ORFADIN® (nitisinone) - Prescribing Information for Republic of Ireland

Please refer to the Summary of Product Characteristics (SmPC) before prescribing.

Composition: Nitisinone, 2 mg, 5 mg, 10 mg or 20 mg hard capsules; 4 mg/ml oral suspension.

Indications: Hereditary tyrosinemia type 1 (HT-1): Treatment of adult and paediatric patients (in any age range) with confirmed diagnosis of hereditary tyrosinemia type 1 (HT-1) in combination with dietary restriction of tyrosine and phenylalanine. Alkaptonuria (AKU): Treatment of adult patients with alkaptonuria (AKU).

Dosage and Administration: Nitisinone treatment should be initiated and supervised by a physician experienced in the treatment of HT-1 and AKU patients. HT-1: Treatment of all genotypes of the disease should be initiated as early as possible to increase overall survival and avoid complications such as liver failure, liver cancer and renal disease. Adjunct to nitisinone treatment, a diet deficient in phenylalanine and tyrosine is required and should be followed by monitoring of plasma amino acids. The recommended initial daily dose in the adult and paediatric population is 1mg/kg body weight administered orally. The dose of nitisinone should be adjusted individually. Due to the limited data in patients with body weight <20kg, it is recommended to divide the total daily dose into two daily administrations in this patient population. During regular monitoring, it is appropriate to follow urine succinyl acetone, liver function test values and alpha-fetoprotein levels (see section 4.4 of the SmPC for further information). If urine succinyl acetone is still detectable one month after the start of nitisinone treatment, the nitisinone dose should be increased to 1.5 mg/kg body weight/day. A dose of 2 mg/kg body weight/day may be needed based on the evaluation of all biochemical parameters. This dose should be considered as a maximal dose for all patients. If the biochemical response is satisfactory, the dose should be adjusted only according to body weight gain. However, in addition to the tests above, during the initiation of therapy, switch from twice daily to once daily dosing or if there is a deterioration, it may be necessary to follow more closely all available biochemical parameters. AKU: The recommended dose in the adult AKU population is 10 mg once daily. The safety and efficacy in children aged 0 to 18 years with AKU have not been established. No data are available. Method of administration: The capsule may be opened and the content suspended in a small amount of water or formula diet immediately before intake. The suspension is administered into the patient's mouth with an oral syringe without dilution. It is recommended that the healthcare professional advises the patient or caregiver how to use the oral syringes to ensure that the correct volume is administered and that the prescription is given in ml. It is recommended that the oral suspension is taken with food.

Contraindications: Hypersensitivity to the active substance or to any of the excipients listed in section 6.1 of the SmPC. Mothers receiving nitisinone must not breast-feed (see sections 4.6 and 5.3 of the SmPC for further detail).

Special warnings and precautions for use: Monitoring visits should be performed every 6 months; shorter intervals between visits are recommended in case of adverse events. Plasma tyrosine level monitoring: It is recommended that a slit-lamp examination of the eyes is performed before initiation of nitisinone treatment and thereafter regularly, at least once a year. The liver function should be monitored regularly by liver function tests and liver imaging. It is recommended that platelet and white blood cell counts are monitored regularly Refer to section 4.4 of the SmPC for full monitoring information for HT-1 and AKU patients. Nitisinone is a moderate CYP2CP inhibitor, therefore Nitisinone treatment may result in increased plasma concentrations of co-administered medicinal products metabolized primarily via CYP2C9. Nitisinone treated patients who are concomitantly treated with medicinal products with a narrow therapeutic window metabolized through CYP2C9, such as Warfarin and phenytoin, should be carefully monitored. Dose-adjustment of these co-administered medicinal products may be needed.

Interactions: Nitisinone is metabolized *in vitro* by CYP 3A4 and dose-adjustment may therefore be needed when nitisinone is co-administered with inhibitors or inducers of this enzyme. Based on data from a clinical interaction study with 80 mg nitisinone at steady-state, nitisinone is a moderate inhibitor of CYP2C9 (2.3-fold increase in tolbutamide AUC), therefore nitisinone treatment may result in increased plasma concentrations of co-administered medicinal products metabolized primarily via CYP2C9. Nitisinone is a weak inducer of CYP2E1 (30% decrease in chlorzoxazone AUC) and a weak inhibitor of OAT1 and OAT3 (1.7-fold increase in AUC of furosemide), whereas nitisinone did not inhibit CYP2D6. Nitisinone capsules has been co-administered with food during the

generation of efficacy and safety data. Therefore, it is recommended that if nitisinone treatment as capsules is initiated with food, this should be maintained on a routine basis. Food does not influence the bioavailability of nitisinone oral suspension, but intake together with food decreases the absorption rate and consequently leads to lower fluctuations in serum concentrations within a dosage interval. Therefore, it is recommended that the oral suspension is taken with food.

Fertility, pregnancy and lactation: Nitisinone should not be used in pregnancy unless the clinical condition of the woman requires treatment. Mothers receiving nitisinone must not breast-feed. There are no data on nitisinone affecting fertility.

Undesirable effects: Please consult SmPC section 4.8 for the full list of possible adverse events. The adverse reactions at least possibly related to treatment are listed below with frequency defined as very common (≥1/10), common (≥1/100 to <1/10) and uncommon (≥1/1,000 to <1/100). Very common: keratopathy, eye pain, elevated tyrosine levels. Common: thrombocytopenia, leukopenia, granulocytopenia, conjunctivitis, corneal opacity, keratitis, photophobia, eye pain, bronchitis, pneumonia, pruritus, rash. Uncommon: leukocytosis, blepharitis, exfoliative dermatitis, erythematous rash. Nitisinone treatment is associated with elevated tyrosine levels that have been associated with corneal opacities and hyperkeratotic lesions. Restriction of tyrosine and phenylalanine in diet should limit the toxicity associated with this type of tyrosinemia.

Overdosage: Accidental ingestion of nitisinone by individuals eating normal diets not restricted in tyrosine and phenylalanine will result in elevated tyrosine levels. Elevated tyrosine levels have been associated with toxicity to eyes, skin and the nervous system. Restriction of tyrosine and phenylalanine in the diet should limit toxicity associated with this type of tyrosinaemia. No information about specific treatment of overdose is available

Legal Category: Prescription Only Medicine (POM). **Marketing Authorisation No**.: Capsules EU/1/04/303/001-004; Oral solution EU/1/04/303/005 **Pack size:** 60 capsules bottle or 100ml bottle with 90ml of oral suspension **Price**: Eire List Price available on request. **Marketing Authorisation Holder**: Swedish Orphan Biovitrum International AB, SE-112 76 Stockholm, Sweden. **Further Information Available From:** Swedish Orphan Biovitrum Ltd, Suite 2, Riverside 3, Cambridgeshire, CB21 6AD. **Date of Preparation**: October 2025. **Company Reference**: PP-29097

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions.

Adverse events should be reported. Reporting forms and information can be found at HPRA Pharmacovigilance, website www.hpra.ie. Adverse events can also be reported to Swedish Orphan Biovitrum Ltd by email at medical.info.uk@sobi.com or by calling +44 (0) 800 111 4754.