

PRODUCT MONOGRAPH
INCLUDING PATIENT MEDICATION INFORMATION

Pr NITISINONE TABLETS

Nitisinone Tablets
2, 5 and 10 mg

ATC Code: A16AX04

Various alimentary tract and metabolism products

Cycle Pharmaceuticals Ltd.
Bailey Grundy Barrett Building,
Little St Mary's Lane,
Cambridge
Cambridgeshire
CB2 1RR
UK
www.cyclepharma.com

Date of Preparation:
October 10, 2019

Imported and distributed by:
C.R.I.,
Unit #400, 3455 North Service Road
Burlington, Ontario
L7N 3G2
Canada

Submission Control No: 224962

Table of Contents

PART I: HEALTH PROFESSIONAL INFORMATION.....	3
SUMMARY PRODUCT INFORMATION	3
INDICATIONS AND CLINICAL USE.....	3
CONTRAINDICATIONS	3
WARNINGS AND PRECAUTIONS.....	3
ADVERSE REACTIONS.....	6
DRUG INTERACTIONS	9
DOSAGE AND ADMINISTRATION	10
OVERDOSAGE	12
ACTION AND CLINICAL PHARMACOLOGY	12
STORAGE AND STABILITY	14
DOSAGE FORMS, COMPOSITION AND PACKAGING	14
PART II: SCIENTIFIC INFORMATION	15
PHARMACEUTICAL INFORMATION.....	15
CLINICAL TRIALS.....	15
DETAILED PHARMACOLOGY	16
TOXICOLOGY	17
PART III: PATIENT MEDICATION INFORMATION	18

PrNITISINONE TABLETS

Nitisinone Tablets
2, 5 and 10 mg

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Oral	Tablet, 2 mg, 5 mg, and 10 mg	Lactose monohydrate. <i>For a complete listing see DOSAGE FORMS, COMPOSITION AND PACKAGING.</i>

INDICATIONS AND CLINICAL USE

Nitisinone Tablets are indicated for the treatment of hereditary tyrosinemia type 1 (HT-1) in combination with dietary restriction of tyrosine and phenylalanine.

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

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

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

CONTRAINDICATIONS

- Patients who are hypersensitive to nitisinone or to any ingredient in the formulation or component of the container. For a complete listing, see the **DOSAGE FORMS, COMPOSITION AND PACKAGING** section.
- Mothers receiving Nitisinone Tablets should not breast feed (see **Nursing Women**).

WARNINGS AND PRECAUTIONS

Endocrine and Metabolism

Elevated plasma tyrosine levels

Treatment with Nitisinone Tablets may cause an increase in plasma tyrosine levels in patients

with HT-1. Patients must maintain concomitant reduction in dietary tyrosine and phenylalanine while on Nitisinone Tablets treatment. Plasma tyrosine levels should be maintained below 500 µmol/L, since levels greater than 500 µmol/L may increase the risk of ocular signs and symptoms.

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

Hematologic

Leukopenia and thrombocytopenia

Leukopenia and thrombocytopenia have been observed during treatment with nitisinone (see **ADVERSE REACTIONS**). Platelet and white blood cell counts should be monitored regularly during therapy with Nitisinone Tablets (see **WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Tests**).

Hepatic/Biliary/Pancreatic

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

Neurologic

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

Ophthalmologic

Ocular signs and symptoms including corneal ulcers, corneal opacities, keratitis, conjunctivitis, eye pain, and photophobia have been reported in patients treated with nitisinone (see **ADVERSE REACTIONS**). It is recommended that ophthalmologic assessment, including slit-lamp examination, is performed prior to initiating treatment with Nitisinone Tablets. Patients who develop photophobia, eye pain, or signs of inflammation such as redness, swelling, or burning of the eyes during treatment with Nitisinone Tablets should undergo slit-lamp re-examination and immediate measurement of plasma tyrosine concentration (see **ADVERSE REACTIONS**).

Special Populations

Pregnant Women

Nitisinone Tablets should be used in pregnancy only when the benefits of continued treatment are judged to outweigh the risks.

There are no adequate and well-controlled studies with nitisinone in pregnant women. Studies in animals have shown reproductive toxicity (see **TOXICOLOGY**).

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

Nursing Women

Because of the potential for serious adverse reactions to nitisinone in nursing infants, mothers taking Nitisinone Tablets should not breast-feed (see **CONTRAINDICATIONS**).

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

Pediatrics (<18 years of age)

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

Geriatrics (>65 years of age)

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

Monitoring and Laboratory Tests

Succinylacetone, 5-ALA, and erythrocyte PBG-synthase

Monitor plasma and/or urine succinylacetone levels, and titrate the dosage of Nitisinone Tablets as necessary (see **DOSAGE AND ADMINISTRATION**). Consider also monitoring urine 5-aminolevulinic acid (ALA) and erythrocyte porphobilinogen (PBG)-synthase activity, particularly when initiating therapy or in the case of deterioration in the patient's condition, situations when biochemical parameters should be followed more closely.

Plasma tyrosine levels

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

Liver monitoring

Liver function parameters and serum alpha-fetoprotein concentrations should be monitored regularly (see **WARNINGS AND PRECAUTIONS, Hepatic/Biliary/Pancreatic**).

Platelets and white blood cells

Platelet and white blood cell counts should be monitored regularly during therapy with Nitisinone Tablets.

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

ADVERSE REACTIONS

Adverse Drug Reaction Overview

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

Clinical Trial Adverse Drug Reactions

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

The *main analysis* of the open-label, uncontrolled study consisted of 207 patients with HT-1, ages 0 to 21.7 years at enrolment (median age 9 months), with a median treatment duration of 22.2 months. The starting dose of nitisinone was 0.6 to 1 mg/kg/day, and was increased to 2 mg/kg/day in some patients, based on weight, biochemical, and enzyme markers (see **CLINICAL TRIALS**).

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

Table 1: Common Adverse Reactions ($\geq 1\%$) Reported in an Open-Label, Uncontrolled Trial

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

The most serious adverse events reported with nitisinone treatment in the *main NTBC analysis* were thrombocytopenia, leukopenia, porphyria, and ocular/visual complaints associated with elevated tyrosine levels (see **WARNINGS AND PRECAUTIONS**). Most patients with ocular/visual events had transient symptoms lasting less than one week, while 6 patients had symptoms lasting 16 to 672 days. Six patients had thrombocytopenia, with platelet counts 30,000/ μL or lower in 3 patients. In 4 patients with thrombocytopenia, platelet counts returned to normal without change in nitisinone dose. In 2 patients, platelet count returned to normal 2 weeks to 5 months after nitisinone treatment was discontinued. No patients developed infections or bleeding as a result of the episodes of leukopenia and thrombocytopenia.

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

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

Adverse events reported in less than 1% of the patients in the open-label, uncontrolled trial, regardless of causality assessment, included:

Blood and lymphatic system disorders: Anemia

Cardiac disorders: Cyanosis

Endocrine disorders: Hypoglycemia

Eye disorders: Retinal disorders

Gastrointestinal disorders: Abdominal pain, diarrhea, enanthema, gastritis, gastroenteritis, gastrointestinal hemorrhage, melena, tooth discoloration, constipation

General disorders and administration site conditions: Death, elective transplantation

Hepatobiliary disorders: Elevated hepatic enzymes, hepatic function disorder, liver enlargement, cirrhosis, hepatomegaly

Infections and infestations: Infection, septicemia, otitis

Metabolism and nutrition disorders: Dehydration, hypoglycemia, thirst

Musculoskeletal and connective tissue disorders: Pathologic fracture

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

Nervous system disorders: Seizures, encephalopathy, headache, hyperkinesia, hypokinesia, convulsions

Psychiatric disorders: Nervousness, somnolence

Renal and urinary disorders: Hematuria

Reproductive system and breast disorders: Amenorrhea

Respiratory, thoracic and mediastinal: Bronchitis, respiratory insufficiency

Abnormal Hematologic and Clinical Chemistry Findings

Elevations in plasma tyrosine

Elevated tyrosine levels have been associated with ocular toxicity, therefore levels should be carefully monitored and dietary restriction of tyrosine and phenylalanine adjusted as necessary (see **WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Tests**).

Thrombocytopenia and leukopenia

Platelet and white blood cell counts should be monitored during therapy (see **WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Tests**).

Post-Market Adverse Drug Reactions

Nervous system disorders: Cognitive dysfunction, learning difficulties

DRUG INTERACTIONS

Overview

No formal drug-drug interaction studies have been conducted with nitisinone.

Nitisinone is a substrate of CYP3A4 *in vitro*, therefore dose-adjustment may be needed when nitisinone is co-administered with inhibitors (e.g. ketoconazole) or inducers (e.g. rifampin) of this enzyme. Nitisinone is not expected to inhibit CYP 1A2, 2C19, or 3A4 based on *in vitro* studies.

In vitro studies indicate there is potential for nitisinone to inhibit CYP2C9. Caution is recommended when Nitisinone Tablets are co-administered with drugs that are metabolized by CYP2C9 (e.g. warfarin) and additional monitoring may be warranted because of a potential for increased systemic exposure of these CYP2C9 substrate drugs. The clinical risk is dependent upon the particular 2C9 substrate and its adverse reaction profile.

The potential for nitisinone to inhibit CYP2D6 and CYP2E1 at the recommended dosage is unknown, due to limited human data. Caution is recommended when Nitisinone Tablets are co-administered with drugs that are metabolized by CYP2D6 and CYP2E1 due to the potential for increased systemic exposure of these drugs.

Drug-Food Interactions

Nitisinone Tablets can be administered with or without food, without significantly affecting bioavailability.

Drug-Herb Interactions

Interactions with herbal products have not been established.

Drug-Laboratory Interactions

Interactions with laboratory tests have not been established.

DOSAGE AND ADMINISTRATION

Dosing Considerations

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

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

Recommended Dose and Dosage Adjustment

The recommended initial dose of Nitisinone Tablets in the pediatric and adult population is 1 mg/kg body weight/day divided in 2 doses administered orally. The dose of nitisinone should be adjusted individually.

In patients whose plasma and urine succinylacetone (SA) are still detectable one month after starting treatment with Nitisinone Tablets, the Nitisinone Tablets dose should be increased to 1.5 mg/kg/day. A maximum dosage of 2 mg/kg/day may be needed, based on the evaluation of all biochemical parameters. If the biochemical response is satisfactory, the dosage of Nitisinone Tablets should be adjusted only according to body weight gain.

In addition to plasma and urine succinylacetone, during the initiation of therapy or if there is a deterioration in the patient's condition, it may be necessary to follow more closely all available biochemical parameters, including urine 5-aminolevulinate (ALA) and erythrocyte porphobilinogen (PBG)-synthase activity (see **WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Tests**).

Administration

Nitisinone Tablets may be taken with or without food.

For infants, tablets can be disintegrated in water using an oral syringe. Do not administer the suspension using a baby bottle.

Additionally, tablets may be crushed between two spoons and mixed with applesauce for administration. Discard any mixture that has not been given within 2 hours.

Preparation and Administration of NITISINONE TABLETS with Water in an Oral Syringe:

- A 5-mL oral syringe with a cap will be provided by a pharmacist.
- Follow the instructions below for one or two intact tablets, depending on the number of tablets needed to achieve the patient's individual dosage.
- 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 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 60 minutes.
4. After 60 minutes, 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 disintegrated prior to administration to the patient. Administer immediately. However, do not administer unless the tablet has fully disintegrated.
6. If the tablet is not fully disintegrated, leave the oral syringe for an additional 10 minutes. Before administration of the suspension to the patient, turn the oral syringe up and down for 30 seconds to re-suspend the particles. Inspect the syringe again to ensure the tablet has disintegrated prior to administration to the patient. Do not administer unless the tablet has fully disintegrated.
7. Administer immediately. However, if this is not possible, 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.
8. Uncap the oral syringe and administer 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.
9. Rinse the oral syringe by drawing up 2 mL of water. Cap the oral syringe and shake well for 10 seconds to suspend any remaining particles.
10. Uncap the oral syringe and administer the suspension into the patient's mouth, this time fully depressing the plunger. If particles are still present in the syringe, repeat steps 9-10.

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 60 minutes.
4. After 60 minutes, 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 disintegrated prior to administration to the patient. Administer immediately. However, do not administer unless the tablets has fully disintegrated.
6. If the tablet is not fully disintegrated, leave the oral syringe for an additional 10 minutes. Before administration of the suspension to the patient, turn the oral syringe up and down for 30 seconds to re-suspend the particles. Inspect the syringe again to ensure the tablet has disintegrated prior to administration to the patient. Do not administer unless the tablet has fully disintegrated.

7. Administer immediately. However, if this is not possible, 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.
8. Uncap the oral syringe and administer 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.
9. Rinse the oral syringe by drawing up 2 mL of water. Cap the oral syringe and shake well for 10 seconds to suspend any remaining particles.
10. Uncap the oral syringe and administer the suspension into the patient's mouth, this time fully depressing the plunger and ensuring the syringe is empty. If particles are still present in the syringe, repeat steps 9-10

OVERDOSAGE

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

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

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

The biochemical defect in hereditary tyrosinemia type 1 (HT-1) is a deficiency of fumarylacetoacetate hydrolase, which is the final enzyme of the tyrosine catabolic pathway. Nitisinone is a competitive inhibitor of 4-hydroxyphenylpyruvate dioxygenase, an enzyme which precedes fumarylacetoacetate hydrolase in the tyrosine catabolic pathway. By inhibiting the normal catabolism of tyrosine in patients with HT-1, nitisinone prevents the accumulation of the toxic intermediates maleylacetoacetate and fumarylacetoacetate. In patients with HT-1, these intermediates are converted to the toxic metabolites succinylacetone and succinylacetoacetate. Succinylacetone inhibits the porphyrin synthesis pathway leading to the accumulation of 5-aminolevulinate.

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

Pharmacokinetics

HT-1 patients

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

Healthy adults

Table 2 displays nitisinone pharmacokinetic parameters following oral administration of a single 10 mg Nitisinone Tablet to 23 healthy adult subjects.

Table 2. Summary of plasma Nitisinone Tablets 10 mg Pharmacokinetic parameters (arithmetic mean)

	C_{max} (ng/mL)	$t_{1/2}$ (h)	T_{max} * (h)	$AUC_{0-\infty}$ (hr*ng/mL)	AUC_{0-72} (hr*ng/mL)	Clearance (mL/hr)	Volume of distribution (mL)
Single dose Arithmetic mean	1155.58	63.87	3 (2-5)	93965.62	50321.77	113.65	9977.78

* Expressed as the median (range) only

Absorption

Nitisinone is rapidly absorbed following oral administration. The median time to maximal serum concentrations (T_{max}) was about 2 to 5 hours (median 3 hours) after oral administration of Nitisinone Tablets in 23 healthy adults.

Administration of Nitisinone Tablets with food resulted in delayed absorption of nitisinone compared to administration fasting, with a median T_{max} of 6 h (range 2.0-10.0 h) in fed conditions, compared to 3 h (range 2.0-8.0 h) in fasting conditions. No clinically significant effect of food was seen on nitisinone AUC_{0-72} , C_{max} , or $t_{1/2}$.

Distribution

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

Metabolism

In vitro studies have shown that nitisinone is relatively stable in human liver microsomes with minor metabolism possibly mediated by CYP3A4. Nitisinone displayed moderate inhibiting activity on CYP2C9 (IC₅₀=46μM), weak inhibition of CYP2D6 and CYP2E1 (IC₅₀>100 μM for both), and did not inhibit human hepatic CYP1A2, CYP2C19, or CYP3A4 activity (see **DRUG INTERACTIONS**).

Excretion

The terminal plasma half-life of Nitisinone Tablets in healthy subjects was found to be 63.87 hours. The route of elimination appears to be via hydroxylation with subsequent excretion in both urine and feces.

STORAGE AND STABILITY

Nitisinone Tablets should be stored in a dry place at room temperature between 15° and 30°C and kept in a safe place out of the reach and sight of children.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Nitisinone Tablets are white to beige, round, flat tablets, which may display light yellow to brown speckles marked with the “strength” on one side and “L” on the other side. Each tablet contains 2, 5 or 10 mg nitisinone. Non medicinal ingredients are: glyceryl dibehenate and lactose monohydrate. Nitisinone Tablets are packed in High-density polyethylene (HDPE) square bottles with a child-resistant tamper-evident Polypropylene (PP) screw cap. Each bottle contains 60 tablets.

The appearance of Nitisinone Tablets is described below:

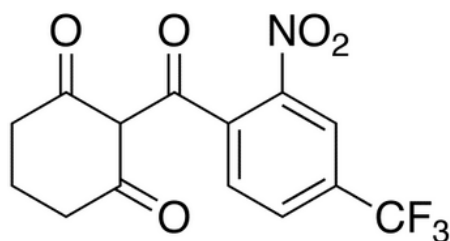
- | | |
|----------------------|--|
| 2 mg tablet: | From white to beige, round, flat tablets, which may display light yellow to brown speckles marked “2” on one side and “L” on the other side |
| 5 mg tablet: | From white to beige, round, flat tablets, which may display light yellow to brown speckles marked “5” on one side and “L” on the other side |
| 10 mg tablet: | From white to beige, round, flat tablets, which may display light yellow to brown speckles marked “10” on one side and “L” on the other side |

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

Common name:	nitisinone
Chemical name:	2-(2-nitro-4-trifluoromethylbenzoyl) cyclohexane-1,3-dione
USAN name:	1,3-Cyclohexanedione, 2-[2-nitro-4-(trifluoromethyl) benzoyl]
Molecular formula:	C ₁₄ H ₁₀ NO ₅ F ₃
Molecular mass:	329.23
Structural formula:	



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

CLINICAL TRIALS

The efficacy and safety of nitisinone were analyzed in a multinational, uncontrolled, open-label study. The study *main analysis* comprised 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 nitisinone was 0.6 to 1 mg/kg/day, and the dose was increased in some patients up to 2 mg/kg/day based on weight, biochemical, and enzyme markers. Median duration of treatment was 22.2 months (range 0.1 to 80 months).

Survival probabilities after 2 and 4 years of treatment with nitisinone are summarized in [Table 3](#), along with historical data for HT-1 patients treated with dietary restriction alone.

Table 3: Survival Probability, HT-1 Patients

Study population	Patients treated with nitisinone, open-label trial		Historical controls (van Spronsen <i>et al.</i> , 1994)	
	2 year	4 year	2 year	4 year
Age 0-2 months at start	88%	88%	29%	29%
Age 0-6 months at start	94%	94%	74% ¹	60% ¹
Age >6 months at start	97%	93%	96%	96%

¹ Patients 2-6 months of age at start of treatment

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

DETAILED PHARMACOLOGY

Pharmacodynamics data in HT-1 patients

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

Pharmacokinetic data

In a study in which 23 healthy adult subjects were administered a single 10 mg Nitisinone Tablet, maximum serum nitisinone concentration was reached 3 hours after dosing (T_{max}). The terminal half-life ($t_{1/2}$) was 63.87 hours, and maximal plasma concentration (C_{max}) was 1155.58 ng/mL. The volume of distribution obtained for nitisinone was 9977.78 mL.

Terminal half-life was found to be 25.3 hours in children in another study. The route of elimination appears to be via hydroxylation with subsequent excretion in both urine and feces.

In vitro metabolism

Nitisinone is relatively stable in human liver microsomes *in vitro*, with only minor metabolism evident, possibly mediated by the CYP3A4 enzyme. Overall, nitisinone was a moderate inhibitor activity on CYP2C9 ($IC_{50}=46\mu M$), a weak inhibitor of CYP2D6 and CYP2E1 ($IC_{50}>100\mu M$ for both), and did not inhibit human hepatic CYP1A2, CYP2C19, or CYP3A4 activity.

TOXICOLOGY

Single and repeat-dose toxicity

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

Carcinogenicity and mutagenicity

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.

Reproductive and developmental toxicity

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

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

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

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

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PATIENT MEDICATION INFORMATION

NITISINONE TABLETS

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

What are NITISINONE TABLETS used for?

NITISINONE TABLETS are used for the treatment of hereditary tyrosinemia type 1 (HT-1), in addition to limiting the amount of tyrosine and phenylalanine in the diet.

How do NITISINONE TABLETS work?

NITISINONE TABLETS stop the build-up of toxic substances which cause the severe liver and kidney problems in patients with HT-1. By doing that, they also prevent the porphyric crises associated with HT-1.

What are the ingredients in NITISINONE TABLETS?

Medicinal ingredients: Nitisinone.

Non-medicinal ingredients: glyceryl dibehenate, lactose monohydrate.

NITISINONE TABLETS come in the following dosage forms:

Tablets: 2 mg, 5 mg, or 10 mg.

Do not use NITISINONE TABLETS if you:

- Are allergic (hypersensitive) to nitisinone or any of the other ingredients in NITISINONE TABLETS.
- Are breast-feeding. Do not breast feed while taking NITISINONE TABLETS.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take NITISINONE TABLETS. Talk about any health conditions or problems you may have, including if you:

- Are pregnant or planning to become pregnant.

Other warnings you should know about:

Dietary Changes

Taking NITISINONE TABLETS can cause high levels of tyrosine in your blood which can be toxic. As a result, while you are taking NITISINONE TABLETS you must limit the amount of tyrosine and phenylalanine in your diet. Talk to your healthcare professional about which foods are safe to eat and which foods should be avoided.

Eye Problems

Your healthcare professional will check your eyes before starting treatment with NITISINONE TABLETS. If you develop eye problems while taking NITISINONE TABLETS, including sensitivity to light, eye pain, redness, swelling or burning, talk to your healthcare professional immediately.

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

How to take NITISINONE TABLETS:

- Take NITISINONE TABLETS exactly as your healthcare professional has told you. Talk to your healthcare professional or pharmacist if you have questions.
- There are a couple of ways to take this medication. Your healthcare professional will discuss these with you and tell you how you should take it.
- NITISINONE TABLETS are usually taken twice a day.
- Your healthcare professional will tell you how many tablets to take.
- Do not change your dose or stop taking this medication without first talking to your doctor.

Preparing and taking the dose:

For patients swallowing the tablets whole

Swallow the tablets whole with a drink of water. NITISINONE TABLETS can be taken with or without food.

For infants and patients who have a problem swallowing the tablets whole

NITISINONE TABLETS may be crushed between two spoons and then mixed with applesauce. As well, NITISINONE TABLETS can be broken down in water in an oral syringe to form a suspension.

Preparing and taking NITISINONE TABLETS by crushing and mixing with applesauce:

1. Wash your hands well before crushing NITISINONE TABLETS.
2. Crush only 1 NITISINONE TABLET at a time.
3. Measure about 1 teaspoon of applesauce and put it into a clean container, such as a glass or bowl.
4. Place 1 NITISINONE TABLET onto a metal teaspoon.
5. Place a second teaspoon on top of the teaspoon holding the tablet.
6. Apply light pressure with the second teaspoon. Press and rotate the two teaspoons against each other until the tablet is crushed to a fine powder.
7. Place all of the NITISINONE TABLET powder from the metal teaspoon into the clean container of applesauce. Be sure that no tablet powder remains on the teaspoon.
8. If the prescribed dose is more than 1 tablet, repeat Steps 4 to 6. Place all of the NITISINONE TABLET powder in the container with the applesauce. You do not need to add more applesauce at this time if you take more than 1 tablet.
9. Stir the NITISINONE TABLET powder and the applesauce. Do this until all the tablet powder is mixed well.

10. Remove the mixture from the container using a teaspoon and swallow. Repeat this step until no mixture is left in the container.
11. Measure another teaspoon of applesauce and place it in the container used before.
12. Stir the fresh applesauce with the mixture that is left in the container.
13. Remove the mixture from the container using a teaspoon and swallow. Repeat this step until no mixture or powder is left in the container.

Take the NITISINONE TABLETS and applesauce mixture within 2 hours.

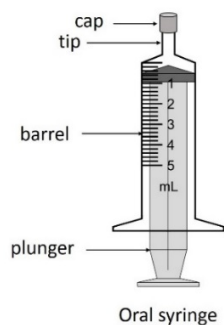
Store the NITISINONE TABLETS and applesauce mixture at room temperature (15 - 30°C).

Keep the NITISINONE TABLETS and applesauce mixture out of direct sunlight until ready for use. The mixture does not need to be refrigerated.

Throw away any mixture that is not used within 2 hours after mixing into a trash can.

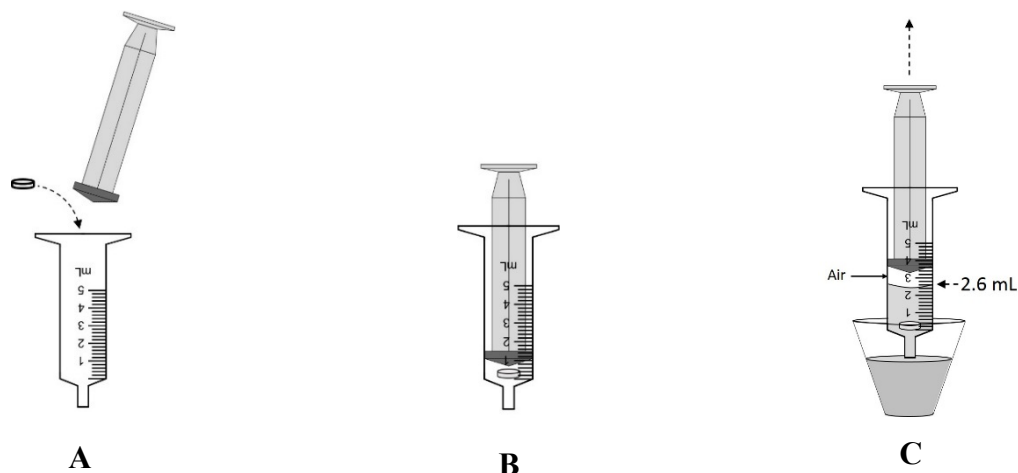
Preparing and taking NITISINONE TABLETS using an oral syringe

- **Prepare only 1 or 2 NITISINONE TABLETS** in an oral syringe at one time.
- Use a 5 mL oral syringe **with a cap** (see below) to prepare NITISINONE TABLETS in an oral syringe. Ask your pharmacist for your oral syringe. You will need more than one 5 mL oral syringe if you take more than 2 NITISINONE TABLETS for your prescribed dose. In this case, use multiple oral syringes to prepare and take your dose as needed.
- The contents of the syringe will appear cloudy and small pieces of tablet will be present.
- Use only **room temperature water** to prepare NITISINONE TABLETS in an oral syringe.
- Wash your hands well before preparing NITISINONE TABLETS using an oral syringe.
- For infants, do NOT give the suspension using a baby bottle.



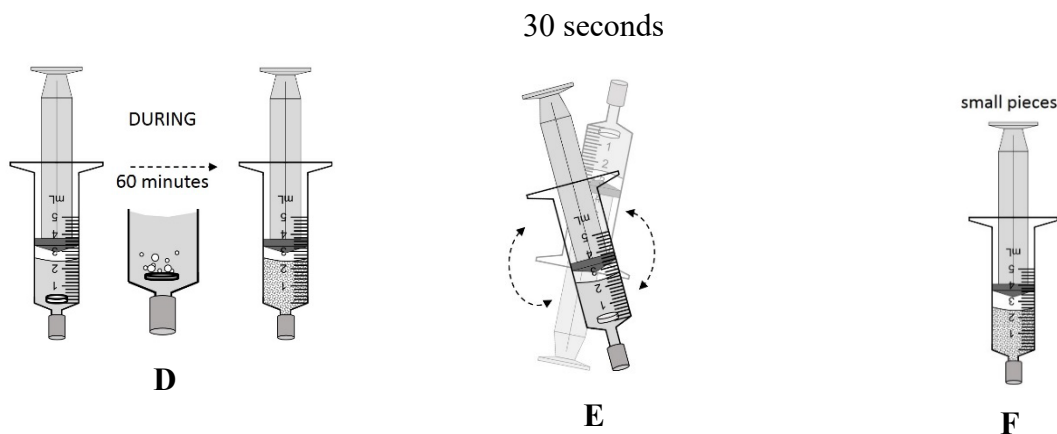
How to prepare and take 1 NITISINONE TABLET using a 5 mL oral syringe:

1. Remove the cap from the 5 mL oral syringe.
2. Remove the plunger from the oral syringe and place 1 whole NITISINONE TABLET inside the oral syringe (See Figure A).
3. Replace the plunger (See Figure B).
4. Draw up **2.6 mL** of **room temperature** water into the oral syringe. There may be some air in the oral syringe. Leave the air in the oral syringe (See Figure C).



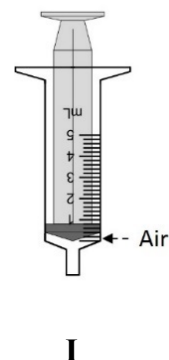
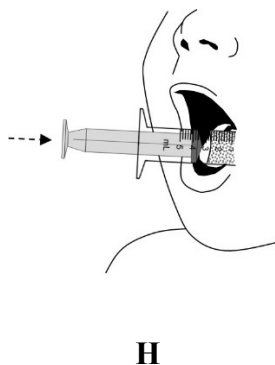
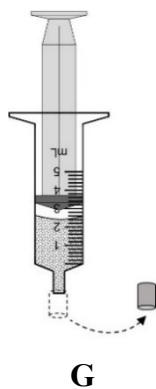
5. Replace the cap on the oral syringe. Let the oral syringe sit for at least **60 minutes** (See Figure D).
6. Turn the oral syringe up and down for at least **30 seconds** (See Figure E).
7. Check the oral syringe to see if the NITISINONE TABLET has broken apart into very small pieces. The pieces should be evenly spread through the water (suspension) (See Figure F). Do NOT take the suspension if you see any large pieces of the NITISINONE TABLET or if they are not evenly spread through the water. In this case, let the oral syringe sit for another 10 minutes.

Before giving the suspension, turn the oral syringe up and down for 30 seconds one more time. Do this to ensure that the pieces of NITISINONE TABLET in the suspension remain evenly spread.

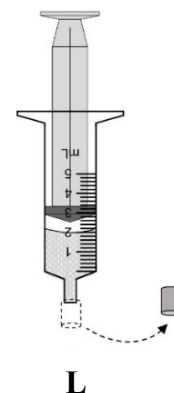
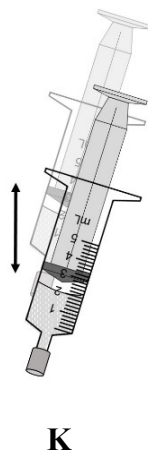
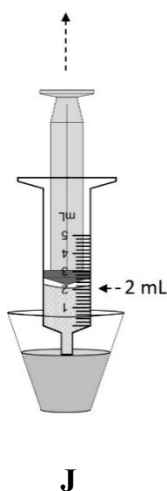


8. **Remove the cap from the oral syringe** (See Figure G).
9. Place the tip of the oral syringe in the mouth right away. If giving to a child, place the tip of the oral syringe along the inner cheek of the child's mouth (See Figure H).

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

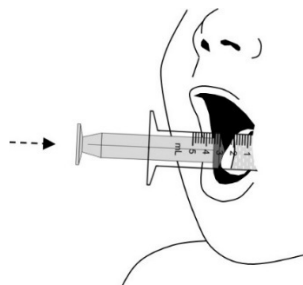


11. Draw up an additional **2 mL** of water into the oral syringe (See Figure J).
12. Replace the cap on the oral syringe. **Shake the oral syringe well for 10 seconds**. Do this to spread the remaining tablet pieces evenly through the water (See Figure K).
13. **Remove the cap from the oral syringe** (See Figure L).

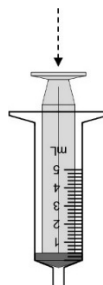


14. Place the tip of the oral syringe in the mouth right away. If giving to a child, place the tip of the oral syringe along the inner cheek of the child's mouth (See Figure M).
15. While keeping the oral syringe in the mouth, slowly push down on the plunger. Do this until the oral syringe is empty (See Figure N). In case any pieces of the tablet are still present in the oral syringe, repeat steps 11 through 15.

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 put the plunger back into the barrel of the oral syringe until ready to use again. This will allow it to dry. Do NOT throw away the oral syringe or plunger.



M



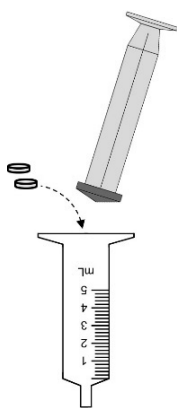
N

If you are not taking the water and NITISINONE 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.

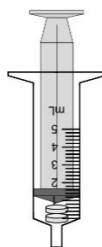
After adding water to the tablet in the oral syringe you can keep the NITISINONE TABLET suspension for 24 hours. Store the NITISINONE TABLET suspension in the oral syringe with the cap on at room temperature (15 - 30°C). Keep the oral syringe out of direct sunlight until ready for use. The suspension does not need to be refrigerated. Throw away any suspension that is not used within 24 hours by emptying the syringe in the drain.

How to prepare and take 2 NITISINONE TABLETS using a 5 mL oral syringe:

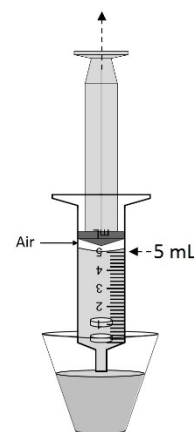
1. Remove the cap from the 5 mL oral syringe.
2. Remove the plunger from the oral syringe and place 2 whole NITISINONE TABLETS inside the oral syringe (See Figure A).
3. Replace the plunger (See Figure B).
4. Draw up 5 mL of **room temperature** water into the oral syringe. There may be some air in the oral syringe. Leave the air in the oral syringe (See Figure C).



A



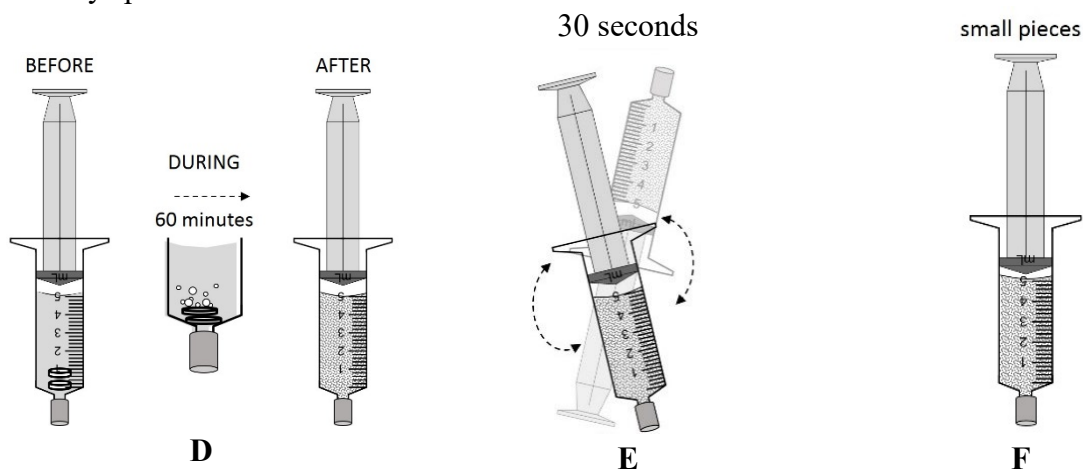
B



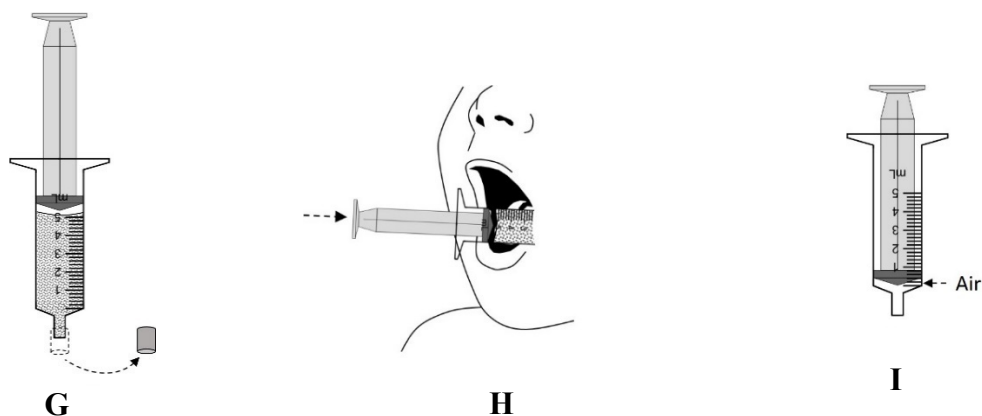
C

5. Replace the cap on the oral syringe. Let the oral syringe sit for at least **60 minutes** (See Figure D).
6. Turn the oral syringe up and down for at least **30 seconds** (See Figure E).
7. Check the oral syringe to see if the NITISINONE TABLETS have broken apart into very small pieces. The pieces should be evenly spread through the water (suspension) (See Figure F). Do **NOT** take the suspension if you see any large pieces of the NITISINONE TABLETS or if they are not evenly spread through the water. In this case, let the oral syringe sit for another 10 minutes.

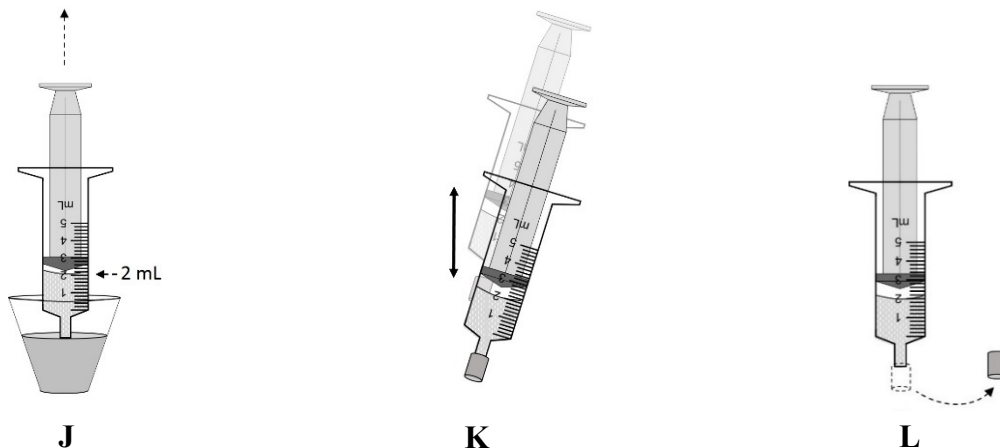
Before giving the suspension, turn the oral syringe up and down for 30 seconds one more time. Do this to ensure that the pieces of NITISINONE TABLETS in the suspension remain evenly spread.



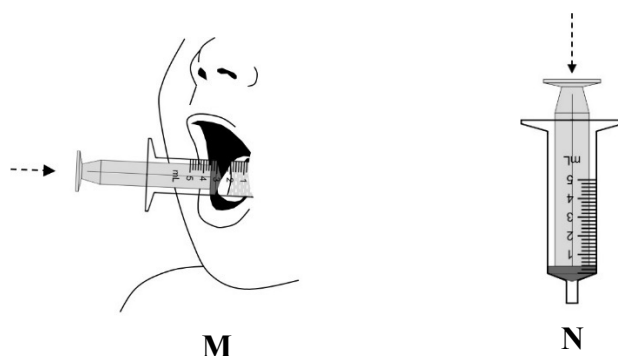
8. **Remove the cap from the oral syringe** (See Figure G).
9. Place the tip of the oral syringe in the mouth right away. If giving to a child, place the tip of the oral syringe along the inner cheek of the child's mouth (See Figure H).
10. While keeping the oral syringe in the mouth, slowly push down on the plunger. Do this **until a small amount of air is left** between the plunger and the tip of the oral syringe (See Figure I). Do **NOT** press all the way down to the end of the syringe.



11. Draw up an additional **2 mL** of water into the oral syringe (See Figure J).
12. Replace the cap on the oral syringe. **Shake the oral syringe well for 10 seconds.** Do this to spread the remaining tablet pieces evenly through the water (See Figure K).
13. **Remove the cap from the oral syringe** (See Figure L).



14. Place the tip of the oral syringe in the mouth right away. If giving to a child, place the tip of the oral syringe along the inner cheek of the child's mouth (See Figure M).
15. While keeping the oral syringe in the mouth, slowly push down on the plunger. Do this 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.
16. After use, remove the plunger from the oral syringe barrel. Rinse the syringe with water after each use and let it dry. Do NOT put the plunger back into the barrel of the oral syringe until ready to use again. This will allow it to dry. Do NOT throw away the oral syringe or plunger.



If you are not taking the water and NITISINONE 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.

After adding water to the tablets in the oral syringe you can keep the NITISINONE TABLETS suspension for 24 hours. Store the NITISINONE TABLETS suspension in the oral syringe with the cap on at room temperature (15 - 30°C). Keep the oral syringe out of direct sunlight until ready for use. The suspension does not need to be refrigerated. Throw away any suspension that is not used within 24 hours by emptying the syringe in the drain.

Usual dose:

Your healthcare professional will tell you how many NITISINONE TABLETS to take and when to take them.

Your healthcare professional may need to adjust your dose after blood tests have been done. This may happen based on how you are responding to treatment.

Overdose:

If you think you have taken too many NITISINONE TABLETS, contact your healthcare professional, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms. If you go to a healthcare professional or to the hospital, take the NITISINONE TABLETS container with you.

Missed Dose:

If you forget a dose, take the next dose as planned. Do not take a double dose to make up for a forgotten dose. If you forget to take a dose, contact your healthcare professional or pharmacist.

What are the possible side effects from using NITISINONE TABLETS?

These are not all the possible side effects you may feel when taking NITISINONE TABLETS. If you experience any side effects not listed here, contact your healthcare professional.

NITISINONE TABLETS can cause abnormal blood test results. While you are taking NITISINONE TABLETS your healthcare professional will decide when to perform blood tests and will interpret the results.

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
COMMON			
Liver problems: nausea, vomiting, loss of appetite combined with itching, yellowing of the skin or eyes, dark urine or stools, unexplained weight loss.		√	
Low Platelets: easy or unusual bruising. Bleeding into the skin		√	

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
causing a rash of pinpoint-sized reddish-purple spots, usually in the lower legs, prolonged bleeding from cuts, bleeding from your gums or nose, blood in urine or stools.			
Low White Blood Cells: infections, fatigue, weakness, fever, aches and pains, flu-like symptoms.		√	
Eye Problems: redness, eye discharge, itchy eyes, burning eyes, blurred vision, sensitivity to light, milky or cloudy area on the eye, eye pain, a feeling that there is something in your eye.		√	
RARE			
Skin Problems: dry/cracked/scaly skin, rashes, small flat red bumps, itching that can be severe, blisters, draining fluid and crusting, swelling, burning, tenderness, loss of hair in patches.		√	

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

<p>Reporting Side Effects</p> <p>You can report any suspected side effects associated with the use of health products to Health Canada by:</p> <ul style="list-style-type: none"> • Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for information on how to report online, by mail or by fax; or by • Calling toll-free at 1-866-234-2345. <p><i>NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.</i></p>

Storage:

- Store your tablets at room temperature (15 - 30°C), in a dry place.
- Keep the container tightly closed.
- There is an expiry date on the label. Do not use the medicine after this date.
- **Keep out of reach and sight of children.**

If you want more information about NITISINONE TABLETS:

- Talk to your healthcare professional.
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the [Health Canada website](http://www.healthcanada.gc.ca) (www.healthcanada.gc.ca); the manufacturer's website <http://www.cyclepharma.com> or by calling 1-855-831-5413 (toll-free).

This leaflet was prepared by Cycle Pharmaceuticals Ltd.

Cycle Pharmaceuticals Ltd.
Bailey Grundy Barrett Building,
Little St Mary's Lane,
Cambridge
Cambridgeshire
CB2 1RR
UK

Imported and distributed by:
C.R.I.,
Unit #400, 3455 North Service Road
Burlington, Ontario
L7N 3G2
Canada

Last Revised: October 10, 2019



CAN-0019 – Date of preparation: March 2021
© 2021 Cycle Pharmaceuticals Limited. All rights reserved.