HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use ORFADIN safely and effectively. See full prescribing information for ORFADIN.

ORFADIN® (nitisinone) capsules, for oral use
ORFADIN® (nitisinone) oral suspension
Initial U.S. Approval: 2002

----------INDICATIONS AND USAGE----------
ORFADIN is a 4-hydroxyphenylpyruvate dioxygenase inhibitor indicated for the treatment of hereditary tyrosinemia type 1 (HT-1) in combination with dietary restriction of tyrosine and phenylalanine. (1)

----------DOSAGE AND ADMINISTRATION----------
Recommended Dosage (2.1):
- The recommended initial dosage is 0.5 mg/kg orally twice daily.
- Titrate the dose based on biochemical and/or clinical response, as described in the full prescribing information.
- The maximum dosage is 1 mg/kg orally twice daily.

Preparation and Administration Instructions (2.2):
- For instructions on preparing, measuring and administering the oral suspension, see the full prescribing information.
- Maintain dietary restriction of tyrosine and phenylalanine
- Take ORFADIN capsules at least one hour before, or two hours after a meal
- For patients who have difficulties swallowing capsules and who are intolerant to the oral suspension, the capsules may be opened and the contents suspended in a small amount of water, formula or apple sauce immediately before use.
- Take ORFADIN oral suspension without regard to meals.

----------DOSAGE FORMS AND STRENGTHS----------
- Capsules: 2 mg, 5 mg, 10 mg, 20 mg. (3)
- Oral suspension: 4 mg/mL (3)

----------CONTRAINDICATIONS----------
None (4)

----------WARNINGS AND PRECAUTIONS----------
- Elevated Plasma Tyrosine Levels, Ocular Symptoms, Developmental Delay and Hyperkeratotic Plaques: Inadequate restriction of tyrosine and phenylalanine intake can lead to elevations in plasma tyrosine, which at levels above 500 micromol/L can result in symptoms, intellectual disability and developmental delay or painful hyperkeratotic plaques on the soles and palms; do not adjust ORFADIN dosage in order to lower the plasma tyrosine concentration. Obtain slit-lamp examination prior to treatment and re-examination if symptoms develop. Assess plasma tyrosine levels in patients with an abrupt change in neurologic status. (5.1)
- Leukopenia and Severe Thrombocytopenia: Monitor platelet and white blood cell counts. (5.2)
- Risk of Adverse Reactions Due to Glycerol Content of ORFADIN Oral Suspension: Doses of 20 mL of ORFADIN oral suspension may cause headache, upset stomach and diarrhea due to the glycerol content. Consider switching patients to ORFADIN capsules. (5.3)

----------ADVERSE REACTIONS----------
Most common adverse reactions (>1%) are elevated tyrosine levels, thrombocytopenia, leukopenia, conjunctivitis, corneal opacity, keratitis, photophobia, eye pain, blepharitis, cataracts, granulocytopenia, epistaxis, pruritus, exfoliative dermatitis, dry skin, maculopapular rash and alopecia. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Swedish Orphan Biovitrum at 1-866-773-5274 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------
CYP2C9 Substrates: Potential for increased systemic exposure of these co-administered drugs, additional monitoring may be warranted. (7.1)

See 17 for PATIENT COUNSELING INFORMATION and FDA approved patient labeling.

Revised: 02/2017

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

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

2 DOSAGE AND ADMINISTRATION

2.1 Dosage

The recommended starting dosage of ORFADIN is 0.5 mg/kg orally twice daily. Titrate the dose for individual patients, as needed based on biochemical and/or clinical response. Adjust the dose of nitisinone individually. Monitor plasma and/or urine succinylacetone concentrations, liver function parameters and alpha-fetoprotein levels. If succinylacetone is still detectable one month after the start of nitisinone treatment, increase the nitisinone dosage to 0.75 mg/kg twice daily. A maximum dosage of 1 mg/kg orally twice daily may be needed based on the evaluation of all biochemical parameters.

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

In addition to the tests above, during the initiation of therapy or if there is a deterioration in the patient's condition, it may be necessary to follow all available biochemical parameters more closely (i.e. plasma succinylacetone, urine 5-aminolevulinate (ALA) and erythrocyte porphobilinogen (PBG)-synthase activity).

2.2 Preparation and Administration Instructions

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).

Administration of ORFADIN Capsules and Oral Suspension

- Maintain dietary restriction of tyrosine and phenylalanine when taking ORFADIN.
- *Capsules:* Take at least one hour before, or two hours after a meal *[see Clinical Pharmacology (12.3)]*. For patients who have difficulty swallowing the capsules and who are intolerant to the oral suspension *[see Warnings and Precautions (5.3)]*, the capsules may be opened and the contents suspended in a small amount of water, formula or apple sauce immediately before use.
- *Oral suspension:* Take without regard to meals *[see Clinical Pharmacology (12.3)]*.

3 DOSAGE FORMS AND STRENGTHS

- Capsules: 2 mg, 5 mg, 10 mg and 20 mg white capsules imprinted with "NTBC" followed by "2 mg", "5 mg", "10 mg" or "20 mg", indicating the actual amount of nitisinone in each capsule.
- Oral suspension: 4 mg/mL, a white, slightly viscous opaque suspension.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Elevated Plasma Tyrosine Levels, Ocular Symptoms, Developmental Delay and Hyperkeratotic Plaques

ORFADIN is an inhibitor of 4-hydroxyphenyl-pyruvate dioxygenase, an enzyme in the tyrosine metabolic pathway [*see Clinical Pharmacology (12.1)*]. Therefore, treatment with ORFADIN may cause an increase in plasma tyrosine levels in patients with HT-1. Maintain concomitant reduction in dietary tyrosine and phenylalanine while on ORFADIN treatment. Do not adjust ORFADIN dosage in order to lower the plasma tyrosine concentration. Maintain plasma tyrosine levels below 500 micromol/L. Inadequate restriction of tyrosine and phenylalanine intake can lead to elevations in plasma tyrosine levels and levels greater than 500 micromol/L may lead to the following:

- Ocular signs and symptoms including corneal ulcers, corneal opacities, keratitis, conjunctivitis, eye pain, and photophobia have been reported in patients treated with ORFADIN *[see Adverse Reactions (6.1)]*. Therefore, ophthalmologic examination including slit-lamp examination should be performed prior to initiating ORFADIN treatment. 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 reexamination and immediate measurement of the plasma tyrosine concentration.

- Variable degrees of intellectual disability and developmental delay. In patients treated with ORFADIN who exhibit an abrupt change in neurologic status, perform a clinical laboratory assessment including plasma tyrosine levels.

- Painful hyperkeratotic plaques on the soles and palms

In patients with HT-1 treated with dietary restrictions and ORFADIN who develop elevated plasma tyrosine levels, assess dietary tyrosine and phenylalanine intake.

5.2 Leukopenia and Severe Thrombocytopenia

In clinical trials, patients treated with ORFADIN and dietary restriction developed transient leukopenia (3%), thrombocytopenia (3%), or both (1.5%) *[see Adverse Reactions (6.1)]*. One patient who developed both leukopenia and thrombocytopenia improved after the dose of ORFADIN was decreased from 1 mg/kg to 0.5 mg/kg twice daily. No patients developed infections or bleeding as a result of the episodes of leukopenia and thrombocytopenia. Monitor platelet and white blood cell counts during ORFADIN therapy.

5.3 Risk of Adverse Reactions Due to Glycerol Content of ORFADIN Oral Suspension

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.

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

ORFADIN was studied in one open-label, uncontrolled study of 207 patients with HT-1, ages 0 to 21.7 years at enrollment (median age 9 months), who were diagnosed with HT-1 by the presence of succinylacetone in the urine or plasma. The starting dose of ORFADIN was 0.3 to 0.5 mg/kg twice daily, and the dose was increased in some patients to 1 mg/kg twice daily based on weight, biochemical, and enzyme markers. The recommended dose is 0.5 mg/kg to 1 mg/kg twice daily *[see Dosage and Administration (2.1)]*. Median duration of treatment was 22.2 months (range 0.1 to 80 months).

The most serious adverse reactions reported during ORFADIN treatment were thrombocytopenia, leukopenia, porphyria, and ocular/visual complaints associated with elevated tyrosine levels *[see Warnings and Precautions (5.1, 5.2)]*. 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/microL or lower. In 4 patients with thrombocytopenia, platelet counts gradually returned to normal (duration up to 47 days) without change in ORFADIN dose. No patients developed infections or bleeding as a result of the episodes of leukopenia 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%).

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

TABLE 1
Most Common Adverse Reactions*

Elevated tyrosine levels	>10%
Leukopenia	3%
Thrombocytopenia	3%
Conjunctivitis	2%
Corneal opacity	2%
Keratitis	2%
Photophobia	2%
Eye pain	1%
Blepharitis	1%
Cataracts	1%
Granulocytopenia	1%
Epistaxis	1%
Pruritus	1%
Exfoliative dermatitis	1%
Dry skin	1%
Maculopapular rash	1%
Alopecia	1%

*reported in at least 1% of patients

Adverse reactions reported in less than 1% of the patients, included death, seizure, brain tumor, encephalopathy, hyperkinesia, cyanosis, abdominal pain, diarrhea, enanthema, gastrointestinal hemorrhage, melena, elevated hepatic enzymes, liver enlargement, hypoglycemia, septicemia, and bronchitis.

7 DRUG INTERACTIONS

7.1 Interaction with CYP2C9 Substrates

If ORFADIN is co-administered with drugs that are metabolized by CYP2C9, additional monitoring may be warranted because of a potential for increased systemic exposure of these drugs *[see Clinical Pharmacology (12.3)]*. The risk is dependent upon the particular 2C9 substrate and its adverse reaction profile.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Limited data on nitisinone use in pregnant women are not sufficient to inform any drug associated risk. Animal reproduction studies have been conducted for nitisinone. In these studies, nitisinone was administered to mice and rabbits during organogenesis with oral doses of nitisinone up to 20 and 8 times respectively, the recommended human dose. In mice, nitisinone caused incomplete skeletal ossification of fetal bones and decreased pup survival at doses 0.4 times the recommended human dose, and increased gestational length at doses 4 times the recommended human dose. In rabbits, nitisinone caused maternal toxicity and incomplete skeletal ossification of fetal bones at doses 1.6 times the recommended human dose *[see Data]*.

The background risk of major birth defects and miscarriage for the indicated population are unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

Data

Animal Data

Reproduction studies have been performed in mice at oral doses of about 0.4, 4 and 20 times the recommended human dose (1 mg/kg/day) and in rabbits at oral doses of about 1.6, 4 and 8 times the recommended human dose based on the body surface area. In mice, nitisinone has been shown to cause incomplete skeletal ossification of fetal bones at 0.4, 4 and 20 times the recommended human dose, increased gestational length at 4 and 20 times the recommended human dose, and decreased pup survival at 0.4 times the recommended human dose based on the body surface area. In rabbits, nitisinone caused incomplete skeletal ossification of fetal bones at 1.6, 4 and 8 times the recommended human dose based on the body surface area.

8.2 Lactation

Risk Summary

There are no data on the presence of nitisinone in human milk, the effects on the breastfed infant, or the effects on milk production. 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. The development and health benefits of breastfeeding should be considered along with the mother's clinical need for ORFADIN and any potential adverse effects on the breastfed infant from ORFADIN or from the underlying maternal condition.

8.4 Pediatric Use

Pediatric patients with HT-1, ages birth to 17 years, have been treated with ORFADIN in one open-label, uncontrolled clinical study [*see Clinical Studies (14)]*. Monitoring of plasma and urine succinylacetone levels are recommended in the pediatric patients to ensure adequate control *[see Dosage and Administration (2.1)]*. A nutritionist skilled in managing children with inborn errors of metabolism should be employed to design a low-protein diet deficient in tyrosine and phenylalanine.

8.5 Geriatric Use

Clinical studies of nitisinone did not include any subjects aged 65 and over. No pharmacokinetic studies of nitisinone have been performed in geriatric patients. In general, dose selection for an elderly patient 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.

10 OVERDOSAGE

Accidental ingestion of ORFADIN by individuals eating normal diets not restricted in tyrosine and phenylalanine will result in elevated tyrosine levels. In healthy subjects given a single 1 mg/kg dose of nitisinone, the plasma tyrosine level reached a maximum of 1200 micromol/L at 48 to 120 hours after dosing. After a washout period of 14 days, the mean value of plasma tyrosine was still 808 micromol/L. Fasted follow-up samples obtained from volunteers several weeks later showed tyrosine values back to normal. There were no reports of changes in vital signs or laboratory data of any clinical significance. One patient reported sensitivity to sunlight. Hyper-tyrosinemia has been reported with ORFADIN treatment *[see Warnings and Precautions (5.1)]*.

11 DESCRIPTION

ORFADIN contains nitisinone, which is a hydroxyphenyl-pyruvate dioxygenase inhibitor indicated as an adjunct to dietary restriction of tyrosine and phenylalanine in the treatment of hereditary tyrosinemia type 1 (HT-1).

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.

Chemically, nitisinone is 2-(2-nitro-4-trifluoromethylbenzoyl) cyclohexane-1,3-dione, and the structural formula is:

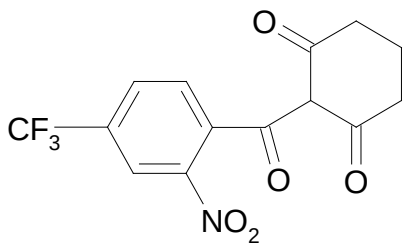

Figure 1. The molecular formula is $C_{14}H_{10}F_3NO_5$ with a relative mass of 329.23

Capsules: Hard, white-opaque capsule, marked as 2 mg, 5 mg, 10 mg or 20 mg strengths of nitisinone, intended for oral administration. Each capsule contains 2 mg, 5 mg, 10 mg or 20 mg nitisinone, plus pre-gelatinized starch. The capsule shell is gelatin and titanium dioxide and the imprint is an iron oxide.

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use ORFADIN safely and effectively. See full prescribing information for ORFADIN.

ORFADIN® (nitisinone) capsules, for oral use
ORFADIN® (nitisinone) oral suspension
Initial U.S. Approval: 2002

----------INDICATIONS AND USAGE----------
ORFADIN is a 4-hydroxyphenylpyruvate dioxygenase inhibitor indicated for the treatment of hereditary tyrosinemia type 1 (HT-1) in combination with dietary restriction of tyrosine and phenylalanine. (1)

----------DOSAGE AND ADMINISTRATION----------
Recommended Dosage (2.1):
- The recommended initial dosage is 0.5 mg/kg orally twice daily.
- Titrate the dose based on biochemical and/or clinical response, as described in the full prescribing information.
- The maximum dosage is 1 mg/kg orally twice daily.

Preparation and Administration Instructions (2.2):
- For instructions on preparing, measuring and administering the oral suspension, see the full prescribing information.
- Maintain dietary restriction of tyrosine and phenylalanine
- Take ORFADIN capsules at least one hour before, or two hours after a meal
- For patients who have difficulties swallowing capsules and who are intolerant to the oral suspension, the capsules may be opened and the contents suspended in a small amount of water, formula or apple sauce immediately before use.
- Take ORFADIN oral suspension without regard to meals.

----------DOSAGE FORMS AND STRENGTHS----------
- Capsules: 2 mg, 5 mg, 10 mg, 20 mg. (3)
- Oral suspension: 4 mg/mL (3)

----------CONTRAINDICATIONS----------
None (4)

----------WARNINGS AND PRECAUTIONS----------
- Elevated Plasma Tyrosine Levels, Ocular Symptoms, Developmental Delay and Hyperkeratotic Plaques: Inadequate restriction of tyrosine and phenylalanine intake can lead to elevations in plasma tyrosine, which at levels above 500 micromol/L can result in symptoms, intellectual disability and developmental delay or painful hyperkeratotic plaques on the soles and palms; do not adjust ORFADIN dosage in order to lower the plasma tyrosine concentration. Obtain slit-lamp examination prior to treatment and re-examination if symptoms develop. Assess plasma tyrosine levels in patients with an abrupt change in neurologic status. (5.1)
- Leukopenia and Severe Thrombocytopenia: Monitor platelet and white blood cell counts. (5.2)
- Risk of Adverse Reactions Due to Glycerol Content of ORFADIN Oral Suspension: Doses of 20 mL of ORFADIN oral suspension may cause headache, upset stomach and diarrhea due to the glycerol content. Consider switching patients to ORFADIN capsules. (5.3)

----------ADVERSE REACTIONS----------
Most common adverse reactions (>1%) are elevated tyrosine levels, thrombocytopenia, leukopenia, conjunctivitis, corneal opacity, keratitis, photophobia, eye pain, blepharitis, cataracts, granulocytopenia, epistaxis, pruritus, exfoliative dermatitis, dry skin, maculopapular rash and alopecia. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Swedish Orphan Biovitrum at 1-866-773-5274 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------
CYP2C9 Substrates: Potential for increased systemic exposure of these co-administered drugs, additional monitoring may be warranted. (7.1)

See 17 for PATIENT COUNSELING INFORMATION and FDA approved patient labeling.

Revised: 02/2017

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

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

2 DOSAGE AND ADMINISTRATION

2.1 Dosage

The recommended starting dosage of ORFADIN is 0.5 mg/kg orally twice daily. Titrate the dose for individual patients, as needed based on biochemical and/or clinical response. Adjust the dose of nitisinone individually. Monitor plasma and/or urine succinylacetone concentrations, liver function parameters and alpha-fetoprotein levels. If succinylacetone is still detectable one month after the start of nitisinone treatment, increase the nitisinone dosage to 0.75 mg/kg twice daily. A maximum dosage of 1 mg/kg orally twice daily may be needed based on the evaluation of all biochemical parameters.

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

In addition to the tests above, during the initiation of therapy or if there is a deterioration in the patient's condition, it may be necessary to follow all available biochemical parameters more closely (i.e. plasma succinylacetone, urine 5-aminolevulinate (ALA) and erythrocyte porphobilinogen (PBG)-synthase activity).

2.2 Preparation and Administration Instructions

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).

Administration of ORFADIN Capsules and Oral Suspension

- Maintain dietary restriction of tyrosine and phenylalanine when taking ORFADIN.
- *Capsules:* Take at least one hour before, or two hours after a meal *[see Clinical Pharmacology (12.3)]*. For patients who have difficulty swallowing the capsules and who are intolerant to the oral suspension *[see Warnings and Precautions (5.3)]*, the capsules may be opened and the contents suspended in a small amount of water, formula or apple sauce immediately before use.
- *Oral suspension:* Take without regard to meals *[see Clinical Pharmacology (12.3)]*.

3 DOSAGE FORMS AND STRENGTHS

- Capsules: 2 mg, 5 mg, 10 mg and 20 mg white capsules imprinted with "NTBC" followed by "2 mg", "5 mg", "10 mg" or "20 mg", indicating the actual amount of nitisinone in each capsule.
- Oral suspension: 4 mg/mL, a white, slightly viscous opaque suspension.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Elevated Plasma Tyrosine Levels, Ocular Symptoms, Developmental Delay and Hyperkeratotic Plaques

ORFADIN is an inhibitor of 4-hydroxyphenyl-pyruvate dioxygenase, an enzyme in the tyrosine metabolic pathway [*see Clinical Pharmacology (12.1)*]. Therefore, treatment with ORFADIN may cause an increase in plasma tyrosine levels in patients with HT-1. Maintain concomitant reduction in dietary tyrosine and phenylalanine while on ORFADIN treatment. Do not adjust ORFADIN dosage in order to lower the plasma tyrosine concentration. Maintain plasma tyrosine levels below 500 micromol/L. Inadequate restriction of tyrosine and phenylalanine intake can lead to elevations in plasma tyrosine levels and levels greater than 500 micromol/L may lead to the following:

- Ocular signs and symptoms including corneal ulcers, corneal opacities, keratitis, conjunctivitis, eye pain, and photophobia have been reported in patients treated with ORFADIN *[see Adverse Reactions (6.1)]*. Therefore, ophthalmologic examination including slit-lamp examination should be performed prior to initiating ORFADIN treatment. 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 reexamination and immediate measurement of the plasma tyrosine concentration.

- Variable degrees of intellectual disability and developmental delay. In patients treated with ORFADIN who exhibit an abrupt change in neurologic status, perform a clinical laboratory assessment including plasma tyrosine levels.

- Painful hyperkeratotic plaques on the soles and palms

In patients with HT-1 treated with dietary restrictions and ORFADIN who develop elevated plasma tyrosine levels, assess dietary tyrosine and phenylalanine intake.

5.2 Leukopenia and Severe Thrombocytopenia

In clinical trials, patients treated with ORFADIN and dietary restriction developed transient leukopenia (3%), thrombocytopenia (3%), or both (1.5%) *[see Adverse Reactions (6.1)]*. One patient who developed both leukopenia and thrombocytopenia improved after the dose of ORFADIN was decreased from 1 mg/kg to 0.5 mg/kg twice daily. No patients developed infections or bleeding as a result of the episodes of leukopenia and thrombocytopenia. Monitor platelet and white blood cell counts during ORFADIN therapy.

5.3 Risk of Adverse Reactions Due to Glycerol Content of ORFADIN Oral Suspension

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.

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

ORFADIN was studied in one open-label, uncontrolled study of 207 patients with HT-1, ages 0 to 21.7 years at enrollment (median age 9 months), who were diagnosed with HT-1 by the presence of succinylacetone in the urine or plasma. The starting dose of ORFADIN was 0.3 to 0.5 mg/kg twice daily, and the dose was increased in some patients to 1 mg/kg twice daily based on weight, biochemical, and enzyme markers. The recommended dose is 0.5 mg/kg to 1 mg/kg twice daily *[see Dosage and Administration (2.1)]*. Median duration of treatment was 22.2 months (range 0.1 to 80 months).

The most serious adverse reactions reported during ORFADIN treatment were thrombocytopenia, leukopenia, porphyria, and ocular/visual complaints associated with elevated tyrosine levels *[see Warnings and Precautions (5.1, 5.2)]*. 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/microL or lower. In 4 patients with thrombocytopenia, platelet counts gradually returned to normal (duration up to 47 days) without change in ORFADIN dose. No patients developed infections or bleeding as a result of the episodes of leukopenia 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%).

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

TABLE 1
Most Common Adverse Reactions*

Elevated tyrosine levels	>10%
Leukopenia	3%
Thrombocytopenia	3%
Conjunctivitis	2%
Corneal opacity	2%
Keratitis	2%
Photophobia	2%
Eye pain	1%
Blepharitis	1%
Cataracts	1%
Granulocytopenia	1%
Epistaxis	1%
Pruritus	1%
Exfoliative dermatitis	1%
Dry skin	1%
Maculopapular rash	1%
Alopecia	1%

*reported in at least 1% of patients

Adverse reactions reported in less than 1% of the patients, included death, seizure, brain tumor, encephalopathy, hyperkinesia, cyanosis, abdominal pain, diarrhea, enanthema, gastrointestinal hemorrhage, melena, elevated hepatic enzymes, liver enlargement, hypoglycemia, septicemia, and bronchitis.

7 DRUG INTERACTIONS

7.1 Interaction with CYP2C9 Substrates

If ORFADIN is co-administered with drugs that are metabolized by CYP2C9, additional monitoring may be warranted because of a potential for increased systemic exposure of these drugs *[see Clinical Pharmacology (12.3)]*. The risk is dependent upon the particular 2C9 substrate and its adverse reaction profile.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Limited data on nitisinone use in pregnant women are not sufficient to inform any drug associated risk. Animal reproduction studies have been conducted for nitisinone. In these studies, nitisinone was administered to mice and rabbits during organogenesis with oral doses of nitisinone up to 20 and 8 times respectively, the recommended human dose. In mice, nitisinone caused incomplete skeletal ossification of fetal bones and decreased pup survival at doses 0.4 times the recommended human dose, and increased gestational length at doses 4 times the recommended human dose. In rabbits, nitisinone caused maternal toxicity and incomplete skeletal ossification of fetal bones at doses 1.6 times the recommended human dose *[see Data]*.

The background risk of major birth defects and miscarriage for the indicated population are unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

Data

Animal Data

Reproduction studies have been performed in mice at oral doses of about 0.4, 4 and 20 times the recommended human dose (1 mg/kg/day) and in rabbits at oral doses of about 1.6, 4 and 8 times the recommended human dose based on the body surface area. In mice, nitisinone has been shown to cause incomplete skeletal ossification of fetal bones at 0.4, 4 and 20 times the recommended human dose, increased gestational length at 4 and 20 times the recommended human dose, and decreased pup survival at 0.4 times the recommended human dose based on the body surface area. In rabbits, nitisinone caused incomplete skeletal ossification of fetal bones at 1.6, 4 and 8 times the recommended human dose based on the body surface area.

8.2 Lactation

Risk Summary

There are no data on the presence of nitisinone in human milk, the effects on the breastfed infant, or the effects on milk production. 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. The development and health benefits of breastfeeding should be considered along with the mother's clinical need for ORFADIN and any potential adverse effects on the breastfed infant from ORFADIN or from the underlying maternal condition.

8.4 Pediatric Use

Pediatric patients with HT-1, ages birth to 17 years, have been treated with ORFADIN in one open-label, uncontrolled clinical study [*see Clinical Studies (14)]*. Monitoring of plasma and urine succinylacetone levels are recommended in the pediatric patients to ensure adequate control *[see Dosage and Administration (2.1)]*. A nutritionist skilled in managing children with inborn errors of metabolism should be employed to design a low-protein diet deficient in tyrosine and phenylalanine.

8.5 Geriatric Use

Clinical studies of nitisinone did not include any subjects aged 65 and over. No pharmacokinetic studies of nitisinone have been performed in geriatric patients. In general, dose selection for an elderly patient 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.

10 OVERDOSAGE

Accidental ingestion of ORFADIN by individuals eating normal diets not restricted in tyrosine and phenylalanine will result in elevated tyrosine levels. In healthy subjects given a single 1 mg/kg dose of nitisinone, the plasma tyrosine level reached a maximum of 1200 micromol/L at 48 to 120 hours after dosing. After a washout period of 14 days, the mean value of plasma tyrosine was still 808 micromol/L. Fasted follow-up samples obtained from volunteers several weeks later showed tyrosine values back to normal. There were no reports of changes in vital signs or laboratory data of any clinical significance. One patient reported sensitivity to sunlight. Hyper-tyrosinemia has been reported with ORFADIN treatment *[see Warnings and Precautions (5.1)]*.

11 DESCRIPTION

ORFADIN contains nitisinone, which is a hydroxyphenyl-pyruvate dioxygenase inhibitor indicated as an adjunct to dietary restriction of tyrosine and phenylalanine in the treatment of hereditary tyrosinemia type 1 (HT-1).

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.

Chemically, nitisinone is 2-(2-nitro-4-trifluoromethylbenzoyl) cyclohexane-1,3-dione, and the structural formula is:

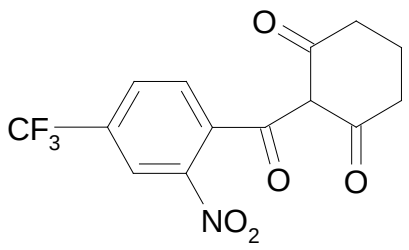

Figure 1. The molecular formula is $C_{14}H_{10}F_3NO_5$ with a relative mass of 329.23

Capsules: Hard, white-opaque capsule, marked as 2 mg, 5 mg, 10 mg or 20 mg strengths of nitisinone, intended for oral administration. Each capsule contains 2 mg, 5 mg, 10 mg or 20 mg nitisinone, plus pre-gelatinized starch. The capsule shell is gelatin and titanium dioxide and the imprint is an iron oxide.

Oral suspension: 4 mg/mL, a white, slightly viscous opaque 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).

12 CLINICAL PHARMACOLOGY

12.1 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 also 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 (5.1)]*.

12.3 Pharmacokinetics

No pharmacokinetic studies of nitisinone have been conducted in children or HT-1 patients.

The single-dose pharmacokinetics of nitisinone have been studied for both ORFADIN capsules and ORFADIN oral suspension in healthy subjects.

Absorption

Following administration of ORFADIN 30 mg under fasting conditions, the peak serum nitisinone concentration (C_{max}) occurred at approximately 3.5 hours postdose for the capsules and 0.38 hours postdose for the oral suspension. The pharmacokinetic parameters are shown in Table 2.

TABLE 2

Nitisinone Geometric Mean Pharmacokinetic Parameters in Healthy Subjects Following a Single Oral Dose of ORFADIN Under Fasting Conditions

Treatment	C_{max} (micromol/L) [range]	t_{max}* (h) [range]	AUC_{72h} (micromol·h/L) [range]
ORFADIN capsule (n=12)	10.2 [8.03 to 18.0]	3.50 [0.75 to 8.00]	403 [315 to 500]
ORFADIN oral suspension (n=12)	9.74 [7.78 to 20.3]	0.38 [0.25 to 4.00]	346 [264 to 456]

* presented as median [range]

Food Effect: No food effect study was conducted with ORFADIN capsules. For ORFADIN oral suspension, a high calorie (800 to 1000 calories) and high fat meal (approximately 50% of total caloric content) did not affect nitisinone total exposure (AUC_{72h}), but decreased the C_{max} by approximately 20% *[see Dosage and Administration (2.2)]*.

Distribution

In vitro binding of nitisinone to human plasma proteins is greater than 95% at 50 micromolar concentration.

Elimination

The mean terminal plasma half-life of nitisinone in healthy male subjects is 54 hours.

Excretion: Not known.

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

Drug Interaction Studies

Based on *in vitro* studies, there is a potential for nitisinone to inhibit CYP2C9 [*see Drug Interaction (7.1)*]. Nitisinone is not expected to inhibit CYP 1A2, 2C19, or 3A4 based on *in vitro* studies. The potential for nitisinone to inhibit CYP2D6 and CYP2E1 at the recommended dosage is unknown due to limited data.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

No long-term studies in animals have been performed to evaluate the carcinogenic potential of nitisinone. 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.

In a single dose-group study in rats given 100 mg/kg (12 times the recommended initial clinical dose 1 mg/kg per day based on relative body surface area), reduced litter size, decreased pup weight at birth, and decreased survival of pups after birth was demonstrated.

14 CLINICAL STUDIES

The efficacy and safety of ORFADIN in patients with HT-1 was evaluated in one open-label, uncontrolled study of 207 patients with HT-1, ages 0 to 22 years at enrollment (median age 9 months). Patients were diagnosed with HT-1 by the presence of succinylacetone in the urine or plasma. All patients were treated with ORFADIN at a starting dose of 0.6 to 1 mg/kg/day (i.e. 0.3 to 0.5 mg/kg twice daily), and the dose was increased in some patients to 2 mg/kg/day (i.e. 1 mg/kg twice daily) based on weight, liver and kidney function tests, platelet count, serum amino acids, urinary phenolic acid, plasma and urine succinylacetone, erythrocyte PBG-

Oral suspension: 4 mg/mL, a white, slightly viscous opaque suspension. The inactive ingredients are hydroxypropyl methylcellulose, glycerol, polysorbate 80, sodium benzoate, citric acid monohydrate, trisodium citrate dihydrate, strawberry aroma (artificial) and purified water.

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synthase, and urine 5-ALA. The median duration of treatment was 22 months (range less than 1 month to 80 months). Efficacy was assessed by comparison of survival and incidence of liver transplant to historical controls.

In this clinical study, for patients presenting with HT-1 younger than 2 months of age who were treated with dietary restriction and nitisinone, 2- and 4-year survival probabilities were 88% and 88%, respectively. Data from historical controls showed that patients treated with dietary restriction alone had 2- and 4-year survival probabilities of 29% and 29%, respectively. For patients presenting between 2 and 6 months of age who were treated with dietary restrictions and nitisinone, 2- and 4-year survival probabilities were 94% and 94%, respectively. Data for historical controls showed that patients treated with dietary restriction alone had 2- and 4-year survival probabilities of 74% and 60%, respectively.

The effects on urine and plasma succinylacetone, porphyrin metabolism, and urinary alpha-1-microglobulin were also assessed in this clinical study.

Urine succinylacetone was measured in 186 patients. In all 186 patients, urinary succinylacetone level decreased to less than 1 mmol/mol creatinine. The median time to normalization was 0.3 months. The probability of recurrence of abnormal values of urine succinylacetone was 1% at a nitisinone concentration of 37 micromol/L (95% confidence interval: 23, 51 micromol/L). Plasma succinylacetone was measured in 172 patients. In 150 patients (87%), plasma succinylacetone decreased to less than 0.1 micromol/L. The median time to normalization was 3.9 months.

Porphyria-like crisis were reported in 3 patients (0.3% of cases per year) during the clinical study. This compares to an incidence of 5 to 20% of cases per year expected as part of the natural history of the disorder. An assessment of porphyria-like crises was performed because these events are commonly reported in patients with HT-1 who are not treated with nitisinone.

Urinary alpha-1-microglobulin, a proposed marker of proximal tubular dysfunction, was measured in 100 patients at baseline. The overall median pretreatment level was 4.3 grams/mol creatinine. After one year of treatment in a subgroup of patients (N=100), overall median alpha-1-microglobulin decreased by 1.5 grams/mol creatinine. In patients 24 months of age and younger in whom multiple values were available (N=65), median alpha-1-microglobulin levels decreased from 5.0 to 3.0 grams/mol creatinine (reference value for age less than or equal to12 grams/mol creatinine). In patients older than 24 months in whom multiple values were available (N=35), median alpha-1-microglobulin levels decreased from 2.8 to 2 grams/mol creatinine (reference for age less than or equal to 6 grams/mol creatinine).

The long term effect of nitisinone on hepatic function was not assessed.

16 HOW SUPPLIED/STORAGE AND HANDLING

Capsules: White capsules marked in black with "NTBC" and identified as 2 mg, 5 mg, 10 mg or 20 mg strengths of nitisinone. The capsules are packed in a high density (HD) polyethylene container with a tamper-resistant low density (LD) polyethylene snap-on cap. Each bottle contains 60 capsules.

2 mg white capsules imprinted "NTBC 2 mg" in black ink, NDC 66658-102-60

5 mg white capsules imprinted "NTBC 5 mg" in black ink, NDC 66658-105-60

10 mg white capsules imprinted "NTBC 10 mg" in black ink, NDC 66658-110-60

20 mg white capsules imprinted "NTBC 20 mg" in black ink, NDC 66658-120-60

Store refrigerated at 2° to 8°C (36° to 46°F). Alternatively, patients/caregivers may store ORFADIN capsules at room temperature up to 25°C (77°F) for up to 45 days. If not used within 45 days, discard ORFADIN capsules.

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.

Oral suspension 4 mg/mL, NDC 66658-204-90

Store refrigerated at 2°C to 8°C (36°F to 46°F) prior to first use. Do not freeze. Store upright.

After first opening, store the product at room temperature (up to 25°C (77°F)) for up to 60 days. If not used within 60 days, discard unused portion. The discard after date should be noted on the bottle

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Instructions for Use).

Preparation and Administration Instructions *[see Dosage and Administration (2.2)]*
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).

Administration of ORFADIN Capsules and Oral Suspension

- Maintain dietary restriction of tyrosine and phenylalanine when taking ORFADIN.
- *Capsules:* Take at least one hour before, or two hours after a meal. For patients who have difficulty swallowing the capsules and for which the oral suspension is not suitable *[see Warnings and Precautions (5.3)]*, the capsules may be opened and the contents suspended in a small amount of water, formula or apple sauce immediately before use. Or, the oral suspension may be used instead.
- *Oral suspension:* Take without regard to meals.

Elevated Plasma Tyrosine Levels, Ocular Symptoms, Developmental Delay and Hyperkeratotic Plaques

- Inform patients that inadequate restriction may be associated with ocular signs and symptoms, intellectual disability and developmental delay, and painful hyperkeratotic plaques on the soles and palms. Advise patients and caregivers of the need to maintain dietary restriction of tyrosine and phenylalanine and to report any unexplained ocular, neurologic, or other symptoms promptly to their healthcare provider *[see Warnings and Precautions (5.1)]*.

Risk of Adverse Reactions Due to Glycerol Content of ORFADIN Oral Suspension

Advise patients receiving doses of greater than 20 mL of ORFADIN oral suspension that they may experience headache, upset stomach and diarrhea due to the glycerol component of the formulation and if they develop symptoms to report these to their healthcare provider *[see Warnings and Precautions (5.3)]*.

Manufactured by:
Apotek Produktion & Laboratorier AB, Sweden

Marketed by:
Sobi, Inc
890 Winter Street
Waltham, MA 02451

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2001014-