This guide was prepared in coordination with the Ministry of Health. As an additional risk minimising measure, it is intended to ensure that health professionals who prescribe and bring fenfluramine into use are aware of and take into account the special safety requirements.

Fintepla® (fenfluramine)

GUIDE ON REDUCING THE RISKS RELATED TO MEDICINES AND THEIR ADMINISTRATION - PRESCRIBERS

Please consult the Physician Prescribing Information (PPI) for full prescribing information. This medicine is subject to additional monitoring. This allows for the rapid identification of new safety findings. Healthcare professionals are asked to report any suspected adverse reactions. See the last page for information on reporting adverse events.

FIN0062

Inspired by patients.
Driven by science.

MEDISON

VALVULAR HEART DISEASE AND PULMONARY ARTERIAL HYPERTENSION

Fenfluramine is indicated for the treatment of seizures associated with Dravet syndrome or Lennox-Gastaut syndrome as an add-on therapy to other antiepileptic medicines for patients 2 years of age and older.

Fenfluramine hydrochloride was first approved in Europe in the **1960s** at a dose of 60-120mg per day as an appetite suppressant for the treatment of obesity in adults. In the late 1990s, it was **withdrawn worldwide** because of the **risks of valvular heart disease and pulmonary arterial hypertension**, which in some cases were severe or fatal[1-8] at doses 2-4 times higher than the maximum recommended dose approved for seizures associated with Dravet syndrome or Lennox-Gastaut syndrome (26mg fenfluramine). Fenfluramine hydrochloride was also often used in combination with phentermine in this indication. The exact mechanism of drug-induced valvular heart and pulmonary arterial hypertension disease remains unclear.

Fintepla should be initiated and supervised by physicians with experience in the treatment of epilepsy.

IMPROPER USE FOR WEIGHT CONTROL

Fenfluramine can cause decreased appetite and weight loss.

Fenfluramine should not be prescribed or used **for weight management** as **the benefit-risk of such use** is **negative** in that indication. The indication stated in the PPI must be strictly adhered to.

If you suspect that fenfluramine might be used to control the weight of other people, remind the patient or their parents/caregivers that fenfluramine should only be taken by the person for whom it was prescribed and not by anyone else.

Please also inform parents/caregivers about the negative benefit-risk use of fenfluramine in weight management.

CARDIAC MONITORING

Given the important risk of valvular heart disease and pulmonary arterial hypertension (PAH), periodic echocardiography must be performed when treating patients with Dravet syndrome or Lennox-Gastaut syndrome. There were no cases of VHD or PAH reported in patients in the clinical trials for the treatment of Dravet syndrome or Lennox-Gastaut syndrome, but post-marketing data show that PAH can also occur with doses used to treat epilepsy.

Prior to starting treatment, all patients must undergo an echocardiogram to exclude any pre-existing valvular heart disease or pulmonary hypertension.

Echocardiogram monitoring should be conducted every 6 months for the first 2 years and annually thereafter during fenfluramine treatment.

Once treatment is discontinued, a final echocardiogram should be conducted 3-6 months after the last dose of fenfluramine.

If an echocardiogram indicates pathological valvular changes, a follow-up echocardiogram should be considered at an earlier timeframe to evaluate whether the abnormality is persistent. If echocardiogram findings are suggestive of pulmonary arterial hypertension, a repeat echocardiogram should be performed as soon as possible and within 3 months to confirm these findings.

If pathological abnormalities on the echocardiogram are observed or echocardiogram finding suggests an increased or high probability of pulmonary arterial hypertension it is recommended to evaluate the benefit versus risk of continuing fenfluramine treatment with the prescriber, caregiver, and cardiologist.

Treatment should be stopped and/or appropriate monitoring and follow-up should be provided in accordance with (Appendix 1 (SmPC)) or local guidelines for the treatment of aortic or mitral valvular heart disease, and latest guidelines of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS).

EDUCATIONAL MATERIAL FOR YOUR PATIENTS

Please ensure that every patient prescribed Fintepla receives the Patient and Caregiver Leaflet.

The Patient and Caregiver Leaflet provides information about Fintepla for patients and caregivers so they understand the risks associated with fenfluramine, including the need for echocardiography assessments before, during and after treatment.

Patient and Caregiver Leaflets are available on www.health.gov.il or by calling 03-9250250.

REPORTING ADVERSE EVENTS

Post-authorisation reporting of suspected adverse events is of great importance. It allows continuous monitoring of the benefit-risk balance of the medicine.

Adverse events can be reported to the Ministry of Health using the online form for adverse event reporting which can be found on the Ministry of Health website: www.health.gov.il or by using the following link: https://sideeffects.health.gov.il/

Adverse events can be also reported to Medison Pharma Ltd. by email: pvisrael@medisonpharma.com or fax: 03-9234218

This guide was revised and approved by the Ministry of Health in February 2025.

LITERATURE

1. Fintepla® EU SmPC. www.ema.europa.eu/en/documents/product-information/ fintepla-epar-product-information_en.pdf. Accessed February 2024.
2. Center for Disease Control and Prevention. Cardiac valvulopathy associated with exposure to fenfluramine or dexfenfluramine: U.S. Department of Health and Human Services Interim Public Health Recommendations, November 1997. Morbidity and Mortality Weekly Report 1997;46(45):1061-1066.
3. Connolly HM, Crary JL, McGoon MD, Hensrud DD, Edwards BS, Schaff HV. Valvular heart disease associated with fenfluramine-phentermine. New Engl J Med 1997;337(9):581 588. Erratum in: New Eng J Med 1997;337(24):1783.
4. Wong J, Reddy SS, Klein AL. Anorectic drugs and valvular heart disease: a biological and clinical perspective. Cleve Clin J Med 1998;65(1):35-41.
5. Perez VA de Jesus. Drug-induced pulmonary hypertension: The First 50 years. Adv Pulm Hypertens 2017;15(3):133-137.
6. Douglas JG, Munro JF, Kitchin AH, Muir AL, Proudfoot AT. Pulmonary hypertension and fenfluramine. Br Med J (Clin Res Ed) 1981;283(6296):881-883.
7. McMurray J, Bloomfield P, Miller HC. Irreversible pulmonary hypertension after treatment with fenfluramine. Br Med J (Clin Res Ed) 1986;293(6538):51-52.
8. Pouwels HM, Smeets JL, Cheriex EC, Wouters EF. Pulmonary hypertension and fenfluramine. Eur Respir J 1990;3(5):606-607.
9. Assessment report Fintepla 15 December 2022: https://www.ema.europa.eu/en/documents/assessment-report/fintepla-epar-public-assessment-report_en.pdf. Accessed February 2024.