PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

# [Pr]ORFADIN

nitisinone

2 mg, 5 mg, 10 mg and 20 mg Capsules
4 mg/ml Oral suspension

**ATC Code: A16AX04**
Various alimentary tract and metabolism products

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## Table of Contents

**ORFADIN**

nitisinone

## PART I: HEALTH PROFESSIONAL INFORMATION

### SUMMARY PRODUCT INFORMATION

| Route of Administration | Dosage Form / Strength | Clinically Relevant Nonmedicinal Ingredients |
|---|---|---|
| Oral | Capsules 2 mg, 5 mg, 10 mg, 20 mg | Orfadin contains no clinically relevant nonmedicinal ingredients.<br>*For a complete listing see DOSAGE FORMS, COMPOSITION AND PACKAGING.* |
| Oral | Oral suspension 4 mg/mL | Glycerol: Each mL contains 500 mg.<br>Sodium: Each mL contains 0.7 mg (0.03 mEq).<br>Sodium Benzoate: Each mL contains 1 mg<br>*For a complete listing see DOSAGE FORMS, COMPOSITION AND PACKAGING.*<br>*See WARNINGS AND PRECAUTIONS, General, Hepatic/Biliary/Pancreatic and Monitoring and Laboratory Tests.* |

### INDICATIONS AND CLINICAL USE

Orfadin is indicated for the treatment of patients with hereditary tyrosinemia type 1 (HT-1) in combination with dietary restriction of tyrosine and phenylalanine.

Treatment with nitisinone should be initiated and supervised by a physician experienced in the treatment of HT-1 patients.

**Geriatrics (≥ 65 years of age):** Clinical studies of nitisinone did not include any subjects aged 65 and over.

**Pediatrics (<18 years of age):** Clinical trials of nitisinone were conducted in patients with HT-1 ranging in age from birth to 21 years of age [see CLINICAL TRIALS].

### CONTRAINDICATIONS

- Patients who are hypersensitive to this drug or to any ingredient in the formulations or component of the container. For a complete listing, see the DOSAGE FORMS,

COMPOSITION AND PACKAGING section of the product monograph.

- Mothers receiving nitisinone must not breastfeed (see **Nursing women** section)

## WARNINGS AND PRECAUTIONS

### General

**Excipients with known effects (oral suspension only):**
Glycerol
Oral doses of glycerol of 10 grams or more have been reported to cause headache, upset stomach and diarrhea. Orfadin oral suspension contains 500 mg/mL of glycerol. Patients receiving more than 20 mL of Orfadin oral suspension (10 grams glycerol) as a single dose are at increased risk of these adverse reactions. Consider switching patients who are unable to tolerate the oral suspension to Orfadin capsules.

Sodium
Each ml contains 0.7 mg (0.03 mmol) of sodium. Consider switching patients on a sodium restricted diet to Orfadin capsules.

Sodium benzoate
Each ml Orfadin oral suspension contains 1 mg sodium benzoate. See WARNINGS AND PRECAUTIONS, Hepatic/biliary/pancreatic, Sodium Benzoate.

**Cytochrome P450**

Nitisinone is a moderate CYP2C9 inhibitor. Caution is recommended when Orfadin (nitisinone) is co-administered with narrow therapeutic index CYP2C9 substrates such as warfarin, and patients co-administered these agents should be monitored [see DRUG INTERACTIONS].

### Endocrine and Metabolism

**Elevated plasma tyrosine levels**
Treatment with Orfadin may cause an increase in plasma tyrosine levels in patients with HT-1. Patients must maintain concomitant reductions in dietary tyrosine and phenylalanine while on Orfadin treatment. Inadequate restriction of tyrosine and phenylalanine intake may increase blood tyrosine levels. Plasma tyrosine levels should be maintained below 500 μmol/L, since levels greater than 500 μmol/L may increase the risk of ocular signs and symptoms.

In patients with HT-1 treated with Orfadin who develop elevated plasma tyrosine levels, dietary tyrosine and phenylalanine intake should be promptly reassessed. Elevated tyrosine levels should not be reduced by decreasing the Orfadin dose, as this may result in deterioration of the patient's clinical condition.

### Hematologic

**Leucopenia and thrombocytopenia**
Reversible leucopenia and thrombocytopenia have been observed during treatment with nitisinone [see **ADVERSE REACTIONS**]. Platelet and white blood cell counts should be monitored regularly during Orfadin therapy [see **WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Tests**].

**Hepatic/Biliary/Pancreatic**

Liver status should be assessed regularly through liver function tests, including serum alpha-fetoprotein levels, and liver imaging, as necessary [see **WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Tests**]. Increases in serum alpha-fetoprotein concentration may be a sign of inadequate treatment. Patients with increasing alpha-fetoprotein or signs of nodules in the liver should always be evaluated for hepatic malignancy.

Sodium benzoate
Orfadin oral suspension contains 1 mg sodium benzoate per mL. Increase in bilirubin following its displacement from albumin, caused by benzoic acid and its salts, may increase jaundice in pre-term and full-term neonates and develop into kernicterus (unconjugated bilirubin deposits in the brain tissue). In newborn patients taking Orfadin oral suspension, bilirubin should be measured before the start of treatment and closely monitored during treatment. In cases of markedly elevated plasma levels of bilirubin and in premature patients with risk factors such as acidosis and low albumin levels, Orfadin capsules should be used instead of the oral suspension. Use of Orfadin oral suspension may be considered once unconjucated plasma bilirubin levels have normalized [see **WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Tests**].

**Neurologic**

Variable degrees of intellectual disability and developmental delay have been observed in HT-1 patients treated with nitisinone. It is uncertain to what extent the observed cases are a result of the disease itself, elevated tyrosine levels, nitisinone treatment, or other factors. In patients treated with nitisinone who exhibit a change in neurologic status, a clinical laboratory assessment including plasma tyrosine level should be performed.

**Ophthalmologic**

Ocular signs and symptoms including corneal ulcers, corneal opacities, keratitis, conjunctivitis, eye pain, and photophobia have been reported in patients treated with nitisinone [see **ADVERSE REACTIONS**]. It is recommended that ophthalmologic assessment, including slit-lamp examination, should be performed prior to initiating Orfadin treatment and thereafter regularly. Patients who develop photophobia, eye pain, or signs of inflammation such as redness, swelling, or burning of the eyes during treatment with Orfadin should undergo slit-lamp re-examination and immediate measurement of plasma tyrosine concentration [see **ADVERSE REACTIONS**].
In a clinical study in a non HT-1 population without dietary restriction and reported tyrosine levels >500 micromol/l both symptomatic and asymptomatic keratopathies have been observed.

If the plasma tyrosine level exceeds 500 µmol/L, a diet more restricted in tyrosine and phenylalanine should be implemented.

## Special Populations

**Pregnant Women:**
Orfadin should be used in pregnancy only when the benefits of continued treatment are judged to outweigh the risks.

There are no studies with nitisinone in pregnant women. Studies in animals have shown reproductive toxicity [see **TOXICOLOGY**].

In a few cases, reported in the literature, of women with HT-1 who became pregnant while taking nitisinone and who elected to continue nitisinone throughout pregnancy, nitisinone was found to cross the placental barrier and was measured in cord blood at levels comparable to the mother's nitisinone blood concentration. Plasma tyrosine levels of the newborns were elevated at birth, but slowly decreased over time.

**Nursing Women:**
Because of the potential for adverse reactions to nitisinone in nursing infants, mothers taking Orfadin should not breast-feed [see **CONTRAINDICATIONS**].

It is not known whether nitisinone is present in human milk. Data suggest that nitisinone is present in rat milk due to findings of ocular toxicity and lower body weight seen in drug naive nursing rat pups [see **TOXICOLOGY**].

**Pediatrics**:
Patients with HT-1, aged from birth to 21.7 years, were treated with nitisinone [see **CLINICAL TRIALS**]. Plasma and urine succinylacetone levels should be monitored in pediatric patients to ensure adequate control [see **DOSAGE AND ADMINISTRATION**]. It is recommended that a dietician experienced in managing children with inborn errors of metabolism be consulted to design a low-protein diet restricted in tyrosine and phenylalanine.

**Geriatrics**:
Clinical studies of nitisinone did not include patients over the age of 65 years, and no pharmacokinetic studies have been conducted in geriatric subjects. In general, dose selection for elderly patients should be cautious, reflecting the greater frequency of decreased hepatic, renal, or cardiac function and concomitant disease or other drug therapy in this patient population.

## Monitoring and Laboratory Tests

Monitoring visits are recommended at least every 6 months, with shorter intervals between visits in the case of adverse events.

**Succinylacetone, 5-ALA, and erythrocyte PBG-synthase**
Monitor plasma and/or urine succinylacetone levels, and titrate Orfadin dosage as necessary (see **DOSAGE AND ADMINISTRATION**). Closer monitoring, including monitoring plasma and urine succinylacetone, urine 5-aminolevulinate (ALA) and erythrocyte porphobilinogen (PBG)-synthase activity, is recommended particularly when initiating therapy, switching from twice a day to once a day dosing, or in the case of deterioration in the patient's condition.

**Plasma tyrosine levels**
In HT-1 patients receiving Orfadin, plasma tyrosine levels should be monitored regularly and maintained below 500 μmol/L. If the plasma tyrosine level exceeds 500 μmol/L, a diet more restricted in tyrosine and phenylalanine should be implemented.

**Liver monitoring**
Liver function parameters, serum alpha-fetoprotein concentrations and liver imaging should be monitored regularly in all patients. (see **WARNINGS AND PRECAUTIONS, Hepatic/Biliary/Pancreatic).**
In newborn patients taking Orfadin oral suspension, bilirubin should be measured before the start of treatment and closely monitored during treatment. (see WARNINGS AND PRECAUTIONS, Hepatic/Biliary/Pancreatic).

**Platelet and white blood cell counts**
Platelet and white blood cell counts should be monitored regularly during Orfadin therapy.

**Ophthalmologic**
Ophthalmologic assessment including slit lamp examination should be conducted prior to initiation of Orfadin and thereafter regularly, and if eye symptoms develop during treatment. [see **WARNINGS AND PRECAUTIONS, Ophthalmologic**].

## ADVERSE REACTIONS

### Adverse Drug Reaction Overview

Nitisinone was studied in a single, multi-national, open-label, uncontrolled study. The most common reported adverse reactions in the trial were thrombocytopenia, leucopenia, granulocytopenia and conjunctivitis, corneal opacity, keratitis, and photophobia. No patients discontinued treatment due to adverse drug reactions.

### Clinical Trial Adverse Drug Reactions

*Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.*

The main analysis of the open-label, uncontrolled study consisted of 207 patients with HT-1,

ages 0 to 21.7 years at enrollment (median age 9 months), with a median treatment duration of 22.2 months. The starting dose of nitisinone was 0.6 to 1 mg/kg/day, and was increased to 2 mg/kg/day in some patients, based on weight, biochemical, and enzyme markers [see **CLINICAL TRIALS**].

The most common adverse reactions reported in the clinical trial main analysis are summarized in Table 1.

**Table 1: Common Adverse Reactions (≥ 1%) Reported in an Open-Label, Uncontrolled Trial**

| | **Nitisinone n = 207 (%)** |
|---|---|
| **Eye disorders** | |
| Conjunctivitis | 2 |
| Corneal opacity | 2 |
| Keratitis | 2 |
| Photophobia | 2 |
| Blepharitis | 1 |
| Eye pain | 1 |
| **Blood and lymphatic System Disorders** | |
| Thrombocytopenia | 3 |
| Leucopenia | 3 |
| Granulocytopenia | 1 |
| **Skin and subcutaneous tissue disorders** | |
| Pruritis | 1 |
| Exfoliative dermatitis | 1 |
| Maculopapular rash | 1 |
| **Investigations** | |
| Elevated tyrosine levels | >10 |

The most serious adverse reactions reported during nitisinone treatment were thrombocytopenia, leucopenia, and ocular/visual complaints associated with elevated tyrosine levels [see **WARNINGS AND PRECAUTIONS**]. Fourteen patients experienced ocular/visual events. The duration of the symptoms varied from 5 days to 2 years. Six patients had thrombocytopenia, three of which had platelet counts 30,000/μL or lower. In 4 patients with thrombocytopenia, platelet counts gradually returned to normal (duration up to 47 days) without change in nitisinone dose. No patients developed infections or bleeding as a result of the episodes of leucopenia and thrombocytopenia.

Patients with HT-1 are at increased risk of developing porphyric crises, hepatic neoplasms, and liver failure requiring liver transplantation. These complications of HT-1 were observed in patients treated with nitisinone for a median of 22 months during the clinical trial (liver transplantation 13%, liver failure 7%, malignant hepatic neoplasms 5%, benign hepatic neoplasms 3%, porphyria 1%).

**Less Common Clinical Trial Adverse Drug Reactions (<1%)**

Adverse events reported in less than 1% of patients in the main analysis of the open-label, uncontrolled trial (N=207), included:

**Cardiac disorders:** Cyanosis

**Endocrine disorders**: Hypoglycemia

**Gastrointestinal disorders:** Abdominal pain, diarrhea, enanthema, gastrointestinal hemorrhage, melena

**General disorders and administration site conditions:** Death

**Hepatobiliary disorders:** Elevated hepatic enzymes, liver enlargement

**Infections and infestations:** Septicemia

**Neoplasms benign, malignant and unspecified (including cysts and polyps**): Brain tumor

**Nervous system disorders:** Seizures, encephalopathy, hyperkinesia

**Respiratory, thoracic and mediastinal:** Bronchitis

**Abnormal Hematologic and Clinical Chemistry Findings**

**Elevations in plasma tyrosine**
Elevated tyrosine levels have been associated with ocular disorders and hyperkeratotic skin lesions, therefore levels should be carefully monitored and dietary restriction of tyrosine and phenylalanine adjusted as necessary [see **WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Tests**].

**Thrombocytopenia and leukopenia**
Platelet and white blood cell counts should be monitored during therapy [see **WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Tests**].

**Post-Market Adverse Drug Reactions**

**Nervous system disorders:**
Cases of intellectual disability and developmental delay have been reported in HT-1 patients treated with nitisinone. It is uncertain whether the cases may have been related to nitisinone exposure, high plasma tyrosine concentrations, low phenylalanine concentrations, acute liver disease in infancy, or to an intrinsic effect of HT-1 [see WARNINGS AND PRECAUTIONS, **Monitoring and Laboratory Tests**].

**DRUG INTERACTIONS**

**Overview**

Nitisinone is a substrate of CYP3A4 *in vitro*, therefore dose-adjustment may be needed when

nitisinone is co-administered with inhibitors (e.g. ketoconazole) or inducers (e.g. rifampin) of this enzyme. Based on *in vitro* studies nitisinone is not expected to inhibit CYP 1A2, 2C19, or 3A4 mediated metabolism or to induce CYP1A2, 2B6 or 3A4/5. Nitisinone is not expected to inhibit P-gp, BCRP, OATP1B1, OATP1B3 and OCT2-mediated transport.

**Drug-Drug Interactions**

In a clinical drug interaction study, nitisinone was co-administered with a CYP substrate cocktail (CYP2C9 substrate tolbutamide; CYP2D6 substrate metoprolol; CYP2E1 substrate chlorzoxazone, or an OAT1/OAT3 substrate furosemide), and the pharmacokinetics of these co-administered drugs were evaluated (Table 1). Nitisinone demonstrated moderate inhibition of CYP2C9, weak induction of CYP2E1 and a weak inhibition of OAT1 and OAT3, whereas nitisinone did not inhibit CYP2D6. Nitisinone treatment may therefore result in increased plasma concentrations of co-medications metabolized primarily via CYP2C9, such as warfarin tolbutamide and phenytoin. Caution is recommended when Orfadin (nitisinone) is co-administered with narrow therapeutic index CYP2C9 substrates such as warfarin, and patients co-administered these agents should be monitored.

**Table 1 – Effects of Nitisinone 80 mg Once Daily on the Pharmacokinetics of Other Co-administered Drugs**

| Co-administered drug | Dose of co-administered drug | Geometric mean ratio (with/without co-administered drug); No effect=1.0 | | Clinical comment |
|---|---|---|---|---|
| | | $AUC_{inf}$ (90% CI) | $C_{max}$ (90% CI) | |
| **Tolbutamide** | 500 mg, oral single dose | 2.3 (2.11; 2.53) | 1.16 (1.11; 1.21) | Monitor blood glucose levels and adjust dosage of tolbutamide as needed. |
| **Metoprolol** | 50 mg, oral, single dose | 0.95 (0.88; 1.03) | 1.06 (0.90; 1.25) | No dosage adjustment of metoprolol is required. |
| **Chlorzoxazone** | 250 mg, oral, single dose | 0.73 (0.67; 0.80) | 0.82 (0.67; 0.99) | No dosage adjustment of chlorzoxazone is required. |
| **Furosemide** | 20 mg/2 mL intravenous, single dose | 1.72 (1.63; 1.81) | 1.12 (1.08; 1.15) | No dosage adjustment of furosemide is required. |

**Drug-Food Interactions**

Interactions of Orfadin capsules with food have not been established (see **DOSING AND ADMINISTRATION, Dosing Considerations**), however, during clinical studies nitisinone was frequently administered with food. It is recommended that whether Orfadin, capsule treatment is initiated with or without food, the same routine should be continued.
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.

**Drug-Herb Interactions**

Interactions with herbal products have not been established.

**Drug-Laboratory Interactions**

Interactions with laboratory tests have not been established.

## DOSAGE AND ADMINISTRATION

**Dosing Considerations**

Treatment of HT-1 with Orfadin should be initiated as early as possible in an effort to increase overall survival and avoid complications such as liver failure, liver cancer and renal disease.

Dietary intake of tyrosine and phenylalanine must be restricted during Orfadin therapy. It is recommended that a dietician skilled in managing patients with inborn errors of metabolism be consulted to design a low-protein diet restricted in tyrosine and phenylalanine.

CYP2C9 substrates
When Orfadin is taken concomitantly with other drugs metabolized primarily via CYP2C9, the dosage of the concomitant drugs may need to be adjusted (see **DRUG INTERACTIONS**).

**Recommended Dose and Dosage Adjustment**

Comparable nitisinone bioavailability was demonstrated between Orfadin hard capsules and Orfadin oral suspension. Switching from one formulation of Orfadin to the other can be done using the same total daily dose.

The recommended initial daily dose of Orfadin in the pediatric and adult population is 1 mg/kg body weight divided into two doses administered orally. The dose of nitisinone should be adjusted individually.

In patients whose plasma or urine succinylacetone (SA) are still detectable one month after starting Orfadin treatment, the Orfadin dose should be increased to 1.5 mg/kg/day, divided into two doses. A maximum dose of 2 mg/kg/day may be needed based on the evaluation of all

biochemical parameters. If the biochemical response is satisfactory, the Orfadin dose should be adjusted only according to body weight gain.

In patients who weigh 20 kg or more, and who have undetectable plasma and urine succinylacetone concentrations after a minimum of 4 weeks on a stable twice a day dosage of Orfadin, the total daily dose of Orfadin may be given once daily (i.e. 1 to 2 mg/kg once daily).

Closer monitoring of all available biochemical parameters, including plasma and urine succinylacetone, urine 5-aminolevulinate (ALA) and erythrocyte porphobilinogen (PBG)-synthase activity is recommended under the following conditions:

- During the initiation of therapy;
- During a switch from twice a day to once a day dosing; or
- If there is a deterioration in the patient's condition,

[see **WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Tests**].

**Administration**

No data are available on the effect of food on the bioavailability of Orfadin capsules; however, in clinical studies nitisinone was usually co-administered with food. It is recommended that if nitisinone treatment is initiated with food, this routine should be maintained.
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.

For patients who are intolerant to the oral suspension, the capsules may be opened and the contents suspended in a small amount of water or formula immediately before intake.

Preparation of the Oral Suspension

The oral suspension will be dispensed with an oral syringe of appropriate size and a bottle adaptor provided by a pharmacist or other healthcare provider.

Preparing a Bottle Without the Adapter Already Inserted:

- Store the bottle in the refrigerator prior to first use.
- Remove the bottle from the refrigerator. Calculate 60 days from when the bottle is removed from the refrigerator. Write this date as the "Discard after" date on the bottle label.
- Allow the bottle to warm to room temperature (30 to 60 minutes).
- Shake the bottle vigorously for at least 20 seconds until the solid cake at the bottom of the bottle is completely dispersed. Check that there are no particles left at the bottom of the bottle. Foam will form in the bottle.
- Insert the bottle adapter.

Preparing a Bottle With the Adapter Inserted:

- Shake the bottle vigorously for at least 5 seconds. Check that there are no particles left at the bottom of the bottle. Foam will form in the bottle.

Measuring and Administering the Dose
Once the bottle is prepared with the adapter:

1. Use the oral syringe to measure the dose.
2. Keep the bottle upright and insert the oral syringe into the adapter.
3. Carefully turn the bottle upside down with the oral syringe in place. Wait for the foam to rise to the top of the bottle.
4. Pull back on the syringe plunger to withdraw the dose.
5. Leave the syringe in the adapter and turn the bottle upright.
6. Remove the syringe from the adapter by gently twisting it out of the bottle.
7. Dispense the dose into the patient's mouth.
8. Do not remove the bottle adapter.
9. Store the bottle at room temperature (not above 25°C).

## OVERDOSAGE

For management of a suspected drug overdose, contact your regional Poison Control Centre.

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 [see **WARNINGS AND PRECAUTIONS**]. Restriction of tyrosine and phenylalanine in the diet should limit toxicity associated with this type of tyrosinemia.

## ACTION AND CLINICAL PHARMACOLOGY

### Mechanism of Action

Nitisinone is a competitive inhibitor of 4-hydroxyphenyl-pyruvate dioxygenase, an enzyme upstream of fumarylacetoacetate hydrolase (FAH) in the tyrosine catabolic pathway. By inhibiting the normal catabolism of tyrosine in patients with HT-1, nitisinone prevents the accumulation of the catabolic intermediates maleylacetoacetate and fumarylacetoacetate. In patients with HT-1, these catabolic intermediates are converted to the toxic metabolites succinylacetone and succinylacetoacetate, which are responsible for the observed liver and kidney toxicity. Succinylacetone can inhibit the porphyrin synthesis pathway leading to the accumulation of 5-aminolevulinate, a neurotoxin responsible for the porphyric crises characteristic of HT-1.

Nitisinone inhibits catabolism of the amino acid tyrosine and can result in elevated plasma levels of tyrosine. Therefore, treatment with nitisinone requires restriction of the dietary intake of tyrosine and phenylalanine to prevent the toxicity associated with elevated plasma levels of tyrosine [see **WARNINGS AND PRECAUTIONS**].

## Pharmacokinetics

***HT-1 patients***

No pharmacokinetic studies of nitisinone have been conducted in children or HT-1 patients. Pharmacokinetic findings in HT-1 patients are available from case reports during the first 3 doses and after treatment discontinuation in seven patients, mostly children. At the start of the treatment, plasma nitisinone concentrations were similar in patients aged from < 6 months and 6-24 months, and higher in patients older than 24 months. Plasma nitisinone concentration increased over 3 years of treatment and then stabilized. The terminal half-life was found to be around 25 hours for children between 2 and 6 years old and around 21 hours for a 21 year-old patient with HT-1. The observed half-life of patients with HT-1 was shorter than the terminal half-life observed in healthy adult males (around 54 hours). The volume of distribution of the 21 years old patient with HT-1 was lower (Vd=0.07 L/kg) than the three children aged between 2 months and 2.25 years (Vd= 0.3 L/kg).

***Healthy adults***

The single-dose pharmacokinetics of nitisinone has been studied in ten healthy male volunteers aged 19-39 years (median 32 years). Nitisinone, 1 mg/kg body weight, was administered as a capsule and an oral solution. The median time for maximum plasma concentration was 3 hours for the capsule and 15 minutes for the solution. The mean terminal plasma half-life of nitisinone in healthy male volunteers was 54 hours.

**Absorption**

After single doses to fasting healthy volunteers, maximum serum concentrations are reached within approximately 3.5 hours after dosing.

**Distribution**

*In vitro* binding of nitisinone to human plasma proteins is greater than 95% at 50 micromolar concentration. Nitisinone was found to cross the placental barrier and was measured in newborn cord blood at levels comparable to the mother's nitisinone blood concentration.

**Metabolism**

*In vitro* studies have shown that nitisinone is relatively stable in human liver microsomes with minor metabolism possibly mediated by CYP3A4 enzyme.

**Excretion**

A population pharmacokinetic analysis has been conducted on a group of 207 HT-1 patients. The clearance and half-life were determined to be 0.0956 L/kg body weight/day and 52.1 hours respectively. The route of elimination appears to be via hydroxylation with subsequent excretion in both urine and feces.

## Special Populations and Conditions

**Pediatrics**

Pediatric patients with HT-1, aged from birth to 17 years have been treated with nitisinone [see **CLINICAL TRIALS**]. The dose recommendation in mg/kg body weight is the same in children

and adults. However, due to the limited data in patients with body weight <20 kg, it is recommended to divide the total daily dose into two daily administrations in this patient population. Monitoring of blood and urine succinylacetone levels are recommended in the children to ensure adequate control [see **DOSAGE AND ADMINISTRATION**]. A dietician skilled in managing children with inborn errors of metabolism should be employed to design a low-protein diet restricted in tyrosine and phenylalanine (see **INDICATIONS AND CLINICAL USE**).

**Geriatrics**
Clinical studies and clinical use of nitisinone did not include any subjects aged 65 and over to determine whether they respond differently from younger subjects. No pharmacokinetic studies of nitisinone have been performed in geriatric subjects. 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 concomitant disease or other drug therapy in this patient population (see **INDICATIONS AND CLINICAL USE).**

**Gender**
The effect of gender on the pharmacokinetics of nitisinone has not been studied.

**Race**
The effect of race on the pharmacokinetics of nitisinone has not been studied.

**Hepatic insufficiency**
Clinical studies have not been performed in patients with hepatic impairment. There are no specific dose recommendations for elderly or patients that have hepatic impairment.

**Renal insufficiency**
Clinical studies have not been performed in patients with renal impairment. There are no specific dose recommendations for elderly or patients that have renal impairment.

**Genetic polymorphism**
The influence of genetic polymorphisms on the pharmacokinetics of nitisinone is unknown.

## STORAGE AND STABILITY

Capsules:
Store in a refrigerator (2°C – 8°C).
During the shelf life, the patient may store Orfadin for a single period of 2 months at a temperature not above 25°C, after which it must be discarded.

Oral suspension:
Store in a refrigerator (2°C – 8°C) prior to first use. Do not freeze. Store upright.
After first opening, store the product at room temperature (up to 25°C) for up to 60 days. If not used within 60 days, discard unused portion. The discard after date should be noted on the bottle.

## SPECIAL HANDLING INSTRUCTIONS

There are no special handling instructions for Orfadin.

## DOSAGE FORMS, COMPOSITION AND PACKAGING

Capsules:
White, opaque hard-gelatin two piece capsules (6x16 mm) imprinted “NTBC 2mg”, “NTBC 5mg”, “NTBC 10mg” or “NTBC 20mg” in black on the body of the capsule. The capsules contain a white to off white powder.

Capsule content: Starch, pregelatinized (maize)
Capsule shell: gelatin, titanium dioxide (E 171)
Imprint: ammonium hydroxide, black iron oxide (E 172), propylene glycol, shellac

The capsules are supplied in HDPE bottles with a tamper-proof closure of LDPE, containing 60 capsules. Each bottle is packaged in a carton.

Oral suspension:
White, slightly viscous opaque suspension. 1 mL contains 4 mg of nitisinone. The suspension is provided in a 100 mL brown bottle (type III glass) with a white child resistant HDPE screw cap with sealing and tamper evidence. Each bottle contains 90 mL oral suspension.

The inactive ingredients are hydroxypropyl methylcellulose, glycerol, polysorbate 80, sodium benzoate, citric acid monohydrate, trisodium citrate dihydrate, strawberry aroma (artificial) and purified water.

Glycerol: Each mL contains 500 mg.

Sodium: Each mL contains 0.7 mg (0.03 mEq).

# PART II: SCIENTIFIC INFORMATION

## PHARMACEUTICAL INFORMATION

### Drug Substance

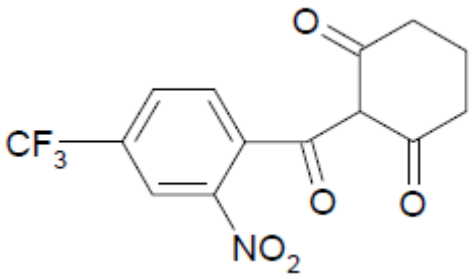
Common name nitisinone

Chemical name: 1,3-Cyclohexanedione, 2-[2-nitro-4-(trifluoromethyl)benzoyl]-

Molecular formula: $C_{14}H_{10}F_3NO_5$

Molecular mass: 329.228 g/mol

Structural formula:




Physicochemical properties: Nitisinone occurs as white to yellowish-white, crystalline powder. It is practically insoluble in water, soluble in 2M sodium hydroxide and in methanol, and sparingly soluble in alcohol.

## CLINICAL TRIALS

### Study demographics and trial design

The efficacy and safety of nitisinone were analyzed in a multinational, uncontrolled, open-label study, as shown in Table 2.

The study was open to patients with HT-1 of any clinical type, without restrictions in age, sex, ethnic origin, or nationality. The only exclusion criterion was previous liver transplantation. The median treatment duration was 3.3 years with a maximum duration of 9.1 years. The majority of patients (229 out of 291, 79%) received at least 1 year of treatment with nitisinone.

**Table 2 - Summary of the open-label clinical trial in HT-1 patients**

| Trial design | Dosage, route of administration and duration | Study subjects (N) | Mean age (Range) | Gender |
|---|---|---|---|---|
| Multicenter, multinational, open-label, uncontrolled study | Oral, twice a day.<br>Initial daily dose: 0.2 mg/kg to 1 mg, followed by individual adjustment.<br>Median treatment duration 3.3 years | 291 | 2.07 (0.00, 21.68) | 162 males (56 %)<br>129 females<br>(44 %) |

N = Number of subjects in the study

**Study results**

Survival probabilities after 2, 4 and 6 years of treatment with nitisinone are summarized in Table 3 and after 1 and 2 years with dietary restriction only, in Table 4.

**Table 3 - Survival probability, HT-1 Patients treated with nitisinone**

| | **Patients treated with nitisinone, open-label (N=250)[1] Survival probability** | | |
|---|---|---|---|
| **Age at start of treatment** | **2 years** | **4 years** | **6 years** |
| ≤ 2 months | 93% | 93% | 93% |
| ≤ 6 months | 93% | 93% | 93% |
| > 6 months | 96% | 95% | 95% |
| Overall | 94% | 94% | 94% |

N = Number of patients in the study.

[1]Patients who started treatment on the recommended dose of 1 mg/kg

**Table 4 – Survival probability, HT-1 Patients treated with dietary restrictions**

| | **Historical controls (dietary restriction only)[1] Survival probability** | |
|---|---|---|
| **Age at onset of symptoms** | **1 year** | **2 years** |
| < 2 months | 38% | 29% |
| 2 - 6 months | 74% | 74% |
| > 6 months | 96% | 96% |

[1] van Spronsen *et al.* (1994).

Treatment with nitisinone was also found to result in reduced risk for the development of hepatocellular carcinoma compared to historical data on treatment with dietary restriction alone. Early initiation of treatment resulted in a further reduced risk for the development of hepatocellular carcinoma.

An open-label study to evaluate the PK, efficacy and safety of once daily dosing, compared to twice a day dosing, was performed in 19 patients with HT-1. All study patients were on a stable Orfadin daily dosage (0.4 – 1.6 mg/kg/day) during both study dosing regimens. After at least 4 weeks of twice a day dosing with Orfadin, both the urine and/or blood succinylacetone concentrations were below the limit of quantitation. Patients were then switched to once a day dosing with the same total daily dose of Orfadin and blood and/or urine succinylacetone concentrations remained undetectable when measured following at least 4 weeks of treatment with once a day dosing. There was insufficient support for the once a day dosing regimen in patients with body weight < 20 kg.

**Comparative Bioavailability Studies**

Nitisinone bioavailability from the administration of Orfadin oral suspension was compared to that of Orfadin capsules in a randomized 3-way crossover study conducted in 12 healthy volunteers. Subjects received single oral 30-mg doses of Orfadin as a suspension (fasting and with food) and as hard gelatin capsules (fasting only). There was a 2-week washout period between the doses (Table 5).

**Table 5 - Pharmacokinetic data for Orfadin oral suspension 4 mg/mL and Orfadin capsules 10 mg**

| nitisinone<br>(1 x 30 mg)<br>From measured data<br><br>Geometric Mean<br>Arithmetic Mean (CV %) | | | | |
|---|---|---|---|---|
| **Parameter** | **Orfadin Oral suspension (fasted)** | **Orfadin Capsules (fasted)** | **% Ratio of Geometric Means** | **90% Confidence Interval** |
| $AUC_{72h}$<br>(μM·h) | 346<br>350 (17) | 403<br>406 (13) | 85.8 | 81 - 91 |
| AUCInf<br>(μM·h) | 559<br>565 (15) | 633<br>645 (20) | 88.0 | 82 - 94 |
| $C_{MAX}$<br>(nM) | 9741<br>10114 (34) | 10213<br>10471 (26) | 95.4 | 85 - 107 |
| $T_{MAX}$*<br>(h) | 0.38 (0.25 – 4.00) | 3.50 (0.75 – 8.00) | - | - |
| $T_{½}$** (h) | 51.4 (16) | 49.1 (26) | | |

*Expressed as median (range) only

**Expressed as arithmetic mean (CV%) only

Study result: Comparable nitisinone bioavailability was demonstrated between the two Orfadin formulations. The mean ratio (suspension/capsule) of $C_{max}$ values and the 90 % CI of the mean ratio of $AUC_{72h}$ were within the 80.0 – 125.0 acceptance range. The faster absorption of the suspension compared to the capsule, when the two are given under fasting conditions, is reflected

in the median $t_{max}$ values for the suspension of 0.38 hours compared to 3.50 hours for the capsule. When given with food the absorption of the suspension is delayed resulting in a median $t_{max}$ of 8.00 hours.

## DETAILED PHARMACOLOGY

### Pharmacodynamic data in HT-1 patients

Urine succinylacetone was measured in 186 patients, and in all patients urinary succinylacetone level decreased to less than 1 mmol/mol creatinine, with a median time to normalization of 0.3 months. Plasma succinylacetone was measured in 172 patients. In 150 patients (87%), plasma succinylacetone decreased to less than 0.1 μmol/L, with a median time to normalization of 3.9 months.

### Pharmacokinetic data

In 10 healthy male volunteers, after administration of a single dose of Orfadin capsules (1 mg/kg body weight) the terminal half-life (median) of nitisinone in plasma was 54 hours (ranging from 39 to 86 hours). In a study in children with HT-1, the terminal half-life was found to be 25.3 hours. The route of elimination appears to be via hydroxylation with subsequent excretion in both urine and feces.

In a study with nitisinone capsules involving 46 healthy adults, the terminal half-life was 63.70 hrs.

## TOXICOLOGY

### Single and repeat-dose toxicity

The acute oral toxicity of nitisinone was low, with a median lethal dose in mice of 600 mg/kg for males and 800 mg/kg for females, and between 100-1000 mg/kg in rats. Limited repeat-dose studies were conducted in the mouse, rat, rabbit, dog, and monkey. In the rat and dog, ocular toxicity (keratitis, corneal inclusions) were observed at doses comparable to human exposures.

### Carcinogenicity and mutagenicity

Nitisinone was not genotoxic in the Ames test and the *in vivo* mouse liver unscheduled DNA synthesis (UDS) test. Nitisinone was mutagenic in the mouse lymphoma cell (L5178Y / $TK^{+/-}$) forward mutation test and in an *in vivo* mouse bone marrow micronucleus test.

No long-term studies have been performed in animals to evaluate the carcinogenicity of nitisinone. In a 26-week carcinogenicity study in transgenic mice (TgrasH2), no nitisinone-related neoplastic or hyperplastic effects were seen.

### Reproductive and developmental toxicity

In a study in rats given maternally toxic doses of 50 mg/kg/day (4 times the maximum clinical dose, based on body surface area), increased stillbirths and reduced live births, birth weights and survival after birth were observed, as well as increased rates of skeletal abnormalities.

In mice and rabbits, embryotoxicity (decreased fetal weights, increased early intra- uterine deaths and increased post-implantation loss) and fetal abnormalities (skeletal abnormalities in both species, and umbilical hernia, gastroschisis, and lung abnormalities in rabbits) were observed at oral nitisinone doses from 5 mg/kg/day (less than the maximum clinical dose, based on body surface area), following administration during organogenesis.

In mice, maternal treatment at oral doses from 5 mg/kg/day (less than the maximum clinical dose, based on body surface area) during organogenesis through weaning was associated with reduced pup survival, weight gain and developmental delays.

In rats, exposure of drug-naïve pups to nitisinone through milk from treated dams given 100 mg/kg/day orally (9 times the maximum clinical dose, based on body surface area) was associated with reduced pup weight and development of corneal opacities.

**READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE**
**PATIENT MEDICATION INFORMATION**

**Orfadin**
**nitisinone capsules**
**nitisinone oral suspension**

Read this carefully before you start taking Orfadin and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about Orfadin.

**What is Orfadin used for?**
Orfadin is used for the treatment of hereditary tyrosinemia type 1 (HT-1), in addition to limiting the amount of tyrosine and phenylalanine in the diet.

**How does Orfadin work?**
Orfadin stops the build-up of toxic substances which cause the severe liver and kidney problems in patients with HT-1. By doing that, it also prevents the porphyric crises (acute attacks of neurological symptoms that can be life-threatening) associated with HT-1.

**What are the ingredients in Orfadin?**
Medicinal ingredients: nitisinone

Capsules:
Non-medicinal ingredients: ammonium hydroxide, black iron oxide, gelatine, pregelatinized starch (maize), propylene glycol, shellac, titanium dioxide.

Oral suspension:
Non-medicinal ingredients: citric acid monohydrate, glycerol, hydroxypropyl methylcellulose, polysorbate 80, purified water, sodium benzoate, strawberry aroma (artificial), trisodium citrate dihydrate.

**Orfadin comes in the following dosage forms:**
Capsules: 2 mg, 5 mg, 10 mg and 20 mg.
Oral suspension: 4 mg/mL.

**Do not use Orfadin if you:**
- are allergic to nitisinone or any of the other ingredients.
- are breast-feeding. Do not breast feed while taking Orfadin.

**To help avoid side effects and ensure proper use, talk to your healthcare professional before you/your child take Orfadin. Talk about any health conditions or problems you may have, including if:**
- you are pregnant or planning to become pregnant.
- your newborn or premature baby, diagnosed with HT-1, has yellowing of the eyes and/or

skin (jaundice)
- you are on a low salt diet

**Other warnings you should know about:**
During treatment with Orfadin, blood tests will be done so your healthcare professional can check that the treatment is working and that the dosing is correct. Your healthcare professional will also check for side effects that can be caused by the treatment. You should see your healthcare professional at least every 6 months.

**Dietary Changes**
Taking Orfadin can cause high levels of tyrosine in your blood. This can cause harmful side effects such as **Eye Problems**. As a result, while you are taking Orfadin you must limit the amount of tyrosine and phenylalanine in your diet. Talk to your healthcare professional about which foods are safe to eat and which foods should be avoided.

**Eye Problems**
Your healthcare professional will check your eyes before starting treatment with Orfadin and thereafter regularly. If you develop eye problems while taking Orfadin, including sensitivity to light, eye pain, redness, swelling or burning, talk to your healthcare professional immediately.

**Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.**

**The following may interact with Orfadin:**

Nitisinone may affect medications which are degraded via the enzyme CYP2C9, such as
- the anticoagulant warfarin,
- the antiepileptic phenytoin, and
- the antidiabetic tolbutamide.

**How to take Orfadin**
- By mouth.
- Orfadin **capsules** can be taken with or without food. However, they should always be taken the same way. Therefore, if you start taking Orfadin capsules with food you should always take them with food.
- It is recommended that you take Orfadin **oral suspension** with food.
- For patients who are unable to take the oral suspension, Orfadin capsules can be opened and the contents sprinkled into a small amount of water or formula immediately before use.

**Preparation of the Oral Suspension**

- You will be provided with:
  - 1 bottle of Orfadin oral suspension
  - 1 oral syringe

- 1 adapter (The adapter may or may not be inserted in your bottle of Orfadin oral suspension when you receive it.)

**Use the oral syringe provided with your Orfadin oral suspension to make sure you measure the right amount.** Talk to your healthcare professional or pharmacist if you have questions about how to use the oral syringe or if you lose the oral syringe.

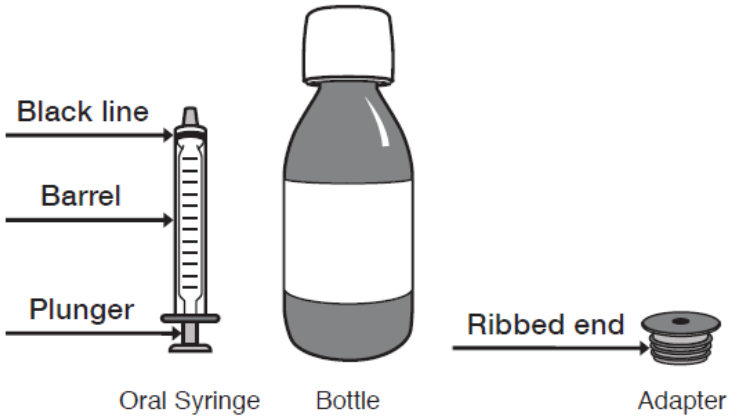



Figure A

If the adapter **is not** inserted in your bottle of Orfadin oral suspension when you receive it, follow the instructions in **"How to prepare a bottle of Orfadin oral suspension if the adapter is not inserted."**

If the adapter **is** inserted in your bottle of Orfadin oral suspension when you receive it, follow the instructions in **"How to prepare a dose of Orfadin oral suspension after the adapter is inserted."**

**How to prepare a bottle of Orfadin oral suspension if the adapter is not inserted:**

1. Store Orfadin oral suspension in the refrigerator until you use it for the first time.

2. Remove the Orfadin oral suspension bottle from the refrigerator 30 minutes to 1 hour before using it to allow it to reach room temperature.
   Orfadin oral suspension should be thrown away (discarded) 60 days after it is removed from the refrigerator and the adapter is inserted in the bottle. Write the discard date on the bottle label.

3. Shake the bottle well for **at least 20 seconds** until the solid cake of particles at the bottom of the bottle is dissolved (See Figure B). Check that there are no particles left at the bottom of the bottle. Foam will form in the bottle.

Figure B

4. Remove the child resistant screw cap by pushing it down firmly and turning it counter-clockwise (See Figure C).

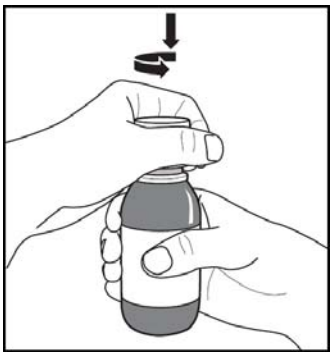


Figure C

5. Place the open bottle upright on a flat surface. Push the ribbed end of the adapter firmly into the neck of the bottle as far as it will go (See Figure D). Replace the child resistant screw cap on the bottle. Do not remove the adapter from the bottle after it is inserted.

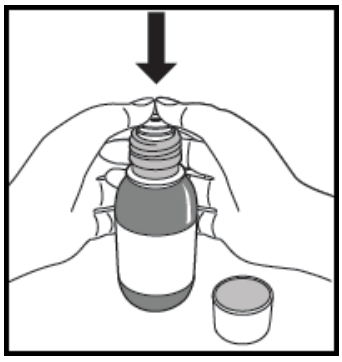


Figure D

6. Follow the instructions in "How to prepare a dose of Orfadin oral suspension after the adapter is inserted."

**How to prepare a dose of Orfadin oral suspension after the adapter is inserted**

1. If the adapter is inserted, Orfadin oral suspension can be stored at room temperature (up to 25°C) for up to 60 days. Write the discard date on the bottle label. Throw the bottle of Orfadin oral suspension away after 60 days even if there is medcine left in the bottle.

2. Shake the Orfadin oral suspension bottle well for **at least 5 seconds** (See Figure E). Check that there are no particles left at the bottom of the bottle. Foam will form in the bottle.

Figure E

3. Remove the child resistant screw cap right away by pushing it down firmly and turning it counter-clockwise (See Figure F).

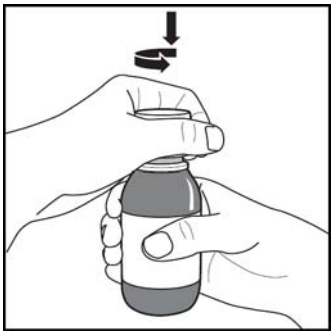


Figure F

4. Hold the oral syringe in one hand. With your other hand, fully push down (depress) the plunger (See Figure G).

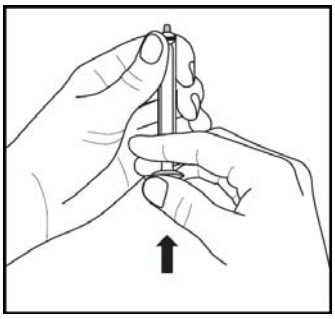


Figure G

5. Keeping the bottle in an upright position, insert the oral syringe firmly into the adapter (See Figure H).

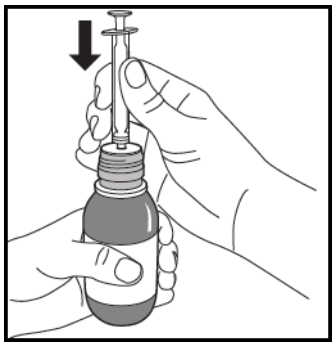


Figure H

6. Carefully turn the bottle upside down with the oral syringe in place (See Figure I). Wait until you can see that the foam is at the top of the bottle to avoid withdrawing bubbles into the syringe.

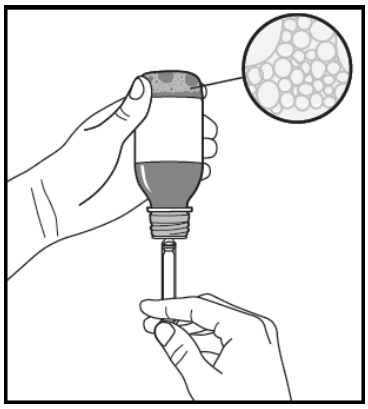


Figure I

7. Pull back slowly on the oral syringe plunger until the top edge of the black ring is at the line marking the dose prescribed by your healthcare professional (See Figure J). Figure J shows a dose of 1 mL as an example. If you see air bubbles in the oral syringe, fully push in the plunger so that the oral suspension flows back into the bottle. Then, withdraw your prescribed dose of oral suspension again.

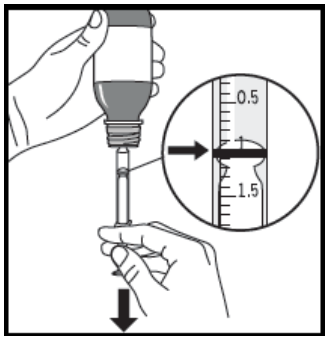



Figure J

8. Leave the oral syringe in the adapter and turn the bottle to an upright position. Place the bottle onto a flat surface. Remove the oral syringe by gently twisting it out of the bottle (See Figure K). Do not pull straight up on the syringe to remove it from the bottle because this can cause the adapter to come out of the bottle.

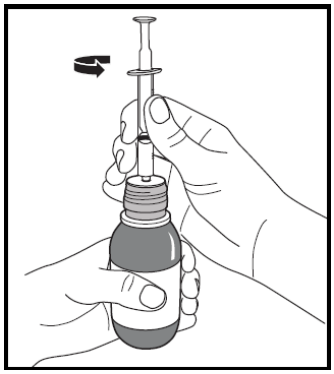


Figure K

9. Place the oral syringe in your/the patient's mouth right away. Slowly push on the plunger until the oral syringe is empty. (See Figure L).

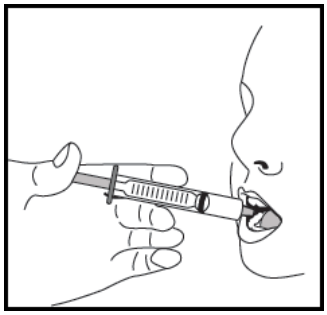


Figure L

10. Leave the adapter in the bottle. Put the child resistant screw cap back on the bottle (See Figure M).

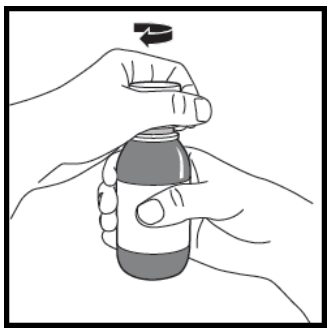


Figure M

11. Remove the plunger from the oral syringe barrel. Rinse the oral syringe with water after each use and let it air dry. Do not replace the plunger into the barrel of the oral syringe until ready to use again for your next dose to allow it to dry. Do not throw away the oral syringe.

12. Store the bottle in an upright position at room temperature (not above 25°C).

**Dosing information**

**Recommended Doses are for Adults and Children**
The dose is adjusted for each individual patient. Your healthcare professional will tell you how much Orfadin to take and when to take it.

**Initial Recommended Daily Dose**
For patients starting on Orfadin, the recommended daily dose is 1 mg/kg body weight. This total daily dose should be divided in half and taken two times a day.

**Increasing the Dose**
The doctor may increase the dose to 1.5 mg/kg and then up to a maximum of 2 mg/kg per day. This depends on if toxic substances, such as succinylacetone, are still detected in the blood and urine.

**Once a day dosing**
1 to 2 mg/kg body weight. The once a day dose should be the same as the total twice a day dose. Switching to once a day dosing may be considered by the healthcare professional if:

- The patient weighs 20 kg or more; and
- There are no detectable toxic substances in the patient's blood and urine; and
- The patient was stable on Orfadin given two times a day for a minimum of 4 weeks

**Overdose:**

If you think you have taken too much Orfadin, contact your healthcare professional, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

**Missed Dose:**
If you forget to take a dose, take it as soon as you remember. If you miss several doses contact your healthcare professional.

**What are possible side effects from using Orfadin?**
These are not all the possible side effects that you may feel when taking Orfadin. If you experience any side effects not listed here, contact your healthcare professional.

Orfadin and HT-1 can cause abnormal blood and urine test results. This can occur when you start on Orfadin, if you switch from two times a day dosing to once a day or if your condition gets worse. While taking Orfadin your healthcare professional will decide when to perform blood and urine tests. They will interpret the results.

Orfadin can cause **Eye Problems.** Your healthcare professional should make sure you have an eye exam before you start on Orfadin. This should be done by an ophthalmologist. If you have any of the symptoms of **Eye Problems**, talk to your healthcare professional immediately as you should get your eyes re-checked.

| **Serious side effects and what to do about them** | | | |
|---|---|---|---|
| Symptom / effect | Talk to your healthcare professional | | Get immediate medical help |
| | Only if severe | In all cases | |
| **COMMON** | | | |
| **Eye Problems**: redness, eye discharge, itchy eyes, swelling or burning eyes, blurred vision, sensitivity to light, milky or cloudy area on the eye, eye pain, a feeling that there is something in your eye. | | x | |
| **Low Platelets**: easy or unusual bruising. Bleeding into the skin causing a rash of pinpoint-sized reddish-purple spots, usually in the lower legs, prolonged bleeding from cuts, bleeding from your gums or nose, blood in urine or stools. | | x | |
| **Low White Blood Cells**: infections, fatigue, weakness, fever, aches and pains, flu-like symptoms. | | x | |
| **UNCOMMON** | | | |
| **Skin Problems**: | | x | |

| | | | |
|---|---|---|---|
| dry/cracked/scaly skin, rashes, small flat red bumps, itching that can be severe, blisters, draining fluid and crusting, swelling, burning, tenderness. | | | |
| **UNKNOWN** | | | |
| **Newborns taking Orfadin oral suspension:** increased yellowing of the skin and/or eyes (jaundice). | | | x |

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

**Reporting Side Effects**

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345

*NOTE: Contact your healthcare professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.*

**Storage:**
Do not use this medicine after the date printed on the bottle and the carton after "EXP".
The expiry date refers to the last day of that month.

Capsules:
Store in a refrigerator (2°C to 8°C).
Orfadin capsules can be stored for a single period of 2 months at a temperature below 25°C.
Do not forget to mark the date on the bottle, when you take it out of the refrigerator. Do not use Orfadin capsules after they have been out of the refrigerator for 2 months.

Oral suspension:
Store refrigerated at 2°C to 8°C prior to first use. Do not freeze. Store upright.

After first opening, store Orfadin oral suspension at room temperature (up to 25°C) for up to 60 days. Store upright. If not used within 60 days, discard unused portion. The discard after date should be noted on the bottle.

Keep out of reach and sight of children.

**If you want more information about Orfadin:**

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website (www.healthcanada.gc.ca); or by calling the sponsor at 1-866-773-5274

This leaflet was prepared by Swedish Orphan Biovitrum AB (publ)

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