Fenfluramine Safety: An Update From Post-Marketing Reports

Rebecca Zhang-Roper, MD, PhD[1]; Najla Dickson, MD[2]; Madhur Goyal, MPharm[2]; Geraldine Prager, MS[3]; Diego Morita, MD[2]; Jenna Roberts, PhD[1]; Mélanie Langlois, PhD[4]; Amélie Lothe, PhD[4]; Laura Maile, PhD, RAC[2]

[1]UCB, Slough, UK
[2]UCB, Morrisville, NC, USA
[3]UCB, Monheim am Rhein, Germany
[4]UCB, Colombes, France

Background

- Fenfluramine (FFA) is approved for the treatment of seizures associated with Dravet syndrome (DS) and Lennox-Gastaut syndrome (LGS) in the United States (US),[1] European Union (EU),[2] United Kingdom,[3] Japan,[4,5] and Israel[6] in patients ≥2 years of age
  - Safety and efficacy of FFA in patients with DS and with LGS have been evaluated in phase 3 randomized clinical trials (RCTs) and their open-label extensions (OLEs)[7-11]
- FFA distribution is regulated via the Risk Evaluation and Mitigation Strategy program in the US and controlled-access programs in other regions; regular echocardiogram monitoring is required
  - FFA was previously used to treat adult obesity at high doses (60-120 mg/day FFA; commonly prescribed with phentermine) until cases of valvular heart disease (VHD) and pulmonary arterial hypertension (PAH) were reported[12,13]
  - FFA is no longer approved for the treatment of obesity, and FFA doses are capped at 0.7 mg/kg/day without stiripentol (maximum, 26 mg/day) or 0.4 mg/kg/day with stiripentol (maximum, 17 mg/day) for the treatment of DS and LGS[9,10]
- Efficacy and safety of FFA were assessed during 3 RCTs in DS, 1 RCT in LGS, and their OLEs; no cases of VHD or PAH were observed[7-11,14]
  - Most frequent adverse events (AEs) in these studies included decreased appetite, diarrhea, fatigue, and pyrexia
  - Continuous safety monitoring is conducted through standard pharmacovigilance practice, with annual post-marketing reports submitted to regulatory agencies

Objective

- To update the safety profile for FFA for the treatment of DS and LGS using data from clinical trials completed, and from the UCB Global Safety Database, during the 1-year reporting period

Methods

- Reporting interval: 06-25-2023 to 06-24-2024
  - Data from clinical trials completed during the reporting period were assessed for AEs
  - Data from the UCB Global Safety Database were searched using MedDRA v27.0 terms
    - The database includes spontaneous and solicited reports, post-marketing surveillance reports, and serious events from clinical studies, irrespective of attribution to FFA
    - Safety cases which were newly reported or had follow-up information available during the reporting period were reviewed and assessed
- Exposure was reported in patient-years
- Suspected PAH and VHD cases were adjudicated by the cardiovascular adverse events (CVAE) adjudication committee, an external committee of cardiologists with expertise in adult and pediatric cardiology with knowledge of FFA
  - Adjudications of cases are updated regularly based on new information

Definitions:

PAH[a]: elevated pulmonary artery systolic pressure (PASP ≥35 mmHg)[2]

VHD: mild or greater aortic regurgitation or moderate or greater mitral regurgitation, with additional characteristics and/or physical signs or symptoms attributable to valvular heart disease (ie, valve thickening, restricted valve motion)[1]

[a]The Food and Drug Administration (FDA) definition of PAH is PASP >35 mmHg; however, the definition of PAH from the European Medicines Agency (EMA) is PASP ≥35 mmHg; for post-marketing assessment, a conservative approach is taken using a broader definition (PASP ≥35 mmHg).[1]

Results

- Positive benefit-risk of FFA in DS and LGS was reaffirmed, and market authorization was retained in all countries during the reporting interval

Safety Data From Clinical Trials Completed During the Reporting Period

- Study 1503: an open-label long-term phase 3 extension to assess long-term safety of FFA treatment (up to 3 years) in children and adults with DS
- Study 1602: an open-label study to assess the safety of adjunctive FFA (up to 108 weeks) in combination with cannabidiol in children and young adults with DS or LGS
- Safety data was consistent with the known safety profile of FFA (**Tables 1** and **2**)
- No patients in the clinical trials were diagnosed with VHD or PAH at any time and no new safety findings were reported
- 3 deaths (all sudden unexpected death in epilepsy), determined to be unrelated to FFA, occurred in Study 1503
- No deaths were reported in Study 1602

Table 1. Most Commonly Reported TEAEs in Study 1503 (Children and Adults With DS)

	(N=374)
Patients with ≥1 TEAE, n (%)	91 (98.9)
TEAEs in ≥10% of Patients, n (%)	
Pyrexia	112 (29.9)
Nasopharyngitis	104 (27.8)
Decreased appetite	100 (26.7)
Blood glucose decreased	89 (23.8)
Diarrhea	73 (19.5)
Abnormal echocardiogram[a]	67 (17.9)
Upper respiratory tract infection	66 (17.6)
Seizure	58 (15.5)
Influenza	51 (13.6)
Vomiting	39 (10.4)
Ear infection	39 (10.4)

[a]Limited to physiologic regurgitation, including trace and mild mitral valve regurgitation and trace aortic valve regurgitation.
DS, Dravet syndrome; TEAE, treatment-emergent adverse event.

Table 2. Most Commonly Reported TEAEs in Study 1602 (Children and Young Adults With DS or LGS)

	(N=9)
Patients with ≥1 TEAE, n (%)	9 (100)
TEAEs in ≥2 Patients, n (%)	
Nasopharyngitis	5 (55.6)
Somnolence	4 (44.4)
Vomiting	3 (33.3)
Pyrexia	3 (33.3)
Upper respiratory tract infection	3 (33.3)
Decreased appetite	3 (33.3)
Urinary tract infection	2 (22.2)
Laceration	2 (22.2)
Hypoglycemia	2 (22.2)
Lethargy	2 (22.2)
Rhinorrhea	2 (22.2)

DS, Dravet syndrome; LGS, Lennox-Gastaut syndrome; TEAE, treatment-emergent adverse event.

Data From UCB Global Safety Database

Exposure to FFA during the 1-year reporting period: 8792 patient-years

Note: limitations of post-marketing case assessment include some poorly documented cases, which pose challenges for causality assessment

Global Cardiovascular Safety Events

PAH

- 3 cases were adjudicated Definite/Probable PAH
  - 1 Probable PAH case was assessed as likely related to FFA with no confounding factors (**index case**)
  - The remaining 2 cases were considered caused by congenital cardiac defects
- PAH was reclassified as an **important identified risk** based on this case and previous literature
- 1 additional case is under adjudication

VHD

- Following the data-lock point of the reporting period, additional information was received, resulting in the re-adjudication of 1 Probable VHD case and 1 Possible VHD case as Definite VHD
  - The case initially adjudicated as Probable VHD was considered unlikely related to FFA due to pre-existing valvulopathy and other cardiac conditions at baseline
  - The case initially adjudicated as Possible VHD was considered possibly related to FFA
- VHD remains an **important potential risk** based on the analysis of data received during the reporting period

Global Non-Cardiovascular Safety Events

- During the reporting period, a comprehensive evaluation was performed for the event of **serotonin syndrome**:
  - 15 cases were reported with an event coded to MedDRA PT of serotonin syndrome or serum serotonin increased
  - Based on the safety data available, the characteristics of the cases received, and the mechanism of action of FFA as a serotonin releasing agent, risk of serotonin syndrome was reclassified as an **important identified risk**
  - Given the unmet medical need of this patient population, the relative infrequency of serotonin syndrome, and the level of experience of the prescribers of FFA to monitor for and recognize symptoms of serotonin syndrome, the benefit-risk of FFA remains positive
- **Suicidal ideation and behavior** is considered a class-based risk for all antiseizure medications; therefore, it is considered an important potential risk for FFA
  - The safety data received during the reporting interval does not change the overall assessment of suicidal ideation and behavior as an **important potential risk**
- **Growth retardation** is considered an important potential risk due to the known effect of appetite suppression and expected adverse drug reactions of decreased appetite and weight
  - Data received during the review period, as well as cumulative review of the topic, did not provide any evidence suggesting an impact of FFA on the overall development of pediatric patients; post-authorization safety studies are currently ongoing in the EU
  - There was no change in characterization of growth retardation as an **important potential risk**

Global Post-Marketing Data on Long-Term Safety

- Long-term exposure was defined as >3 years of FFA treatment; the longest reported exposure was 5.25 years
  - 55 cases were identified in the UCB Global Safety Database with long-term FFA exposure
  - Seizure (n=11) and decreased appetite (n=5) were most commonly reported in patients with long-term FFA exposure (**Table 3**)
- The reported AEs following long-term exposure did not present a different safety profile compared to the overall safety profile of FFA

Table 3. Most Commonly Reported AEs in Cases With FFA Exposure >3 Years[a]

AE	n
Seizure	11
Decreased Appetite	5
Nasopharyngitis	3
Pharyngitis Streptococcal	3
Pneumonia	3

[a]n=55 cases received during the reporting interval in the UCB global safety database.
AE, adverse event; FFA, fenfluramine.

FFA Use (Off-Label) for Weight Management

- Potential use of FFA in the treatment of obesity is a concern due to the original indication for weight management and its unfavorable benefit-risk assessment for the indication of weight management
- No cases of off-label use relating to obesity were received

Conclusions

- No new safety concerns were identified from the clinical studies completed during the reporting period and post-marketing case review
- PAH and serotonin syndrome were reclassified as important identified risks in this FFA safety profile update and should continue to be considered when treating patients with DS or LGS with FFA
- VHD, suicidal ideation and behavior, and growth retardation remain as important potential risks
- There is no evidence that FFA is being utilized for off-label use for weight management based on a review of the data
- Long-term data suggest that FFA continues to be well tolerated with a consistent safety profile as previously reported
- The benefit-risk balance of FFA continues to remain favorable for patients with DS or LGS
- Quality and timely AE reporting from health care professionals is important for safety profile assessment and updates for medications in a timely manner

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Disclosures

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