

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use HARLIKU safely and effectively. See full prescribing information for HARLIKU.

HARLIKU™ (nitisinone) tablets, for oral use
Initial U.S. Approval: 2002

INDICATIONS AND USAGE

HARLIKU is a hydroxyphenyl-pyruvate dioxygenase inhibitor indicated for the reduction of urine homogentisic acid (HGA) in adult patients with alkaptonuria (AKU). (1)

DOSAGE AND ADMINISTRATION

The recommended dosage of HARLIKU is 2 mg administered orally, once daily. (2.1)

DOSAGE FORMS AND STRENGTHS

Tablets: 2 mg. (3)

CONTRAINDICATIONS

None. (4)

WARNINGS AND PRECAUTIONS

Ocular Symptoms and Hyperkeratotic Plaques Due To Elevated Plasma Tyrosine Levels: Inadequate restriction of tyrosine and phenylalanine intake can lead to elevations in plasma tyrosine and levels above 500 micromol/L may lead to ocular signs and symptoms or painful hyperkeratotic plaques on the soles and palms. (5.1)

- Assess plasma tyrosine levels in patients presenting with ocular signs and symptoms. (5.1)

- Obtain slit-lamp examination prior to treatment and regularly thereafter. (5.1)
- Implement diet restriction and/or treatment interruption as appropriate. (5.1)

Leukopenia and Severe Thrombocytopenia: Monitor platelet and white blood cell counts. (5.2)

ADVERSE REACTIONS

Most common adverse reactions (>1%) are elevated tyrosine levels, keratitis and thrombocytopenia. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Cycle Pharmaceuticals Ltd at 1-855-831-5413 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

Sensitive CYP2C9 Substrates: Reduce dosage of co-administered drug metabolized by CYP2C9 by half. (7.1)

OAT1/OAT3 Substrates: Avoid concomitant use of HARLIKU with OAT1/OAT3 substrates. Concomitant use with OAT1/OAT3 substrates may increase the risk of adverse reactions related to the co-administered drug. (7.1)

See 17 for PATIENT COUNSELING INFORMATION

Revised: 6/2025

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

HARLIKU™ is indicated for the reduction of urine homogentisic acid (HGA) in adult patients with alkaptonuria (AKU).

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage

The recommended dosage of HARLIKU is 2 mg administered orally, once daily.

Administer HARLIKU with or without food [*see Clinical Pharmacology (12.3)*].

Missed Dose

If a dose of HARLIKU is missed, do not administer two doses at once to make up for a missed dose. Take the next dose at the scheduled time.

3 DOSAGE FORMS AND STRENGTHS

Tablets: 2 mg white to beige, round, flat tablets, which may display light yellow to brown speckles, debossed with “2” mg on one side and “L” on the other side.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Ocular Symptoms and Hyperkeratotic Plaques Due to Elevated Plasma Tyrosine Levels

Treatment with HARLIKU may cause elevated plasma tyrosine levels in patients with AKU. Tyrosine levels greater than 500 micromol/L may lead to the following:

- Ocular signs and symptoms including keratitis, corneal opacities, corneal irritation, corneal ulcers, conjunctivitis, eye pain, and photophobia. These ocular adverse reactions have been reported in patients treated with nitisinone [*see Adverse Reactions (6.1)*]. In a clinical trial in the AKU population, without dietary restriction and reported tyrosine levels > 500 micromol/L, both symptomatic and asymptomatic keratopathies have been observed. Perform a baseline ophthalmologic examination including slit-lamp examination prior to initiating HARLIKU treatment and regularly thereafter. Patients who develop photophobia, eye pain, or signs of inflammation such as redness, swelling, or burning of the eyes or tyrosine levels are > 500 micromol/L during treatment with HARLIKU should undergo slit-lamp re-examination and immediate measurement of the plasma tyrosine concentration.
- Painful hyperkeratotic plaques on the soles and palms.

There is no routine dietary restriction requirement for AKU patients taking HARLIKU. However, in patients who develop keratopathies, monitor plasma tyrosine levels, and implement a diet restricted in tyrosine and phenylalanine to keep the plasma tyrosine level below 500 micromol/L. Consider temporarily interrupting HARLIKU until resolution of symptoms.

5.2 Leukopenia and Severe Thrombocytopenia

In clinical trials, patients with hereditary tyrosinemia type 1 (HT-1) treated with another oral formulation of nitisinone and dietary restriction developed reversible leukopenia (3%), thrombocytopenia (3%), or both (1.5%). Ten percent of patients in Trial 1 developed thrombocytopenia [see *Adverse Reactions (6.1)*]. No patients developed infections or bleeding as a result of the episodes of leukopenia and thrombocytopenia. Monitor platelet and white blood cell counts during HARLIKU therapy.

6 ADVERSE REACTIONS

Serious and/or clinically significant adverse reactions described elsewhere in labeling include:

- Ocular Symptoms and Hyperkeratotic Plaques Due to Elevated Plasma Tyrosine Levels [see *Warnings and Precautions (5.1)*]
- Leukopenia and Severe Thrombocytopenia [see *Warnings and Precautions (5.2)*]

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 practice.

The safety of HARLIKU was evaluated in Trial 1, a three-year, open-label, randomized, no-treatment controlled trial in 40 patients with AKU. Patients were between 38 and 68 years of age (27 male, 13 female) [see *Clinical Studies (14)*]. Patients received either HARLIKU 2 mg orally once daily or no treatment [see *Dosage and Administration (2)*].

The serious adverse reactions reported with HARLIKU were ocular/visual complaints associated with elevated tyrosine levels (keratitis) [see *Warnings and Precautions (5.1)*]. Keratitis led to permanent treatment discontinuation in 1 (5%) treated patient.

The most common adverse reactions (>1%) reported in Trial 1 are summarized in TABLE 1.

TABLE 1. Most Common Adverse Reactions* in Patients with AKU Treated with Nitisinone**

Adverse Reactions	Nitisinone (N=20) n (%)	No Treatment (N=20) n (%)
Elevated tyrosine levels	19 (95)	0 (0)
Keratitis***	3 (15)	0 (0)
Thrombocytopenia	2 (10)	0 (0)

* reported in at least 1% of patients; ** another oral formulation of nitisinone;

*** keratitis also includes eye irritation, eye pain and photophobia.

7 DRUG INTERACTIONS

7.1 Effects of HARLIKU on Other Drugs

Sensitive CYP2C9 Substrates

Reduce the dosage of the co-administered drug metabolized by CYP2C9 by half. Additional dosage adjustments may be needed to maintain therapeutic drug concentrations where minimal concentration changes may lead to serious adverse reactions. See prescribing information for those drugs.

Nitisinone is a moderate CYP2C9 inhibitor. Nitisinone may increase exposure of co-administered drugs metabolized by CYP2C9 [see *Clinical Pharmacology (12.3)*].

OAT1/OAT3 Substrates

The concomitant use of HARLIKU with OAT1/OAT3 substrates may increase the risk of adverse reactions related to the co-administered drug. See prescribing information for those drugs.

Nitisinone is an OAT1/OAT3 inhibitor which can lead to increased exposure of the co-administered drug. [see *Clinical Pharmacology (12.3)*].

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Available data from published case reports with nitisinone use in pregnant women are insufficient to identify a drug-associated risk of major birth defects, miscarriage or other adverse maternal or fetal outcomes. 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 600 and 240 times respectively, the maximum recommended human daily dose (MRHDD) of 2 mg/day. In mice, nitisinone caused incomplete skeletal ossification of fetal bones and decreased pup survival at doses 12 times the MRHDD, and increased gestational length at doses 120 times the MRHDD. In rabbits, nitisinone caused maternal toxicity and incomplete skeletal ossification of fetal bones at doses 48 times the MRHDD (*see Data*).

The background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. 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

In an embryo-fetal development study in mice, nitisinone was administered via oral gavage to pregnant mice at dose levels of 12, 120 and 600 times the maximum recommended human daily dose (MRHDD) of 2 mg/day. Nitisinone caused incomplete skeletal ossification of fetal bones and decreased pup survival at doses 12 times the MRHDD and increased gestational length at doses 120 times the MRHDD.

In an embryo-fetal development study in rabbits, nitisinone was administered via oral gavage to pregnant rabbits at dose levels of 48, 120 and 240 times the MRHDD of 2 mg/day. Nitisinone caused maternal toxicity and incomplete skeletal ossification of fetal bones at doses 48 times the MRHDD.

In a single dose-group study in rats given 100 mg/kg (486 times the MRHDD of 2 mg/day), reduced litter size, decreased pup weight at birth, and decreased survival of pups after birth was demonstrated.

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 developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for HARLIKU and any potential adverse effects on the breastfed infant from HARLIKU or from the underlying maternal condition.

8.4 Pediatric Use

The safety and effectiveness of HARLIKU have not been established in pediatric patients with AKU.

8.5 Geriatric Use

There was 1 patient 65 years of age and older in the clinical studies for AKU [see *Clinical Studies (14)*]. Of the total number of HARLIKU-treated patients in these studies, 1 (2.5 %) were 65 years of age and older, while 0 (0%) were 75 years of age and older.

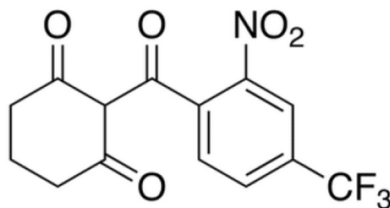
Clinical studies of HARLIKU did not include sufficient number of patients 65 years of age and older to determine whether they respond differently from younger adult patients.

11 DESCRIPTION

HARLIKU (nitisinone) is a hydroxyphenyl-pyruvate dioxygenase inhibitor.

Nitisinone occurs as a 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.

The chemical name of nitisinone is 2-(2-nitro-4-trifluoromethylbenzoyl) cyclohexane-1,3-dione. The molecular formula is $C_{14}H_{10}F_3NO_5$ and the molecular weight is 329.23. The structural formula is:



Each HARLIKU (nitisinone) tablet contains 2 mg of nitisinone to be administered orally. The inactive ingredients are glyceryl dibehenate and lactose monohydrate.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Nitisinone is a competitive inhibitor of hydroxyphenyl-pyruvate dioxygenase, an enzyme upstream of homogentisate 1,2-dioxygenase (HGD) in the tyrosine catabolic pathway.

12.2 Pharmacodynamics

In patients with AKU, HGA accumulates in various tissues and urine. In an open-label, single center, randomized, no-treatment controlled trial nitisinone treatment resulted in reduction of urinary HGA concentrations in patients with AKU [see *Clinical Studies (14)*].

Nitisinone exposure-response relationship and time course of pharmacodynamic response for the effectiveness have not been fully characterized.

Nitisinone inhibits catabolism of the amino acid tyrosine and can result in elevated plasma levels of tyrosine in patients with AKU. Treatment with nitisinone does not require routine dietary restriction in patients with AKU; however, patients who develop keratopathies should be monitored and dietary restriction of tyrosine and phenylalanine should be implemented [see *Warnings and Precautions (5.1)*].

12.3 Pharmacokinetics

The single-dose pharmacokinetics of nitisinone tablets have been studied in healthy adult subjects. Nitisinone pharmacokinetic parameters are presented as geometric mean [range] unless otherwise specified. Nitisinone maximum concentration (C_{max}) and area under the curve from time 0 to 120 hours (AUC_{0-120h}) were 1278 [780 to 1649] ng/mL and 77874 [42335 to 104211] ng•h/mL following oral administration of 10 mg (5 times the recommended dosage) nitisinone under fasting conditions.

Absorption

Nitisinone time to C_{max} (T_{max}) is 3.5 hours (median, ranging from 1 to 4 hours) following single oral administration of 10 mg (5 times the recommended dosage) nitisinone under fasting conditions.

Effect of Food: In a food effect study, a high-fat and high-calorie breakfast (973.6 cal distributed in carbohydrate 250.1 cal, proteins 157 cal, fat 566.5 cal) did not significantly affect the total exposure (AUC_{0-120h}) and C_{max} of nitisinone following single oral administration of 10 mg nitisinone (5 times the recommended dosage). The median T_{max} was delayed to 6 hours under fed conditions [see *Dosage and Administration (2)*].

Distribution

The arithmetic mean (SD) apparent volume of distribution of nitisinone is 8.2 (1.6) L in healthy subjects (n=23).

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

Elimination

The arithmetic mean (SD) terminal half-life of nitisinone is 59.3 (8.9) hours in healthy subjects (n=23). The mean (CV%) apparent plasma clearance in 18 healthy adults following multiple once daily doses of nitisinone

80 mg (40 times the recommended dosage) is 113 (16) mL/hr. The mean of the fraction of dose excreted renally as unchanged nitisinone in the urine ($f_e(\%)$) was 3% ($n=3$) following multiple oral doses of 80 mg (40 times the recommended dosage) daily in healthy subjects.

Metabolism

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

Excretion

The estimated mean (CV%) renal clearance of nitisinone was 0.003 L/h (25%).

Drug Interaction Studies

Clinical Studies

Nitisinone does not inhibit CYP2D6. Nitisinone is a moderate inhibitor of CYP2C9 and a weak inducer of CYP2E1 (TABLE 2). Nitisinone is an inhibitor of OAT1/3 (TABLE 2).

TABLE 2. Percent Change in AUC_{0-inf} and C_{max} for Co-administered Drugs in the Presence of Nitisinone in 18 Healthy Subjects

Co-administered Drug ^a	Dose of Co-administered Drug (Route of Administration)	Effect of Nitisinone on the Pharmacokinetics of Co-administered Drug ^b	
		AUC_{0-inf}	C_{max}
CYP2C9 Substrate Tolbutamide ^c	500 mg (oral)	131% ↑	16% ↑
CYP2E1 Substrate Chlorzoxazone	250 mg (oral)	27% ↓	18% ↓
OAT1/3 Substrate Furosemide	20 mg (intravenous)	72% ↑	12% ↑

↑ = Increased; ↓ = Decreased

^a The interacting drug was administered alone on Day 1 and together with nitisinone on Day 17.

^b Multiple doses of 80 mg nitisinone (40 times the recommended dosage) were administered daily alone from Day 3 to Day 16.

^c 16 subjects in Period 2 received nitisinone and tolbutamide while 18 subjects in Period 1 received nitisinone alone.

In Vitro Studies

CYP450 Enzymes: Nitisinone does not inhibit CYP1A2, 2C19, or 3A4. Nitisinone does not induce CYP1A2, 2B6 or 3A4/5.

Transporter Systems: Nitisinone does not inhibit P-gp, BCRP, OATP1B1, OATP1B3 and OCT2.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

The carcinogenic potential of nitisinone was assessed in a 26-week oral (gavage) carcinogenicity study in Tg.rasH2 mice. There were no drug-related neoplastic findings in male or female Tg.rasH2 mice at doses up to

100 mg/kg/day nitisinone (approximately 243 times the maximum recommended human daily dose of 2 mg/day).

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.

14 CLINICAL STUDIES

The effectiveness of HARLIKU was evaluated in an open-label, single center, randomized, no-treatment controlled trial in 40 adult patients diagnosed with AKU (NCT00107783). Patients received either HARLIKU at 2 mg orally once daily or no treatment for three years.

One patient in the HARLIKU group died after experiencing atrial fibrillation and had discontinued treatment one month prior to death, and 2 patients in the no treatment control group discontinued the study early. Among the 40 patients enrolled in the trial, 27 (67.5%) were male and 13 (32.5%) were female, ranging in age from 38 to 68 with a mean age of 51.7 years. Thirty-seven (92.5%) patients were White, 2 (5%) were Asian, and 1 (2.5%) was American Indian or Alaska Native. Thirty-nine (97.5%) patients were not Hispanic or Latino and 1 (2.5%) patient was Hispanic or Latino.

HARLIKU was effective at reducing levels of urinary HGA. The HARLIKU group had an average percent reduction from baseline of 88% (95% CI: 79, 97%) after 1 year of treatment, which was sustained through three years of treatment with an average percent reduction from baseline of 91% at year 3 (95% CI: 85, 97%). In contrast, the untreated controls had an average increase of 107% from baseline to year 1 (95% CI: 0, 216%) and 108% from baseline to year 3 (95% CI: 19, 198%).

16 HOW SUPPLIED/STORAGE AND HANDLING

How Supplied

HARLIKU (nitisinone) tablet is white to beige, round, flat which may display light yellow to brown speckles, debossed with the “strength” in mg on one side and “L” on the other side. Each tablet contains 2 mg nitisinone.

HARLIKU is supplied in a high-density polyethylene (HDPE) square bottle with a child-resistant tamper-evident polypropylene (PP) screw cap. Each bottle contains 60 tablets.

2 mg tablets: NDC 70709-112-60

Storage and Handling

Store HARLIKU tablets at room temperature between 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C and 30°C (59°F and 86°F) [see USP Controlled Room Temperature].

Pharmacist: Dispense in tight and light resistant container as defined in USP.

17 PATIENT COUNSELING INFORMATION

Ocular Symptoms and Hyperkeratotic Plaques Due to Elevated Plasma Tyrosine Levels

Advise the patient or caregiver to report any unexplained ocular or other symptoms promptly to their healthcare provider [see *Warnings and Precautions (5.1)*].

How Supplied/Storage and Handling

Advise the patient or caregiver to store HARLIKU in the container that it is dispensed in and keep the container tightly closed [*see How Supplied/Storage and Handling (16)*].

Manufactured by:

PCI Pharma Services
23-24 Tafarnaubach Industrial Estate
Tredegar, Gwent
NP22 3AA, United Kingdom

Rivopharm SA
Centro Insema
6928 Manno, Switzerland

Marketed by:

Cycle Pharmaceuticals Ltd
The Broers Building
21 JJ Thomson Ave
Cambridge, CB3 0FA, United Kingdom

Patented: see www.cyclepharma.com/product-patent-information



HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use NITYR safely and effectively. See full prescribing information for NITYR.

NITYR® (nitisinone) tablets, for oral use
Initial U.S. Approval: 2002

RECENT MAJOR CHANGES

Preparation and Administration Instructions. (2.3) 1/2024

INDICATIONS AND USAGE

NITYR is a hydroxyphenyl-pyruvate dioxygenase inhibitor indicated for the treatment of adult and pediatric patients with hereditary tyrosinemia type 1 (HT-1) in combination with dietary restriction of tyrosine and phenylalanine. (1)

DOSAGE AND ADMINISTRATION

- The recommended starting dosage is 0.5 mg/kg (actual body weight) administered orally twice daily. (2.1)
- Administer NITYR with or without food. (2.1)
- Maintain dietary restriction of tyrosine and phenylalanine when administering NITYR. (2.1)
- The recommended maintenance dosage of NITYR in patients 5 years of age and older who have undetectable serum and urine succinylacetone concentrations after a minimum of 4 weeks on a stable dosage of nitisinone, is 1 to 2 mg/kg once daily. (2.1)
- See the full prescribing information for dosage titration and monitoring. (2.2)
- See the full prescribing information for preparation and administration instructions. (2.2)

DOSAGE FORMS AND STRENGTHS

Tablets: 2 mg, 5 mg, 10 mg. (3)

CONTRAINDICATIONS

None. (4)

WARNINGS AND PRECAUTIONS

Ocular Symptoms, Developmental Delay and Hyperkeratotic Plaques Due To Elevated Plasma Tyrosine Levels: Inadequate restriction of tyrosine and phenylalanine intake can lead to elevations in plasma tyrosine and levels above 500 micromol/L may lead to ocular signs and symptoms, intellectual disability and developmental delay, or painful hyperkeratotic plaques on the soles and palms. (5.1)

- Do not adjust NITYR dosage in order to lower the plasma tyrosine concentration. (5.1)
- Obtain slit-lamp examination prior to treatment and regularly thereafter. Reexamine patients if symptoms develop or tyrosine levels are > 500 micromol/L. 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)

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 Cycle Pharmaceuticals Ltd at 1-855-831-5413 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

CYP2C9 Substrates: Increased systemic exposure of these co-administered drugs; reduce the dosage. Additional dosage adjustments may be needed to maintain therapeutic drug concentrations for narrow therapeutic index drugs. (7)

OAT1/OAT3 Substrates: Increased systemic exposure of these co-administered drugs; monitor for potential adverse reactions. (7)

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

Revised: 1/2024

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

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

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage

The recommended starting dosage of NITYR is 0.5 mg/kg (actual body weight) administered orally twice daily. Titrate the dose in each individual patient based on biochemical and/or clinical response.

Administer NITYR with or without food [*see Clinical Pharmacology (12.3)*].

Maintain dietary restriction of tyrosine and phenylalanine when administering NITYR.

Maintenance Dosage

The recommended maintenance dosage of NITYR in patients 5 years of age and older who have undetectable serum and urine succinylacetone concentrations after a minimum of 4 weeks on a stable dosage of nitisinone, is 1 to 2 mg/kg once daily [*see Clinical Pharmacology (12.2)*].

A maximum total daily dosage of 2 mg/kg may be needed based on the evaluation of all biochemical parameters.

Missed Dose

If a dose of NITYR is missed, do not administer two doses at once to make up for a missed dose. Take the next dose at the scheduled time.

2.2 Dosage Titration and Monitoring

Monitor plasma and/or urine succinylacetone concentrations, liver function parameters and alpha-fetoprotein levels.

Monitor all biochemical parameters more closely (i.e. plasma and/or urine succinylacetone, urine 5-aminolevulinate (ALA), and erythrocyte porphobilinogen (PBG)-synthase activity during initiation of therapy, when switching from twice daily to once daily dosing, or if there is a deterioration in the patient's condition.

If succinylacetone is still detectable in blood or urine 4 weeks after the start of nitisinone treatment, increase the NITYR dosage to 0.75 mg/kg twice daily. If the biochemical response is satisfactory (undetectable blood and/or urine succinylacetone), the dosage should be adjusted *only* according to body weight gain and not according to plasma tyrosine levels.

Maintain plasma tyrosine levels below 500 micromol/L by dietary restriction of tyrosine and phenylalanine intake [*see Warnings and Precautions (5.1)*]. In patients who develop plasma tyrosine levels above 500 micromol/L, assess dietary tyrosine and phenylalanine intake. Do not adjust the NITYR dosage in order to lower the plasma tyrosine concentration.

2.3 Preparation and Administration Instructions

For patients who have difficulty swallowing intact tablets, disintegrate NITYR in water and administer using an oral syringe. For patients who can swallow semi-solid foods, NITYR tablets can be crushed and mixed with applesauce.

Administration of NITYR with other liquids or foods has not been studied and is not recommended.

Preparation and Administration of NITYR with Water in an Oral Syringe:

Do not prepare more than two tablets at once within the same oral syringe.

If patient's dosage requires more than two tablets, follow the steps below using multiple oral syringes and prescribed number of tablets to achieve the required dose.

One Tablet

1. Remove the plunger from the 5-mL oral syringe and insert a single, intact tablet.
2. Replace the plunger and draw up 2.6 mL of room temperature water.
3. Cap the oral syringe and leave the oral syringe for at least the length of time below:
 - 15 minutes for a 2 mg tablet
 - 60 minutes for a 5 mg or 10 mg tablet
4. Turn the oral syringe up and down for at least 30 seconds to suspend the material.
5. Inspect the syringe to ensure the tablet has fully disintegrated. If the tablet is not fully disintegrated, leave the oral syringe for an additional 10 minutes. Do not administer unless the tablet has fully disintegrated. Before administration of the suspension, turn the oral syringe up and down for 30 seconds to ensure the particles are suspended.
6. Uncap the oral syringe and administer all the suspension into the patient's mouth. To facilitate full administration, avoid depressing the plunger to the end of the oral syringe and leave a gap between the plunger and the oral syringe.
7. Fill the oral syringe by drawing up 2 mL of water. Shake well and administer while this time fully depressing the plunger. If particles are still present in the syringe, repeat this step.

Two Tablets

1. Remove the plunger from the 5-mL oral syringe and insert two intact tablets.
2. Replace the plunger and draw up 5 mL of room temperature water.
3. Cap the oral syringe and leave it for at least the length of time below:
 - 15 minutes for 2 mg tablets
 - 60 minutes for 5 mg or 10 mg tablets

4. Turn the oral syringe up and down for at least 30 seconds to suspend the material.
5. Inspect the syringe to ensure the tablets have fully disintegrated. If the tablet is not fully disintegrated, leave the oral syringe for an additional 10 minutes. Do not administer unless the tablet has fully disintegrated. Before administration of the suspension, turn the oral syringe up and down for 30 seconds to ensure the particles are suspended.
6. Uncap the oral syringe and administer all the suspension into the patient's mouth. To facilitate full administration, avoid depressing the plunger to the end of the oral syringe and leave a gap between the plunger and the oral syringe.
7. Fill the oral syringe by drawing up 2 mL of water. Shake well and administer while this time fully depressing the plunger. If particles are still present in the syringe, repeat this step.

Storage Instructions for the NITYR with water in an Oral Syringe

The suspension can be stored at room temperature in the capped oral syringe, protected from direct sunlight for up to 24 hours after adding water to the tablets. Discard after 24 hours.

Preparation and Administration of NITYR Mixed in Applesauce

For patients who can swallow semi-solid food, NITYR can be crushed and mixed with applesauce.

1. Measure approximately one teaspoon of applesauce and transfer it into a clean container (e.g., clean glass).
2. Crush only 1 tablet at a time between two teaspoons forming a fine powder. Repeat this step if more than 1 tablet is needed.
3. Transfer the powder to the applesauce container ensuring all the powder is transferred and no powder residue remains on the teaspoon.
4. Mix the powder into the applesauce until the powder is well dispersed.
5. Administer the entire NITYR-applesauce mixture to the patient immediately or within 2 hours of mixing.
6. To ensure that there is not any remaining NITYR-applesauce mixture, add approximately one teaspoon of applesauce to the same container and administer to the patient.

Storage Instructions for the NITYR Mixed in Apple Sauce

The mixture can be stored at room temperature, out of direct sunlight, for up to 2 hours after adding the crushed tablets to the applesauce. Discard after 2 hours.

3 DOSAGE FORMS AND STRENGTHS

Tablets: 2 mg, 5 mg, and 10 mg white to beige, round, flat tablets, which may display light yellow to brown speckles, debossed with “L” on one side and the strength (“2” mg, “5” mg, or “10” mg), on the other side.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

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

Treatment with NITYR may cause elevated plasma tyrosine levels in patients with HT-1. 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. All of which have been reported in patients treated with nitisinone [see *Adverse Reactions (6.1)*]. 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. Therefore, perform a baseline ophthalmologic examination including slit-lamp examination prior to initiating NITYR treatment and regularly thereafter. Patients who develop photophobia, eye pain, or signs of inflammation such as redness, swelling, or burning of the eyes or tyrosine levels are > 500 micromol/L during treatment with NITYR 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 NITYR 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.

Maintain concomitant reduction in dietary tyrosine and phenylalanine while on NITYR treatment. In patients with HT-1 who are treated with NITYR and dietary restriction and develop elevated plasma tyrosine levels, assess dietary tyrosine and phenylalanine intake. Do not adjust NITYR dosage in order to lower the plasma tyrosine concentration. Maintain plasma tyrosine levels below 500 micromol/L.

5.2 Leukopenia and Severe Thrombocytopenia

In clinical trials, patients treated with another oral formulation of nitisinone and dietary restriction developed reversible leukopenia (3%), thrombocytopenia (3%), or both (1.5%) [see *Adverse Reactions (6.1)*]. No patients developed infections or bleeding as a result of the episodes of leukopenia and thrombocytopenia. Monitor platelet and white blood cell counts during NITYR therapy.

6 ADVERSE REACTIONS

Serious and or clinically significant adverse reactions described elsewhere in labeling include:

- Ocular Symptoms, Developmental Delay and Hyperkeratotic Plaques Due To Elevated Plasma Tyrosine Levels Due to Elevated Plasma Tyrosine Levels, [see *Warnings and Precautions (5.1)*]
- Leukopenia and Severe Thrombocytopenia [see *Warnings and Precautions (5.2)*]

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 practice.

The safety of NITYR has been established based on studies of another oral formulation of nitisinone in patients with HT-1 [see *Clinical Studies (14)*]. Below is a display of the adverse reactions of nitisinone in these studies.

Nitisinone was studied in one open-label, uncontrolled study of 207 patients with HT-1, ages 0 to 22 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 nitisinone 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 starting dosage of NITYR is 0.5 mg/kg twice daily [see *Dosage and Administration (2.1)*]. Median duration of treatment was 22 months (range 0.1 to 80 months).

The most serious adverse reactions reported during nitisinone 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 the nitisinone 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* in Patients with HT-1 Treated with Nitisinone**

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; ** another oral formulation of nitisinone

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

Nitisinone is a moderate CYP2C9 inhibitor, a weak CYP2E1 inducer and an inhibitor of OAT1/OAT3. TABLE 2 includes drugs with clinically significant drug interactions when administered concomitantly with NITYR and instructions for preventing or managing them.

TABLE 2. Clinically Significant Interactions Affecting Co-Administered Drugs

Sensitive CYP2C9 Substrates (e.g., celecoxib, tolbutamide) or CYP2C9 Substrates with a Narrow Therapeutic Index (e.g., phenytoin, warfarin)	
Clinical Impact	Increased exposure of the co-administered drugs metabolized by CYP2C9. [<i>see Clinical Pharmacology (12.3)</i>]
Prevention or Management	Reduce the dosage of the co-administered drugs metabolized by CYP2C9 drug by half. Additional dosage adjustments may be needed to maintain therapeutic drug concentrations for narrow therapeutic index drugs. See prescribing information for those drugs.
OAT1/OAT3 Substrates (e.g., adefovir, ganciclovir, methotrexate)	
Clinical Impact	Increased exposure of the interacting drug [<i>see Clinical Pharmacology (12.3)</i>]
Prevention or Management	Monitor for potential adverse reactions related to the co-administered drug.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Limited available data with nitisinone use in pregnant women are not sufficient to determine a drug-associated risk of adverse developmental outcomes. 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 initial dose of 1 mg/kg/day. In mice, nitisinone caused incomplete skeletal ossification of fetal bones and decreased pup survival at doses 0.4 times the recommended initial dose, and increased gestational length at doses 4 times the recommended initial dose. In rabbits, nitisinone caused maternal toxicity and incomplete skeletal ossification of fetal bones at doses 1.6 times the recommended initial 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 initial dose (1 mg/kg/day) and in rabbits at oral doses of about 1.6, 4 and 8 times the recommended initial 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 initial dose, increased gestational length at 4 and 20 times the recommended initial dose, and decreased pup survival at 0.4 times the recommended initial 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 initial 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 NITYR and any potential adverse effects on the breastfed infant from NITYR or from the underlying maternal condition.

8.4 Pediatric Use

The safety and effectiveness of nitisinone have been established for the treatment of HT-1 in combination with dietary restriction of tyrosine and phenylalanine in pediatric patients. Use of NITYR for this indication is supported by evidence from one open-label, uncontrolled clinical study conducted with another oral formulation of nitisinone in 207 patients with HT-1 ages 0 to 22 years (median age 9 months) [see *Clinical Studies (14)*].

8.5 Geriatric Use

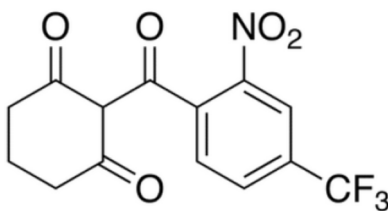
Clinical studies of nitisinone did not include any subjects aged 65 and over to determine whether they respond differently from younger subjects. No pharmacokinetic studies of nitisinone have been performed in geriatric patients. In general, dose selection for an elderly patient should be cautious reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy in this patient population.

11 DESCRIPTION

NITYR (nitisinone) is a hydroxyphenyl-pyruvate dioxygenase inhibitor.

Nitisinone occurs as a 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.

The chemical name of nitisinone is 2-(2-nitro-4-trifluoromethylbenzoyl) cyclohexane-1,3-dione. The empirical formula is $C_{14}H_{10}F_3NO_5$ and the molecular weight is 329.23. The structural formula is:



Each NITYR (nitisinone) tablet contains 2, 5 or 10 mg of nitisinone. Inactive ingredients are: glyceryl dibehenate, and lactose monohydrate. NITYR tablets are intended for oral administration.

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.

12.2 Pharmacodynamics

In a clinical study, patients with HT-1 were diagnosed by the presence of succinylacetone in urine or plasma and treated with another oral formulation of nitisinone [see *Clinical Studies (14)*]. In all 186 patients whose urine succinylacetone was measured, the urinary succinylacetone concentration decreased to less than 1 mmol/mol creatinine, the lower limit of quantitation. The median time to normalization of urine succinylacetone 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). In 87% (150/172) of patients whose plasma succinylacetone was measured, the plasma succinylacetone concentration decreased to less than 0.1 micromol/L, the lower limit of quantitation. The median time to normalization of plasma succinylacetone was 3.9 months.

In another study, comparing two dosing regimens of another oral formulation of nitisinone, succinylacetone was measured in urine and/or blood in 16 patients with HT-1 aged 5 years to 24 years. All study patients were on a stable nitisinone daily dosage (0.4 mg/kg/day to 1 mg/kg/day) during both study dosing regimens. After at least 4 weeks of twice daily dosing with nitisinone, both the urine and/or blood succinylacetone concentrations were below the limit of quantitation for the assay. Patients were then switched to once daily dosing with the same total daily dosage of nitisinone and blood and/or urine succinylacetone concentrations remained undetectable when measured following at least 4 weeks of treatment with once daily dosing.

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

The single-dose pharmacokinetics of nitisinone have been studied for NITYR tablets in healthy adult subjects.

Absorption

The pharmacokinetic characteristics following single oral administration of 10 mg NITYR under fasting conditions are shown in TABLE 3.

TABLE 3. Geometric Mean Pharmacokinetic Parameters in Healthy Subjects Following a Single Oral 10 mg Dose of NITYR Under Fasting Conditions

Treatment	C _{max} (ng/mL) [range]	T _{max} * (h) [range]	AUC _{0-120h} (ng•h/mL) [range]
Single 10 mg NITYR Tablet fasted (n=23)	1278 [780 to 1649]	3.5 [1.0 to 4.0]	77874 [42335 to 104211]

*presented as median [range]

Effect of Food: In a food effect study, a high-fat and high-calorie breakfast (973.6 cal distributed in carbohydrate 250.1 cal, proteins 157 cal, fat 566.5 cal) did not significantly affect the total exposure (AUC_{0-120h}) and C_{max} of nitisinone following single oral administration of 10 mg NITYR. The median T_{max} was delayed to 6 hours under fed conditions [see Dosage and Administration (2.2)].

Distribution

In vitro binding of nitisinone to human plasma proteins is greater than 95% at 50 micromolar concentration. For NITYR, the arithmetic mean (SD) apparent volume of distribution of nitisinone is 8.2 (1.6) L in healthy subjects (n=23).

Elimination

For NITYR, the arithmetic mean (SD) terminal half-life of nitisinone is 59.3 (8.9) hours in healthy subjects (n=23).

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

Excretion: Renal elimination of nitisinone is of minor importance, since the mean of the fraction of dose excreted as unchanged nitisinone in the urine (fe(%)) was 3.0% (n=3) following multiple oral doses of 80 mg daily in healthy subjects. The estimated mean (CV%) renal clearance of nitisinone was 0.003 L/h (25%).

Drug Interaction Studies

Nitisinone does not inhibit CYP2D6. Nitisinone is a moderate inhibitor of CYP2C9, and a weak inducer of CYP2E1 (TABLE 4). Nitisinone is an inhibitor of OAT1/3 (TABLE 4).

TABLE 4. Percent Change in AUC_{0-∞} and C_{max} for Co-administered Drugs in the Presence of Nitisinone in 18 Healthy Subjects

Co-administered Drug ^a	Dose of Co-administered Drug (Route of Administration)	Effect of Nitisinone on the Pharmacokinetics of Co-administered Drug ^b	
		AUC _{0-∞}	C _{max}
CYP2C9 Substrate Tolbutamide ^c	500 mg (oral)	131% ↑	16% ↑
CYP2E1 Substrate Chlorzoxazone	250 mg (oral)	27% ↓	18% ↓
OAT1/3 Substrate Furosemide	20 mg (intravenous)	72% ↑	12% ↑

↑ = Increased; ↓ = Decreased

^a The interacting drug was administered alone on Day 1 and together with nitisinone on Day 17.

^b Multiple doses of 80 mg nitisinone were administered daily alone from Day 3 to Day 16.

^c 16 subjects in Period 2 received nitisinone and tolbutamide while 18 subjects in Period 1 received nitisinone alone.

In Vitro Studies Where Drug Interaction Potential Was Not Further Evaluated Clinically

In vitro studies showed that nitisinone does not inhibit CYP1A2, 2C19, or 3A4. Nitisinone does not induce CYP1A2, 2B6 or 3A4/5. Nitisinone does not inhibit P-gp, BCRP, OATP1B1, OATP1B3 and OCT2-mediated transports at therapeutically relevant concentrations.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

The carcinogenic potential of nitisinone was assessed in a 26-week oral (gavage) carcinogenicity study in Tg.rasH2 mice. There were no drug-related neoplastic findings in male or female Tg.rasH2 mice at doses up to 100 mg/kg/day nitisinone (approximately 8.1 times the recommended initial dose of 1 mg/kg/day on a body surface area basis).

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 (16.2 times the recommended initial dose of 1 mg/kg/day on a body surface area basis), reduced litter size, decreased pup weight at birth, and decreased survival of pups after birth was demonstrated.

14 CLINICAL STUDIES

The safety and efficacy of NITYR have been established based on studies of another oral formulation of nitisinone in patients with HT-1. Below is a display of the results of these studies.

The efficacy and safety of nitisinone 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 nitisinone at a starting dose of 0.3 to 0.5 mg/kg orally twice daily, and the dose was increased in some patients to 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- 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.

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 presenting with HT-1 younger than 2 months of age treated with dietary restriction alone had 2- and 4-year survival probabilities of 29% and 29%, respectively. For patients presenting between 2 months 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 presenting with HT-1 between 2 months and 6 months of age treated with dietary restriction alone had 2- and 4-year survival probabilities of 74% and 60%, respectively.

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

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 to 3 grams/mol creatinine (reference value for age less than or equal to 12 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).

16 HOW SUPPLIED/STORAGE AND HANDLING

How Supplied

NITYR (nitisinone) tablet is white to beige, round, flat which may display light yellow to brown speckles, debossed with the “strength” in mg on one side and “L” on the other side. Each tablet contains 2, 5 or 10 mg nitisinone.

NITYR is supplied in a high-density polyethylene (HDPE) square bottle with a child-resistant tamper-evident polypropylene (PP) screw cap. Each bottle contains 60 tablets.

2 mg tablets: NDC 70709-002-60

5 mg tablets: NDC 70709-005-60

10 mg tablets: NDC 70709-000-60

Storage and Handling

Store NITYR tablets at room temperature between 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C and 30°C (59°F and 86°F) [see USP Controlled Room Temperature].

Pharmacist: Dispense in tight and light resistant container as defined in USP.
Dispense 5-mL oral syringe with a cap to use for preparation.

17 PATIENT COUNSELING INFORMATION

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

Dosage and Administration Instructions

Advise the patient or caregiver to:

- Combine NITYR with dietary restriction of tyrosine and phenylalanine.
- Take NITYR with or without food.
- Disintegrate the tablet(s) in water if patient has difficulty swallowing intact tablet(s), or if patient can swallow semi-solid foods, crush the tablet(s) and mix with applesauce.

[see Dosage and Administration (2)]

How Supplied/Storage and Handling

Advise the patient or caregiver to store NITYR in the container that it is dispensed in and keep the container tightly closed *[see How Supplied/Storage and Handling (16)]*.

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

Advise the patient or caregiver that inadequate dietary restriction may be associated with ocular signs and symptoms, intellectual disability and developmental delay, and painful hyperkeratotic plaques on the soles and palms. Additionally, advise the patient or caregiver 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)]*.

Manufactured by:

PCI Pharma Services
23-24 Tafarnaubach Industrial Estate
Tredegar, Gwent
NP22 3AA, United Kingdom

Rivopharm SA
Centro Insema
6928 Manno, Switzerland

Marketed by:

Cycle Pharmaceuticals Ltd
The Broers Building
21 JJ Thomson Ave
Cambridge, CB3 0FA, United Kingdom

Patented: see www.cyclepharma.com/product-patent-information



INSTRUCTIONS FOR USE
NITYR® (ni-TIR)
(nitisinone)
tablets, for oral use

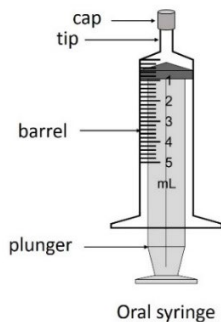
This Instructions for Use contains information on how to take NITYR tablets using an oral syringe or mixed in applesauce.

Read this Instructions for Use before you start giving or taking NITYR and each time you get a refill, since there may be new information. This information does not take the place of talking to your healthcare provider about your medical condition or your treatment.

- People who have a problem swallowing NITYR tablets whole, including children, can take NITYR tablets mixed with water in an oral (by mouth) syringe or crushed and mixed with applesauce. NITYR tablets should not be mixed in any other liquid or food.
- Follow the diet restrictions for tyrosine and phenylalanine that your healthcare provider has given you during treatment with NITYR.
- NITYR can be taken with or without food.

Important Information You Need to Know Before Taking NITYR Using an Oral Syringe

- **Prepare only 1 or 2 NITYR tablets** in an oral syringe at one time.
- Each tablet is white to beige in color and can have yellow to brown tiny specks.
- Use a 5 mL oral syringe **with a cap** (see below) to prepare NITYR tablets in an oral syringe. Ask your pharmacist for your oral syringe. You may need more than one 5 mL oral syringe if you take more than 2 NITYR tablets for your prescribed dose.
- Use only room temperature water to prepare NITYR tablets in an oral syringe.
- Wash your hands well before preparing NITYR tablets using an oral syringe.
- Talk to your healthcare provider or pharmacist if you have questions about NITYR tablets or how to use the oral syringe. You can also contact CYCLE VITA by calling the United States (U.S.) toll free phone number 1-888-360-8482.

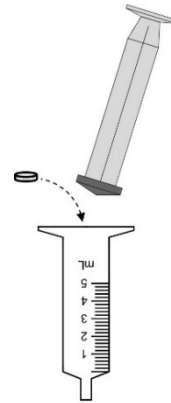


Before preparing NITYR using an oral syringe

Lay out the prescribed number of NITYR tablets and syringes for your dose. Place the tablet or tablets on a clean flat surface.

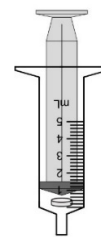
How to prepare and take 1 NITYR tablet using a 5 mL oral syringe:

Step 1. Remove the cap from the 5 mL oral syringe.



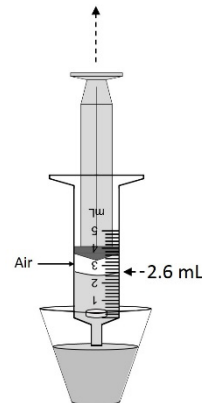
A

Step 2. Remove the plunger from the oral syringe and place 1 whole NITYR tablet inside the oral syringe (See Figure A).



B

Step 3. Replace the plunger (See Figure B).

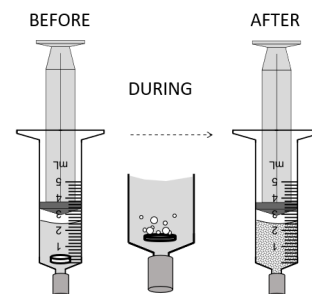


C

Step 4. Draw up **2.6 mL** of room temperature water into the oral syringe. Each line on the barrel of the syringe is 0.2 mL. There may be some air in the oral syringe. Leave the air in the oral syringe (See Figure C).

Step 5. Replace the cap on the oral syringe and note the time. Let the oral syringe sit for at least the length of time below:

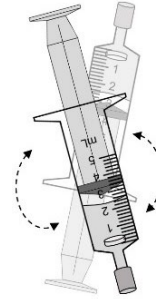
- **15 minutes** for a 2 mg tablet
 - **60 minutes** for a 5 mg or 10 mg tablet
- (See Figure D)



D

Step 6. Turn the oral syringe up and down for at least 30 seconds (See Figure E).

30 seconds



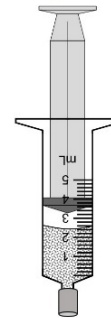
E

Step 7. Check the oral syringe to see if the NITYR tablet has broken apart into very small pieces and the pieces are evenly spread through the water (suspension) (See Figure F). Do not take the suspension if there are any large pieces of the NITYR tablet in the suspension or if there are any pieces of the tablet that are not evenly spread through the water.

If there are any pieces of the tablet that are not evenly spread through the water, let the oral syringe sit for 10 minutes.

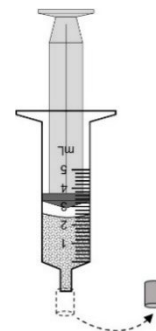
Before giving the suspension, turn the oral syringe up and down for 30 seconds to continue to spread the pieces of NITYR tablet in the suspension.

small pieces



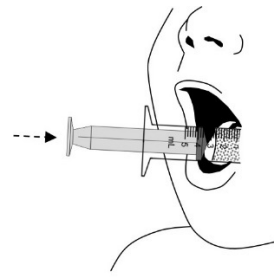
F

Step 8. Remove the cap from the oral syringe (See Figure G).



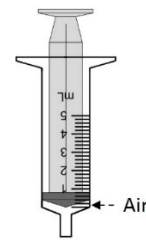
G

Step 9. Place the tip of the oral syringe in the mouth. If giving to a child, place the tip of the oral syringe along the inner cheek of the child's mouth (See Figure H).



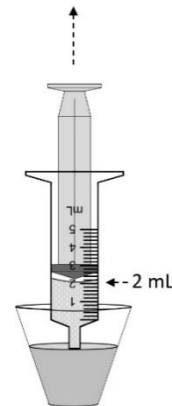
H

Step 10. While keeping the oral syringe in the mouth, slowly push down on the plunger until a small amount of air is left in the oral syringe, between the plunger and the tip of the oral syringe (See Figure I). Do not press the plunger all the way down to the end of the syringe.



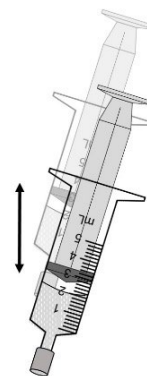
I

Step 11. Draw up an additional 2 mL of water into the oral syringe (See Figure J).



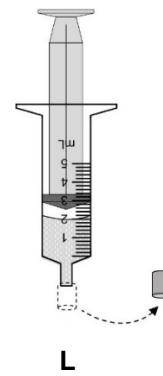
J

Step 12. Replace the cap on the oral syringe. Shake well to spread the remaining tablet pieces evenly through the water in the oral syringe (See Figure K).

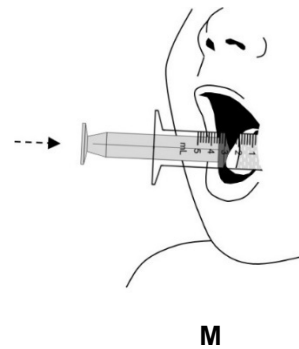


K

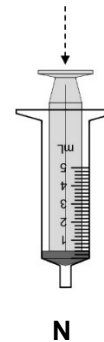
Step 13. Remove the cap from the oral syringe (See Figure L).



Step 14. Place the tip of the oral syringe in the mouth. If giving to a child, place the tip of the oral syringe along the inner cheek of the child's mouth (See Figure M).



Step 15. While keeping the oral syringe in the mouth, slowly push down on the plunger until the oral syringe is empty (See Figure N). In case any pieces of the tablet are still present in the oral syringe, repeat steps 11 through 15.



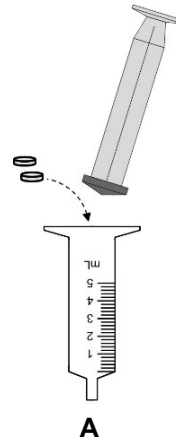
Step 16. After use, remove the plunger from the syringe barrel. Rinse the syringe and the plunger with water after each use and let it dry. Do not replace the plunger into the barrel of the oral syringe until ready to use again to allow it to dry. Do not throw away the oral syringe or plunger.

If you are not taking the water and NITYR tablet suspension as soon as it is prepared, complete steps 1 through 5. When you are ready to take the suspension, complete steps 6 through 16.

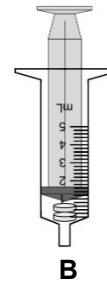
How to prepare and take 2 NITYR tablets using a 5 mL oral syringe:

Step 1. Remove the cap from the 5 mL oral syringe.

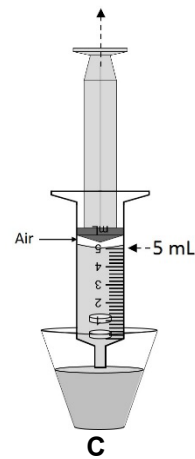
Step 2. Remove the plunger from the oral syringe and place 2 whole NITYR tablets inside the oral syringe (See Figure A).



Step 3. Replace the plunger (See Figure B).



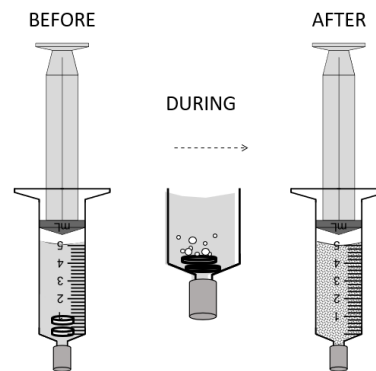
Step 4. Draw up 5 mL of room temperature water into the oral syringe. Each line on the barrel of the syringe is 0.2 mL. There may be some air in the oral syringe. Leave the air in the oral syringe (See Figure C).



Step 5. Replace the cap on the oral syringe and note the time. Let the oral syringe sit for at least the length of time below:

- **15 minutes** for 2 mg tablets
- **60 minutes** for 5 mg or 10 mg tablets

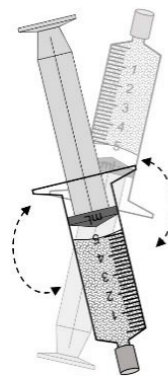
(See Figure D)



D

Step 6. Turn the oral syringe up and down for at least 30 seconds (See Figure E).

30 seconds



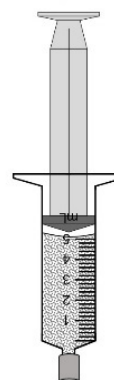
E

Step 7. Check the oral syringe to see if the NITYR tablets have broken apart into very small pieces and the pieces are evenly spread through the water (suspension) (See Figure F). Do not take the suspension if there are any large pieces of the NITYR tablets in the suspension or if there are any pieces of the tablets that are not evenly spread through the water.

If there are any pieces of the tablets that are not evenly spread through the water, let the oral syringe sit for 10 minutes.

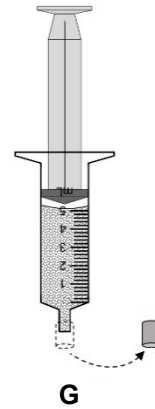
Before giving the suspension, turn the oral syringe up and down for 30 seconds to continue to spread the pieces of NITYR tablets in the suspension.

small pieces

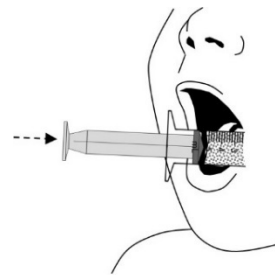


F

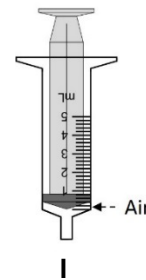
Step 8. Remove the cap from the oral syringe (See Figure G).



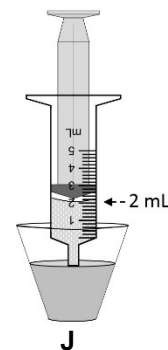
Step 9. Place the tip of the oral syringe in the mouth. If giving to a child, place the tip of the oral syringe along the inner cheek of the child's mouth (See Figure H).



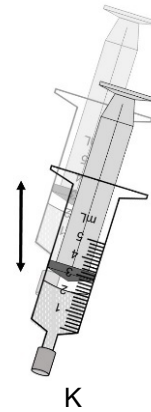
Step 10. While keeping the oral syringe in the mouth, slowly push down on the plunger until a small amount of air is left in the oral syringe, between the plunger and the tip of the oral syringe (See Figure I). Do not press all the way down on the plunger.



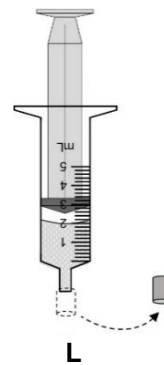
Step 11. Draw up 2 mL of water into the oral syringe (See Figure J).



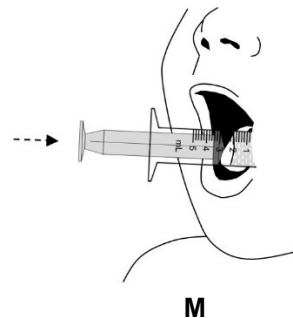
Step 12. Replace the cap on the oral syringe. Shake well to spread the remaining tablet pieces evenly through the water in the oral syringe (See Figure K).



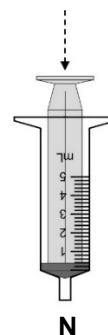
Step 13. Remove the cap from the oral syringe (See Figure L).



Step 14. Place the tip of the oral syringe in the mouth. If giving to a child, place the tip of the oral syringe along the inner cheek of the child's mouth (See Figure M).



Step 15. While keeping the oral syringe in the mouth, slowly push down on the plunger until the oral syringe is empty (See Figure N). In case any pieces of the tablets are still present in the oral syringe, repeat steps 11 through 15.



Step 16. After use, remove the plunger from the oral syringe barrel. Rinse the oral syringe with water after each use and let it dry. Do not replace the plunger into the barrel of the oral syringe until ready to use again to allow it to dry. Do not throw away the oral syringe.

If you are not taking the water and NITYR tablets suspension as soon as it is prepared, complete steps 1 through 5. When you are ready to take the suspension, complete steps 6 through 16.

How to prepare and take more than 2 NITYR tablets using an oral syringe:

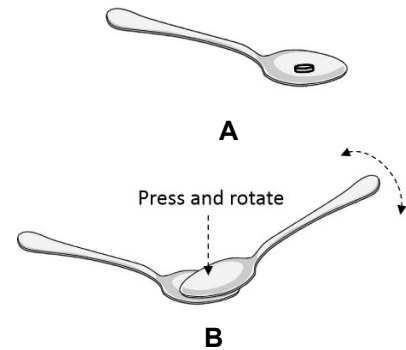
If more than two NITYR tablets are needed for the prescribed dose follow the instructions for “*How to prepare and take 1 NITYR tablet using an oral syringe*” and “*How to prepare and take 2 NITYR tablets using an oral syringe*” until you get your prescribed dose. **You should not** add more than 2 tablets to one syringe at a time.

How to prepare and take NITYR tablets in applesauce:

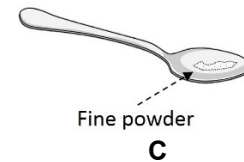
- Wash your hands well before preparing NITYR tablets in applesauce.
- Crush only 1 NITYR tablet at a time.

Step 1. Measure about 1 teaspoon of applesauce and put it into a clean container, such as a glass or bowl.

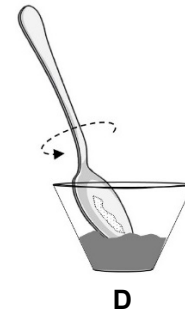
Step 2. Place 1 NITYR tablet onto a metal teaspoon (See Figure A).



Step 3. Crush 1 tablet at a time between two spoons (See Figure B) until the tablet is crushed to a fine powder (See Figure C).

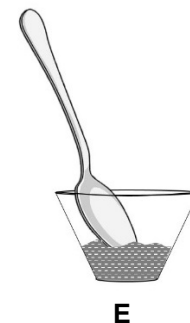


Step 4. Carefully place all of the NITYR tablet powder from the teaspoon into the clean container of applesauce. Be sure that no tablet powder remains on the teaspoon (See Figure D).

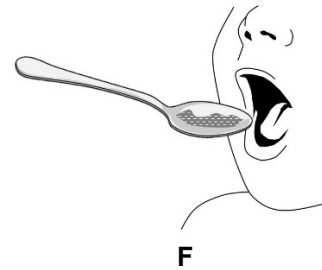


Step 5. If the prescribed dose is more than 1 tablet, repeat Steps 2 and 3, placing all of the NITYR tablet powder together in the container with the applesauce. You do not need to add more applesauce at this time if you take more than 1 tablet.

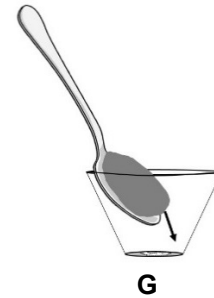
Step 6. Stir the NITYR tablet powder and the applesauce until all of the tablet powder is mixed well in the applesauce (See Figure E).



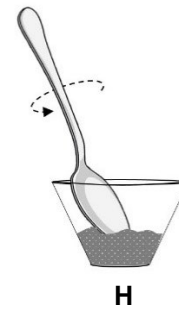
Step 7. Remove the NITYR tablet powder and applesauce mixture from the container using a teaspoon and swallow the mixture right away or within 2 hours of mixing (See Figure F). Repeat this step until no mixture is left in the container.



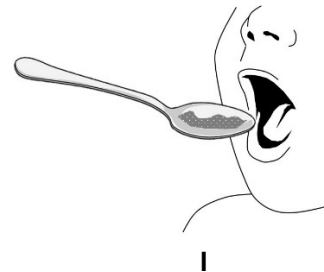
Step 8. Measure another 1 teaspoon of applesauce and place it in the container used to mix the NITYR tablet powder and applesauce (See Figure G).



Step 9. Stir the fresh applesauce with the remaining NITYR tablet powder and applesauce mixture until they are mixed well (See Figure H).



Step 10. Remove the NITYR tablet and applesauce mixture from the container using a teaspoon and swallow the mixture right away (See Figure I). Repeat this step until no mixture or powder is left in the container.



Storing NITYR

- NITYR tablets do not need to be refrigerated.
- Store NITYR tablets at room temperature between 68°F to 77°F (20°C to 25°C).
- Store NITYR tablets in the container that it comes in and keep the container tightly closed.
- Keep NITYR tablets and NITYR that has been prepared in an oral syringe with water or in applesauce out of direct sunlight.

After adding water to the tablet in the oral syringe you can keep NITYR tablet suspension at room temperature for **24 hours**. Store the suspension in the oral syringe with the cap on and out of direct sunlight until use. The suspension does not need to be refrigerated. Throw away any suspension that is not used within 24 hours after adding water to the tablets in the oral syringe. Empty the syringe in the drain and throw away (dispose of) the syringe by placing it in a trash can.

Take the NITYR tablet and applesauce mixture **within 2 hours** after adding the NITYR tablet powder to the applesauce. Store the NITYR tablet and applesauce mixture at room temperature and out of direct sunlight until use. The mixture does not need to be refrigerated. Throw away any mixture that is not used within 2 hours after mixing in a trash can.

Keep NITYR and all medicines out of the reach of children.

What are the ingredients in NITYR?

Active ingredient: nitisinone

Inactive ingredients: glyceryl dibehenate and lactose monohydrate

Talk to your healthcare provider or pharmacist if you have questions about NITYR tablets or how to use the oral syringe. You can also contact the CYCLE VITA on the U.S. toll free number 1-888-360-8482.

For more information visit: www.nityr.us

Manufactured by:

PCI Pharma Services

23-24 Tafarnaubach Industrial Estate

Tredegar, Gwent

NP22 3AA, United Kingdom

Rivopharm SA

Centro Insema

6928 Manno, Switzerland

Marketed by:

Cycle Pharmaceuticals Ltd

The Broers Building

21 JJ Thomson Ave

Cambridge, CB3 0FA, United Kingdom



This Instructions for Use has been approved by the U.S. Food and Drug Administration.

Revised: 1/2024