Inspired by patients.
Driven by science.

Environmental Risk Assessment
FINTEPLA®

PEC – Predicted Environmental Concentration

The PEC for fenfluramine (the active ingredient) base in EU has been calculated in the original ERA for Dravet syndrome to be 0,00066 µg/L. The PEC for fenfluramine base in EU for Lenox-Gastaut syndrome is 0,00264 µg/L therefore the combined PEC for both syndromes is 0,0033 µg/L.

The following PEC calculation of fenfluramine base in EU is for Lennox-Gastaut syndrome. The calculation of the PEC in surface water (PECSURFACEWATER) assumes that the predicted amount used per year is evenly distributed over the year and throughout the geographic area, the sewage system is the main route of entry, there is no biodegradation or retention of the drug substance in the sewage treatment plant (STP) and metabolism in the patient is not taken into account.

An Fpen default value of 0.01 (1%) is proposed in the guideline. However, because data as confirmed by the Committee for Orphan Medicinal Products (COMP) are available to estimate a more accurate refined Fpen value in the EU for Lennox-Gastaut syndrome, these data, together with EU prevalence data from a recent literature search (conducted August 2021), have been utilised in the calculation of the PECSURFACEWATER. Table below gives the value that has been used in the refined market penetration (Fpen) calculation.

Input Value	Abbreviation	Value
Prevalence for EU region: <2 in 10,000 people with Lennox-Gastaut Syndrome https://www.ema.europa.eu/en/documents/orphan-maintenance-report/epidyolex-orphan-maintenance-assessment-report-initial-authorisation_en.pdf	P_{region} = refined F_{pen}	0.0002

Since the indication is not linked to a specific time of the year, the predicted amount of fenfluramine hydrochloride used per year is assumed to be evenly distributed over the year and throughout the geographic area (EU Members States where drug product is to be used).

The worst-case (highest) calculation of the PECSURFACEWATER in the EU is shown below:

$$PEC_{SURFACEWATER} = \frac{DOSE_{ai} \times \text{Refined } F_{pen}}{WASTEW_{inhab} \times DILUTION}$$

$$PEC_{SURFACEWATER}\ (mg/L) = \frac{26.4 \times 0.0002}{200 \times 10}$$

$PEC_{SURFACEWATER}$ (µg/L) for fenfluramine base in EU = 0.00264 µg/L

The combined PECSURFACEWATER for fenfluramine base in EU from its use in Dravet syndrome and Lennox-Gastaut syndrome is 0.0033 µg/L.

The PEC value is below the action limit for the Phase I ERA (0.01 µg/L). The proposed use of FINTEPLA® is therefore considered unlikely to represent an unacceptable risk to the aquatic compartment

Additional Data

The experimental Log Kow for fenfluramine was shown to be 3.36, based on the following

sources: http://www.chemspider.com/Chemical-Structure.3220.html accessed 12 September 2018

https://comptox.epa.gov/dashboard/dsstoxdb/results?search=Fenfluramine accessed 12

September 2018

https://www.drugbank.ca/drugs/DB00574 accessed 12 September 2018

A confirmatory experimental GLP study using the shake-flask method (OECD 107) has been provided in the original ERA, submitted with the marketing authorisation application (MAA) for Dravet syndrome (sequence 0002, Module 1.6.1), and results of this study show that Log POWvalues are 4.3 at pH 5, 3.4 at pH 7 and 3.4 at pH 9 (Charles River Study No. 20181030).

On the basis of this information, fenfluramine hydrochloride does not present a persistence, bioaccumulation or toxicity (PBT) risk.