7 mg/kg/day vs placebo. The proportion of subjects who achieved improvement (minimally improved, much improved, or very much improved) in the Clinical Global Impression of Improvement (CGI-I), as assessed by study investigators was a secondary endpoint.

14.2 Lennox-Gastaut Syndrome

The effectiveness of FINTEPLA for the treatment of seizures associated with LGS in patients 2 years of age and older was established in a randomized, double-blind, placebo-controlled study in 263 patients 2 to 35 years of age (Study 3; NCT03355209).

Study 3 compared a 0.7 mg/kg/day and a 0.2 mg/kg/day dose of FINTEPLA with placebo. Patients had a diagnosis of LGS and were inadequately controlled on at least one AED, with or without vagal nerve stimulation and/or ketogenic diet. The study had a 4-week baseline period, during which patients were required to have a minimum of 8 drop seizures while on stable AED therapy. Drop seizures were generalized tonic-clonic, secondarily generalized tonic-clonic, tonic, atonic, or tonic-atonic seizures that were confirmed to result in drops. The baseline period was followed by randomization into a 2-week titration period and a subsequent 12-week maintenance period, where the dose of FINTEPLA remained stable.

In Study 3, 99% of patients were taking between 1 and 4 concomitant AEDs. The most frequently used concomitant AEDs (in at least 25% of patients) were clobazam (45%), lamotrigine (34%), and valproate (56%).

The primary efficacy endpoint in Study 3 was the median percent change from baseline in the frequency of drop seizures per 28 days during the combined 14-week titration and maintenance periods (i.e., treatment period). The proportion of patients who achieve improvement (minimally, much, or very much improved) in the Clinical Global Impression of Change (CGI-I) as assessed by Principal Investigator was a secondary endpoint.

1 In Study 3, the median percent change from baseline (reduction) in the frequency of drop seizures per 28 days was significantly greater for the 0.7 mg/kg/day dose group of FINTEPLA compared with placebo (Table 6). A reduction in drop seizures was observed within 2 weeks of initiating treatment with FINTEPLA, and the effect remained generally consistent over the 14-week treatment period.

The median percent reduction from baseline in drop seizure frequency per 28 days for the lower dose of FINTEPLA (0.2 mg/kg/day) did not reach statistical significance compared to placebo (Table 6).

Table 5: Change in Drop Seizure Frequency during the Treatment Period in Patients with Lennox-Gastaut Syndrome (Study 3)

Drop Seizure Frequency (per 28 days)	Placebo	FINTEPLA 0.2 mg/kg/day	FINTEPLA 0.7 mg/kg/day
Study 3	**N=85***	**N=86***	**N=83***
Baseline Period Median Seizure Frequency	55.0	77.8	80.0
Median Percentage Change from Baseline During Treatment	-8.7%	-13.2%	-23.7%
p-value compared to placebo		0.1917#	0.0037

*The total number of patients upon which the efficacy analysis was based is less than the total number randomized in the double-blind, placebo-controlled study because patients with missing data were excluded from the efficacy analysis.
Not statistically significant

Figure 4 displays the percentage of patients by category of reduction from baseline in drop seizure frequency per 28 days during the treatment period in Study 3.

1 Study 3 met the primary efficacy endpoint, demonstrating a statistically significant benefit for FINTEPLA 0.7 mg/kg/day in reducing DSF (per 28 days) compared with placebo:

- FINTEPLA 0.7 mg/kg/day: -23.7% (P=0.0037)
- Placebo: -8.7%

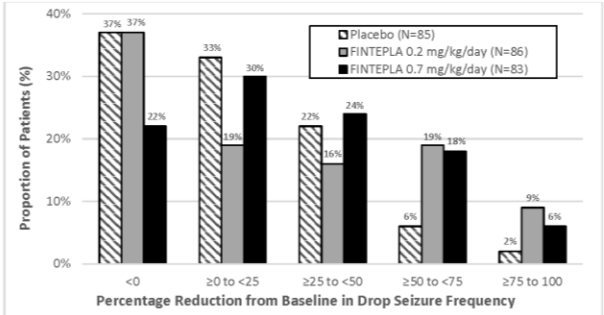
→ ≈15% reduction compared to placebo

A reduction in drop seizures was observed within 2 weeks of initiating treatment with FINTEPLA, and the effect remained generally consistent over the 14-week treatment period.

Table 6 also shows that treatment with FINTEPLA 0.2 mg/kg/day did not reach statistical significance compared to placebo (-13.2% vs -8.7%, respectively; P=0.1917).

Figure 4 displays the percentage of patients by category of reduction from baseline in drop seizure frequency per 28 days during the treatment period in Study 3.

Figure 4: Proportion of Patients by Category of Seizure Response for FINTEPLA and Placebo in Patients with Lennox–Gastaut Syndrome (Study 3)



Numerically greater improvements on the CGI-I by Investigator were observed in patients treated with FINTEPLA compared with placebo.

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

FINTEPLA oral solution is a clear, colorless, cherry flavored liquid containing 2.2 mg/mL fenfluramine and is supplied in a white plastic bottle with a child resistant closure as follows:

- Carton containing one 360 mL bottle (NDC 43376-322-36)
- Carton containing one 30 mL bottle (NDC 43376-322-30)

Before dispensing, the pharmacist will insert a press-in bottle adapter into the dispensing bottle. The pharmacy will provide 3 mL or 6 mL calibrated oral dosing syringes.

16.2 Storage and Handling

Store FINTEPLA at room temperature between 20°C to 25°C (68°F to 77°F); excursions are permitted between 15°C to 30°C (59°F to 86°F) *[see USP Controlled Room Temperature]*.

Do not refrigerate or freeze. Store the bottle and syringe together.

Discard any unused portion 3 months after first opening the bottle or the "Discard After" date on the bottle, whichever is sooner.

1. Figure 4 in the FINTEPLA PI shows the percentage of patients by category of reduction from baseline in DSF per 28 days during the treatment period in Study 3. Note that within the categories of ≥50% to <75% response and ≥75% to 100% response, results for FINTEPLA 0.2 mg/kg/day were slightly higher than results for FINTEPLA 0.7 mg/kg/day, despite the fact that FINTEPLA 0.2 mg/kg/day did not meet the primary endpoint.

2. Numerically greater improvements on the CGI-I by Investigator were observed in patients treated with FINTEPLA compared with placebo.

Take Home Points

Dravet Syndrome

- Studies 1 and 2 were randomized, double-blind, placebo-controlled trials in patients aged 2 to 18 years with DS who were inadequately controlled on ≥1 AED or other antiseizure treatment:
  - Study 1 involved 117 patients and compared two doses of FINTEPLA (0.7 mg/kg/day and 0.2 mg/kg/day) with placebo in patients who were not receiving stiripentol
  - Study 2 involved 85 patients and compared a FINTEPLA 0.4 mg/kg/day dose with placebo in patients who were receiving stiripentol and either clobazam, valproate, or both
- Both studies included a 6-week baseline period in which patients were required to have ≥6 convulsive seizures while on stable AED therapy
  - Study 1 included a 2-week titration period followed by a 12-week maintenance period with a stable FINTEPLA dose
  - Study 2 included a 3-week titration period followed by a 12-week maintenance period with a stable FINTEPLA dose
- The primary efficacy endpoint in both studies was the change from baseline in the frequency of convulsive seizures per 28 days during the combined 14-week (Study 1) or 15-week (Study 2) titration and maintenance periods (i.e., treatment period)
  - Results were statistically significantly greater for all dose groups of FINTEPLA (0.2 mg/kg/day and 0.7 mg/kg/day in Study 1 and FINTEPLA 0.4 mg/kg/day in Study 2) compared to placebo
- Seizure response results were as follows:
  - Study 1: FINTEPLA 0.7 mg/kg/day: ≥75% to 100% reduction from baseline in convulsive seizure frequency in >50% of patients
  - Study 2: FINTEPLA 0.4 mg/kg/day: ≥75% to 100% reduction from baseline in convulsive seizure frequency in 40% of patients
- The proportion of patients who reported no convulsive seizures during the treatment periods was as follows:
  - Study 1 (14 weeks):
    - FINTEPLA 0.7 mg/kg/day: 8%
    - FINTEPLA 0.2 mg/kg/day: 8%
    - Placebo: 0
  - Study 2 (15 weeks):
    - FINTEPLA 0.4 mg/kg/day: 2%
    - Placebo: 0

Take Home Points (continued)

Lennox-Gastaut Syndrome

- Study 3 was a randomized, double-blind, placebo-controlled trial comparing 2 doses of FINTEPLA to placebo: 0.7 mg/kg/day and 0.2 mg/kg/day
- A total of 263 patients 2 to 35 years of age participated in Study 3; patients were inadequately controlled on ≥1 AED or other antiseizure treatment, including vagal nerve stimulation and/or ketogenic diet
- The design of Study 3 included a 4-week baseline period, during which patients were required to have ≥8 drop seizures while on stable AED therapy; a 2-week titration period, and a 12-week maintenance period
- The primary endpoint of Study 3 was the change in DSF per 28 days between baseline and the 14-week treatment period with fenfluramine 0.7 mg/kg/day vs placebo
- Study 3 met the primary efficacy endpoint, demonstrating a statistically significant benefit for FINTEPLA 0.7 mg/kg/day in reducing DSF (per 28 days) compared with placebo:
  - FINTEPLA 0.7 mg/kg/day: -23.7% (P=0.0037)
  - Placebo: -8.7%
- A reduction in drop seizures was observed within 2 weeks of initiating treatment with FINTEPLA, and the effect remained generally consistent over the 14-week treatment period
- A secondary endpoint in Study 3 was the percentage of subjects who achieved investigator-assessed improvement in CGI-I. Numerically greater improvements on the CGI-I by Investigator were observed in patients treated with FINTEPLA compared with placebo.

Knowledge Check

During the 6-week baseline period of Study 1 and Study 2, patients were required to have _____ convulsive seizures.

- ☐ ≥2
- ☐ ≥4
- ☐ ≥6
- ☐ ≥8

SHOW ANSWER

Knowledge Check

During the 6-week baseline period of Study 1 and Study 2, patients were required to have _____ convulsive seizures.

- ☐ ≥2
- ☐ ≥4
- ☑ **≥6**
- ☐ ≥8

NEXT QUESTION

Knowledge Check

Which of the following statements about both Study 1 and Study 2 is (are) true? (Select all that apply.)

- [ ] The reduction in convulsive seizure frequency per 28 days (the primary endpoint) was statistically significant for all dose groups of FINTEPLA (0.2 mg/kg/day and 0.7 mg/kg/day in Study 1 and FINTEPLA 0.4 mg/kg/day in Study 2) compared to placebo.
- [ ] The frequency of patients who reported 0 or 1 convulsive seizure during the entire treatment period in both Studies 1 and 2 was the same in patients treated with FINTEPLA or placebo.
- [ ] Only FINTEPLA 0.7 mg/kg/day was associated with a statistically significant longer interval between convulsive seizures compared to placebo.
- [ ] All of the above

SHOW ANSWER

Knowledge Check

Which of the following statements about both Study 1 and Study 2 is (are) true? (Select all that apply.)

- [x] **The reduction in convulsive seizure frequency per 28 days (the primary endpoint) was statistically significant for all dose groups of FINTEPLA (0.2 mg/kg/day and 0.7 mg/kg/day in Study 1 and FINTEPLA 0.4 mg/kg/day in Study 2) compared to placebo.**
- [ ] The frequency of patients who reported 0 or 1 convulsive seizure during the entire treatment period in both Studies 1 and 2 was the same in patients treated with FINTEPLA or placebo.
- [ ] Only FINTEPLA 0.7 mg/kg/day was associated with a statistically significant longer interval between convulsive seizures compared to placebo.
- [ ] All of the above

NEXT QUESTION

Knowledge Check

What was the duration of the treatment period in Study 3?

- [ ] 6 weeks
- [ ] 10 weeks
- [ ] 14 weeks
- [ ] 20 weeks

SHOW ANSWER

Knowledge Check

What was the duration of the treatment period in Study 3?

- ☐ 6 weeks
- ☐ 10 weeks
- ☑ **14 weeks**
- ☐ 20 weeks

NEXT QUESTION

Knowledge Check

In Study 3, treatment with FINTEPLA 0.7 mg/kg/day was associated with a ____% reduction in DSF, compared with an 8.7% reduction in DSF in the placebo group.

- ☐ 23.7
- ☐ 33.3
- ☐ 41.7
- ☐ 46.8

SHOW ANSWER

Knowledge Check

In Study 3, treatment with FINTEPLA 0.7 mg/kg/day was associated with a ____% reduction in DSF, compared with an 8.7% reduction in DSF in the placebo group.

- [x] **23.7**
- [ ] 33.3
- [ ] 41.7
- [ ] 46.8

NEXT PAGE

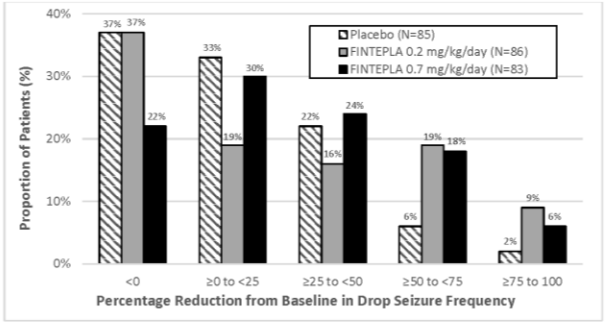
Chapter 6: How Supplied, Storage and Handling, and Patient Counseling Information

Learning Objectives

Upon completion of this chapter, you will be able to:

- Describe how FINTEPLA is supplied
- Explain the storage and handling of FINTEPLA
- Discuss the guidance provided in the patient counseling information section of the FINTEPLA PI

Figure 4: Proportion of Patients by Category of Seizure Response for FINTEPLA and Placebo in Patients with Lennox–Gastaut Syndrome (Study 3)



Numerically greater improvements on the CGI-I by Investigator were observed in patients treated with FINTEPLA compared with placebo.

1

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

FINTEPLA oral solution is a clear, colorless, cherry flavored liquid containing 2.2 mg/mL fenfluramine and is supplied in a white plastic bottle with a child resistant closure as follows:

- Carton containing one 360 mL bottle (NDC 43376-322-36)
- Carton containing one 30 mL bottle (NDC 43376-322-30)

Before dispensing, the pharmacist will insert a press-in bottle adapter into the dispensing bottle. The pharmacy will provide 3 mL or 6 mL calibrated oral dosing syringes.

2

16.2 Storage and Handling

Store FINTEPLA at room temperature between 20°C to 25°C (68°F to 77°F); excursions are permitted between 15°C to 30°C (59°F to 86°F) *[see USP Controlled Room Temperature]*.

Do not refrigerate or freeze. Store the bottle and syringe together.

Discard any unused portion 3 months after first opening the bottle or the "Discard After" date on the bottle, whichever is sooner.

1 In Section 16 of the PI, how FINTEPLA is supplied and its storage and handling are presented.

As described in Section 16.1, FINTEPLA oral solution:

- Is a clear, colorless, cherry flavored liquid
- Contains 2.2 mg/mL fenfluramine
- Is supplied in a white, plastic bottle with a child-resistant closure

FINTEPLA is supplied as a carton containing one 360 mL bottle or a carton containing one 30 mL bottle.

A press-in bottle adaptor will be inserted by the pharmacist before FINTEPLA is dispensed. In addition, 3 mL or 6 mL calibrated oral dosing syringes will be provided.

2 The storage and handling of FINTEPLA, as described in Section 16.2 of the PI, is as follows:

- FINTEPLA should be stored at room temperature between 20°C to 25°C (68°F to 77°F); excursions are permitted between 15°C to 30°C (59°F to 86°F)
- FINTEPLA should not be refrigerated or frozen
- The bottle and syringe should be stored together
- FINTEPLA should be discarded if there is any unused portion 3 months after first opening the bottle or the "Discard After" date on the bottle has been reached, whichever is sooner

1

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide and Instructions for Use).

Administration Information

Advise patients who are prescribed FINTEPLA to use the oral dosing syringes provided by the pharmacy *[see Dosage and Administration (2.6) and Instructions for Use]*. Instruct patients to discard any unused FINTEPLA 3 months after first opening the bottle or if the "discard after" date on the dispensing bottle has passed, whichever is sooner *[see How Supplied/Storage and Handling (16.1), 16.2]*.

Valvular Heart Disease and Pulmonary Arterial Hypertension

Advise patients that cardiac monitoring must be performed using echocardiography to monitor for serious heart valve changes or high blood pressure in the arteries of the lungs *[see Warnings and Precautions (5.1)]*.

FINTEPLA REMS Program

FINTEPLA is available only through a restricted program called the FINTEPLA REMS program *[see Warnings and Precautions (5.2)]*. Inform the patient of the following notable requirements:

- Patients must enroll in the program and comply with ongoing echocardiogram monitoring requirements *[see Warnings and Precautions (5.1)]*.

FINTEPLA is only prescribed by certified health care providers and only dispensed from certified pharmacies participating in the program. Therefore, provide patients with the telephone number and website for information on how to obtain the product *[see Warnings and Precautions (5.2)]*.

Decreased Appetite and Decreased Weight

Advise patients that decreased appetite is frequent during treatment with FINTEPLA, which can cause decrease in weight *[see Warnings and Precautions (5.3)]*.

Somnolence, Sedation, and Lethargy

Inform patients that FINTEPLA can cause somnolence, sedation, and lethargy. Caution patients about operating hazardous machinery, including motor vehicles, until they are reasonably certain that FINTEPLA does not affect them adversely (e.g., impair judgment, thinking, or motor skills) *[see Warnings and Precautions (5.4)]*.

Suicidal Thinking and Behavior

Counsel patients, their caregivers, and their families that antiepileptic drugs may increase the risk of suicidal thoughts and behavior and advise them to be alert for the emergence or worsening of symptoms of depression, any unusual changes in mood or behavior, or the emergence of suicidal thoughts, behavior, or thoughts of self-harm. Instruct patients, caregivers, and families to report behaviors of concern immediately to healthcare providers *[see Warnings and Precautions (5.5)]*.

Withdrawal of Antiepileptic Drugs (AEDs)

Advise patients not to discontinue use of FINTEPLA without consulting with their healthcare provider. FINTEPLA should normally be gradually withdrawn to reduce the potential for

1 Section 17 of the FINTEPLA PI is the patient counseling information. It explains that physicians should advise the patient to read the FDA-approved patient labeling. It also provides guidance on:

- FINTEPLA administration
- Monitoring of valvular heart disease and pulmonary arterial hypertension
- The FINTEPLA REMS Program
- Potential decreased appetite and decreased weight
- Possible somnolence, sedation, and lethargy
- Risk for suicidal thinking and behavior

increased seizure frequency and status epilepticus *[see Dosage and Administration (2.7), Warnings and Precautions (5.6)]*.

Serotonin Syndrome

Inform patients about the risk of serotonin syndrome, which can be life-threatening. Advise patients on the signs and symptoms of serotonin syndrome and that certain over-the-counter medications and herbal supplements can increase this risk *[see Warnings and Precautions (5.7)]*.

Increase in Blood Pressure

Inform patients that FINTEPLA can cause an increase in blood pressure *[see Warnings and Precautions (5.8)]*.

Glaucoma

Inform patients that FINTEPLA can cause mydriasis and can precipitate angle closure glaucoma. Instruct patients to contact their healthcare provider if they have any acute decreases in visual acuity or ocular pain *[see Warnings and Precautions (5.9)]*.

Pregnancy Registry

Advise patients to notify their healthcare provider if they become pregnant or intend to become pregnant during FINTEPLA therapy. Encourage women who are taking FINTEPLA to enroll in the North American Antiepileptic Drug (NAAED) Pregnancy Registry if they become pregnant. This registry is collecting information about the safety of antiepileptic drugs during pregnancy *[see Use in Specific Populations (8.1)]*.

Marketed by: Zogenix, Inc.
5959 Horton Street, Suite 500, Emeryville CA, 94608

1 Section 17 continues onto the next page of the FINTEPLA PI and provides further guidance on:

- Potential for increased seizure frequency and status epilepticus when AEDs are withdrawn
- Risk for serotonin syndrome
- Potential for increase in blood pressure
- Potential for glaucoma

This section also provides guidance if a patient becomes pregnant or intends to become pregnant during FINTEPLA therapy. It also discusses the NAAED Pregnancy Registry.

Take Home Points

- FINTEPLA oral solution is a clear, colorless, cherry flavored liquid
- FINTEPLA contains 2.2 mg/mL fenfluramine
- FINTEPLA is supplied in a white, plastic bottle with a child-resistant closure
- A press-in bottle adaptor will be inserted by the pharmacist before FINTEPLA is dispensed
- 3 mL or 6 mL calibrated oral dosing syringes will be provided
- FINTEPLA should be stored at room temperature between 20°C to 25°C (68°F to 77°F); excursions are permitted between 15°C to 30°C (59°F to 86°F)
- FINTEPLA should not be refrigerated or frozen
- FINTEPLA should be discarded if there is any unused portion 3 months after first opening the bottle or the "Discard After" date on the bottle has been reached, whichever is sooner
- The patient counseling information explains that physicians should advise the patient to read the FDA-approved patient labeling; it also provides guidance on:
  - FINTEPLA administration
  - Monitoring of valvular heart disease and pulmonary arterial hypertension
  - The FINTEPLA REMS Program
  - Potential decreased appetite and decreased weight
  - Possible somnolence, sedation, and lethargy
  - Risk for suicidal thinking and behavior
  - Potential for increased seizure frequency and status epilepticus when AEDs are withdrawn
  - Risk for serotonin syndrome
  - Potential for increase in blood pressure
  - Potential for glaucoma
  - Pregnancy registry

Knowledge Check

FINTEPLA oral solution is a clear, colorless, _____ flavored liquid.

- [ ] Grape
- [ ] Cherry
- [ ] Strawberry
- [ ] Orange

SHOW ANSWER

Knowledge Check

FINTEPLA oral solution is a clear, colorless, _____ flavored liquid.

- [ ] Grape
- [x] **Cherry**
- [ ] Strawberry
- [ ] Orange

NEXT QUESTION

Knowledge Check

FINTEPLA contains _____ fenfluramine.

- ☐ 2.2 mg/mL
- ☐ 3.4 mg/mL
- ☐ 4.7 mg/mL
- ☐ 5.0 mg/mL

SHOW ANSWER

Knowledge Check

FINTEPLA contains _____ fenfluramine.

- [x] **2.2 mg/mL**
- [ ] 3.4 mg/mL
- [ ] 4.7 mg/mL
- [ ] 5.0 mg/mL

NEXT QUESTION

Knowledge Check

Which of the following statements about FINTEPLA is (are) true? (Select all that apply.)

- [ ] 2 mL and 4 mL calibrated oral dosing syringes will be provided.
- [ ] FINTEPLA should be stored at room temperature between 20°C to 25°C (68°F to 77°F).
- [ ] FINTEPLA may be frozen.
- [ ] All of the above

SHOW ANSWER

Knowledge Check

Which of the following statements about FINTEPLA is (are) true? (Select all that apply.)

- ☐ 2 mL and 4 mL calibrated oral dosing syringes will be provided.
- ☑ **FINTEPLA should be stored at room temperature between 20ºC to 25ºC (68ºF to 77ºF).**
- ☐ FINTEPLA may be frozen.
- ☐ All of the above

NEXT PAGE

Glossary

adjunctive	treatment added to the primary or first-line treatment
aortic regurgitation	the backward flow of blood from the aorta into the left ventricle due to an imperfect closure of the aortic valve; also called valvular insufficiency, incompetence, or "leaky valve"
area under the curve (AUC)	the integrated quantity of drug (the serum drug concentration with respect to time after taking a single dose)
ataxia	defective muscular coordination, especially that manifested when voluntary muscular movements are attempted
bioavailability	the rate and extent to which an active drug or metabolite enters the body, permitting access to the site of action; it is is determined either by measurement of the concentration of the drug in body fluids or by the magnitude of the pharmacologic response
cannabidiol (CBD)	an anxiolytic constituent of *Cannabis sativa* (marijuana); it is one of the two major psychoactive components of the drug; the other is tetrahydrocannabinol (THC)
carcinogenic	relating to any substance or agent that produces cancer or increases the risk of developing cancer in humans or animals
clonic seizure	seizure that causes repeated jerking movements of muscles on both sides of the body
C_{max}	maximum concentration of a drug achieved after dosing
cyproheptadine	an antihistamine that can also be used to prevent headache pain
developmental and epileptic encephalopathy (DEE)	condition in which cognitive development and behavior are impaired independently of epilepsy onset, and epilepsy is characterized by a high frequency of seizures and epileptiform abnormalities; in addition, both developmental impairment and epileptic activity have an impact on the cognitive and behavioral characteristics of the patient
dexfenfluramine	an isomer of fenfluramine (ie, a substance with the same molecular formula but different chemical and physical properties) approved by the FDA in 1996 for the long-term treatment of obesity and later withdrawn due to cardiac safety concerns

Glossary (continued)

double-blind	pertaining to a method, study, or clinical trial in which neither the subjects nor the investigators know the identities of the subjects nor what treatment or medication, if any, the subjects receive
fluvoxamine	antidepressant belonging to the class of products known as selective serotonin reuptake inhibitors
gene	functional unit of heredity that occupies a specific place on a chromosome and directs the formation of an enzyme or other protein
lethargy	sleepiness, drowsiness, somnolence, or mental sluggishness
ketogenic diet	special high-fat, low-carbohydrate regimen that is designed to mimic the metabolic effects of starvation; typically used in younger children as adjunctive therapy to reduce seizure frequency if first-line therapies are not effective
mutagenesis	production of a genetic mutation
neurotransmitter	chemical agent released by a presynaptic neuron that crosses the synapse to stimulate or inhibit the postsynaptic neuron
paroxetine	antidepressant belonging to the class of products known as selective serotonin reuptake inhibitors
placebo-controlled	method by which study patients are randomly assigned to test therapy or to an identical-appearing therapy that does contain the drug being studied
pyrexia	fever
QT interval	time from electrocardiogram Q wave to the end of the T wave corresponding to electrical systole
randomized	method used to assign subjects to experimental groups without introducing biases into a study
sedation	an act or process of calming nervous excitement
seizure	clinically detectable event caused by a sudden discharge of electrical activity in the brain
serotonin syndrome	refers to the adverse effects of excessive levels of serotonin in the brain, usually caused by exposure to multiple drugs (e.g., restlessness, agitation, tremor)

Glossary (continued)

somnolence	prolonged drowsiness or sleepiness
status epilepticus	defined as repeated seizure or a seizure prolonged for at least 30 minutes
time to maximum plasma concentration (T_{max})	length of time it takes for a drug to achieve its maximal concentration in the body
tonic-clonic seizure	event during which a person loses consciousness and experiences muscle stiffening and jerking movements; also called a convulsion
vagal nerve stimulation (VNS)	a treatment for seizures and treatment-resistant depression in which a generator sends electrical impulses along the left vagus nerve; the impulse generator is typically inserted under the clavicle on the left side of the chest during a brief surgical procedure; the device is set to generate electrical impulses of appropriate amplitude, frequency, and pulse width to control a patient's symptoms

References

1. American Heart Association (AHA). Roles of your four heart valves. 2020. Accessed June 29, 2020. https://www.heart.org/en/health-topics/heart-valve-problems- and-disease/about-heart-valves/roles-of-your-four-heart-valves
2. American Lung Association (ALA). Learn about pulmonary arterial hypertension. 2020. Accessed June 29, 2020. https://www.lung.org/lung-health-and-diseases/lung-disease-lookup/pulmonary-arterial-hypertension/learn-pulmonary-arterial-hypertension.html
3. Camfield PR. Definition and natural history of Lennox-Gastaut syndrome. *Epilepsia*. 2011;52 Suppl 5:3-9.
4. Cross H, Auvin S, Falip M, et al. Expert opinion on the management of Lennox-Gastaut syndrome: treatment algorithms and practical considerations. *Front Neurol*. 2017;8(505):1-18.
5. Depakene (valproic acid) [prescribing information]. North Chicago, IL: AbbVie Inc.; February 2019.
6. Diacomit (stiripentol) [prescribing information]. France: Biocodex; August 2018.
7. Drug Enforcement Administration (DEA). Drug scheduling. Accessed June 29, 2020. https://www.dea.gov/drug-scheduling
8. Epilepsy Foundation. Ketogenic diet. 2017. Accessed June 29, 2020. https://www.epilepsy.com/learn/treating-seizures-and-epilepsy/dietary-therapies/ketogenic
9. Epilepsy Foundation. Tonic-clonic seizures. 2017. Accessed June 29, 2020. https://www.epilepsy.com/learn/types-seizures/tonic-clonic-seizures
10. Fisher RS, Acevedo C, Arzimanoglou, et al. A practical clinical definition of epilepsy. *Epilepsia*. 2014;55(4):475-482.
11. Food and Drug Administration (FDA). Guidance for industry: E 10 choice of control group and related issues in clinical trials. May 2001. Accessed June 29, 2020. https://www.fda.gov/media/71349/download
12. Fintepla. Prescribing information. Emeryville, CA: Zogenix, Inc.; March 2022.
13. Glaucoma Research Foundation. Angle-closure glaucoma. 2018. Accessed June 29, 2020. https://www.glaucoma.org/glaucoma/angle-closure-glaucoma.php
14. Lagae L, Sullivan J. Knupp K, et al. A randomized, placebo-controlled trial of fenfluramine for the treatment of seizures in Dravet Syndrome. *Lancet* manuscript draft 2019. (Study 1501).

References (continued)

15. Merriam-Webster Medical Dictionary. Accessed June 29, 2020. https://www.merriam-webster.com/medical
16. National Alliance of Mental Illness (NAMI). Types of Medication. Accessed November 17, 2021. https://www.nami.org/About-Mental-Illness/Treatments/Mental-Health-Medications/Types-of-Medication
17. National Institutes of Health (NIH): MedlinePlus. Heart valve diseases. Accessed June 29, 2020. https://medlineplus.gov/heartvalvediseases.html
18. National Institutes of Health (NIH): MedlinePlus. Valproic acid. 2019. Accessed June 29, 2020. https://medlineplus.gov/druginfo/meds/a682412.html
19. National Institute of Neurological Disorders and Stroke (NINDS). Epilepsy and seizures: hope through research. 2018. Accessed June 29, 2020. https://catalog.ninds.nih.gov/ninds/facet/Health-Topics/term/Epilepsy
20. Onfi (clobazam) [prescribing information]. Deerfield, IL: Lundbeck; June 2018.
21. Raga S, Specchio N, Rheims S, and Wilmshurst JM. Developmental and epileptic encephalopathies: recognition and approaches to care. *Epileptic Disorders*. 2021;23(1):40-52.
22. Resnick T and Sheth RD. Early diagnosis and treatment of Lennox-Gastaut Syndrome. *J Child Neurol*. 2017;32(11):947-955.
23. Shmuely S, Sisodiya S, Gunning WB, et al. Mortality in Dravet syndrome: a review. *Epilepsy Behav*. 2016;64:69-74.
24. Stedman's Medical Dictionary. Accessed June 29, 2020. https://stedmansonline.com/
25. Taber's Medical Dictionary. https://www.tabers.com/. Accessed June 29, 2020
26. Wirrell EC, Laux L, Donner E, et al. Optimizing the diagnosis and management of Dravet syndrome: recommendations from a North American Consensus Panel. *Pediatr Neurol*. 2017;68:18-34.
27. Zogenix Data on file. Study ZX008-1601: A Two-Part Study of ZX008 in Children and Adults with Lennox-Gastaut Syndrome (LGS); Part 1: A Randomized, Double-blind, Placebo-controlled Trial of Two Fixed Doses of ZX008 (Fenfluramine Hydrochloride) Oral Solution as Adjunctive Therapy for Seizures in Children and Adults with LGS. CLINICAL STUDY REPORT for Part 1 Cohort A. September 11, 2021.