PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

[Pr]MDK-Nitisinone

Nitisinone capsules

Capsules, 2 mg, 5 mg, 10 mg and 20 mg

ATC Code: A16AX04
Various alimentary tract and metabolism products

MendeliKABS Inc
4601, rue de Tonnancour
Saint-Hubert (Quebec)
Canada, J3Y 9J3

Date of Revision:
November 29, 2017

Submission Control No: 202740

TABLE OF CONTENTS

MDK-Nitisinone

Nitisinone capsules

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Oral	Capsules 2 mg, 5 mg, 10 mg, 20 mg	*For a complete listing see DOSAGE FORMS, COMPOSITION AND PACKAGING section.*

INDICATIONS AND CLINICAL USE

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

Treatment with MDK-Nitisinone 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 this drug or to any ingredient in the formulation or component of the container. For a complete listing, see the **DOSAGE FORMS, COMPOSITION AND PACKAGING** section of the Product Monograph.
- Mothers receiving MDK-Nitisinone should not breast feed (see **Nursing Women**).

WARNINGS AND PRECAUTIONS

Endocrine and Metabolism

Elevated plasma tyrosine levels
Treatment with MDK-Nitisinone may cause an increase in plasma tyrosine levels in patients with HT-1. Patients must maintain concomitant reductions in dietary tyrosine and phenylalanine while

on MDK-Nitisinone treatment. Inadequate restriction of tyrosine and phenylalanine intake may increase blood tyrosine levels. Plasma tyrosine levels should be maintained below 500 µmol/L, since levels greater than 500 µmol/L may increase the risk of ocular signs and symptoms.

In patients with HT-1 treated with MDK-Nitisinone 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 MDK-Nitisinone dose, as this may result in deterioration of the patient's clinical condition.

Hematologic

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

Hepatic/Biliary/Pancreatic

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

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, should be performed prior to initiating MDK-Nitisinone treatment. Patients who develop photophobia, eye pain, or signs of inflammation such as redness, swelling, or burning of the eyes during treatment with MDK-Nitisinone should undergo slit-lamp re-examination and immediate measurement of plasma tyrosine concentration [see **ADVERSE REACTIONS**].

Special Populations

Pregnant Women:
MDK-Nitisinone 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 MDK-Nitisinone should not breast-feed [see **CONTRAINDICATIONS**].

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

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

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

Monitoring and Laboratory Tests

Succinylacetone, 5-ALA, and erythrocyte PBG-synthase
Monitor plasma and/or urine succinylacetone levels, and titrate MDK-Nitisinone dosage as necessary (see **DOSAGE AND ADMINISTRATION**). Consider also monitoring urine 5-aminolevulinate (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 MDK-Nitisinone, 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 cell counts
Platelet and white blood cell counts should be monitored regularly during MDK-Nitisinone therapy.

Ophthalmologic assessment including slit lamp examination should be conducted prior to initiation of MDK-Nitisinone, and if eye symptoms develop during treatment.

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

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

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

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

The most serious adverse reactions reported during nitisinone treatment were thrombocytopenia, leucopenia, and ocular/visual complaints associated with elevated tyrosine levels [see **WARNINGS AND PRECAUTIONS**]. 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 leucopenia and thrombocytopenia.

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

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

Adverse events reported in less than 1% of patients in the 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 and hyperkeratotic skin lesions, therefore levels should be carefully monitored and dietary restriction of tyrosine and phenylalanine adjusted as necessary [see **WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Tests**].

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

Post-Market Adverse Drug Reactions

Nervous system disorders: 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.

Based on *in vitro* studies, there is a potential for nitisinone to inhibit CYP2C9. Caution is recommended when MDK-Nitisinone is 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 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 MDK-Nitisinone is co-administered with drugs that are metabolized by CYP2D6 and CYP2E1 because of a potential for increased systemic exposure of these drugs.

Drug-Food Interactions

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

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

Recommended Dose and Dosage Adjustment

The recommended initial dose of MDK-Nitisinone 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 MDK-Nitisinone treatment, the MDK-Nitisinone 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 MDK-Nitisinone dosage 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

No data are available on the effect of food on the bioavailability of nitisinone; however, in clinical studies nitisinone was usually co-administered with food. It is recommended that if nitisinone treatment is initiated with food, this routine should be maintained. For pediatric patients, the capsules may be opened and the contents suspended in a small amount of water or formula immediately before intake.

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

Nitisinone is a competitive inhibitor of 4-hydroxyphenyl-pyruvate dioxygenase, an enzyme upstream of fumarylacetoacetate hydrolase (FAH) in the tyrosine catabolic pathway. By inhibiting the normal catabolism of tyrosine in patients with HT-1, nitisinone prevents the accumulation of the catabolic intermediates maleylacetoacetate and fumarylacetoacetate. In

patients with HT-1, these catabolic intermediates are converted to the toxic metabolites succinylacetone and succinylacetoacetate, which are responsible for the observed liver and kidney toxicity. Succinylacetone can inhibit the porphyrin synthesis pathway leading to the accumulation of 5-aminolevulinate, a neurotoxin responsible for the porphyric crises characteristic of HT-1.

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

Pharmacokinetics

HT-1 patients

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

Healthy adults

The single-dose pharmacokinetics of nitisinone has been studied in ten healthy male volunteers aged 19-39 years (median 32 years). Nitisinone, 1 mg/kg body weight, was administered as a capsule and a liquid. The median time for maximum plasma concentration was 3 hours for the capsule and 15 minutes for the liquid. The capsule and liquid formulation were found to be bioequivalent based on an analysis of area under the plasma concentration-time curve and maximum plasma concentration (C_{max}). The mean terminal plasma half-life of nitisinone in healthy male volunteers was 54 hours.

Following oral administration of a single 10 mg dose of MDK-Nitisinone by 46 healthy patients, nitisinone C_{max} was 1104 ng/mL, T_{max} was 2.5 hr and $T_{1/2}$ was 63.7 hr.

Table 2: Summary of Nitisinone Pharmacokinetic Parameters in HT-1 patients and Healthy Adults

	C_{max} ng/mL	T_{max} (h)	$AUC_{0-\infty}$ (units)	$t_{½}$ (h)
HT-1 patients	N/A	N/A	N/A	21
Healthy adults	1103.87	2.50	76,244.45	63.70

Absorption

Following administration of MDK-Nitisinone 10 mg under fasting conditions, the peak serum nitisinone concentration (C_{max}) occurred at approximately 2.5 hours post-dose (range: 0.750-2.50). The pharmacokinetic parameters are shown in Table 2. This T_{max} value implies that nitisinone is absorbed in the proximal small intestine.

Distribution

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

Metabolism

In vitro studies have shown that nitisinone is relatively stable in human liver microsomes with minor metabolism possibly mediated by CYP3A4 enzyme. Nitisinone displayed moderate inhibiting activity on CYP2C9 (IC_{50}=46μM), weak inhibition of CYP2D6 and CYP2E1 (IC_{50}>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 MDK-Nitisinone in healthy subjects was found to be 63.70 hours. The route of elimination appears to be via hydroxylation with subsequent excretion in both urine and feces.

Special Populations and Conditions

Pediatrics:
Pediatric patients with HT-1, aged from birth to 17 years have been treated with nitisinone [see **CLINICAL TRIALS**]. Monitoring of blood and urine succinylacetone levels are recommended in the children to ensure adequate control [see **DOSAGE AND ADMINISTRATION**]. A dietician skilled in managing children with inborn errors of metabolism should be employed to design a low-protein diet restricted in tyrosine and phenylalanine (see **INDICATIONS AND CLINICAL USE**).

Geriatrics:
Clinical studies and clinical use of nitisinone did not include any subjects aged 65 and over to determine whether they respond differently from younger subjects. No pharmacokinetic studies of nitisinone have been performed in geriatric subjects. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and concomitant disease or other drug therapy in this patient population (see **INDICATIONS AND CLINICAL USE).**

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

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

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

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

Genetic polymorphism:
The influence of genetic polymorphisms on the pharmacokinetics of MDK-Nitisinone is unknown.

STORAGE AND STABILITY

Store refrigerated between 2-8°C (36-46°F). Keep out of reach and sight of children.

Capsules of 2 mg can be stored for a single period of 1 month after initial opening at room temperature, not above 25°C, after which it must be discarded.

Capsules of 5, 10 and 20 mg can be stored for a single period of 3 months after initial opening at room temperature, not above 25°C, after which it must be discarded.

SPECIAL HANDLING INSTRUCTIONS

Disposal of unused/expired drug product

The release of pharmaceuticals in the environment should be minimized. Medicines should not be disposed of via wastewater and disposal through household waste should be avoided. Use established collection systems, if available in your location.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Dosage forms

MDK-Nitisinone is supplied as a hard gelatin capsule for daily oral administration.

2 mg capsules: white hard gelatin capsule printed with black ink “2 mg” on the cap and “Nitisinone” on the body, containing white to off-white powder.

5 mg capsules: white hard gelatin capsule printed with black ink “5 mg” on the cap and “Nitisinone” on the body, containing white to off-white powder.

10 mg capsules: white hard gelatin capsule printed with black ink “10 mg” on the cap and “Nitisinone” on the body, containing white to off-white powder.

20 mg capsules: white hard gelatin capsule printed with black ink “20 mg” on the cap and “Nitisinone” on the body, containing white to off-white powder.

Composition

Each capsule contains 2, 5, 10 or 20 mg of nitisinone and pre-gelatinized maize starch. The capsule shell contains gelatin and titanium dioxide. The markings on the capsules are in black ink, which contains iron oxide and shellac glaze.

Packaging

Capsules are packaged in HDPE plastic bottles with LDPE plastic caps containing 60 capsules.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

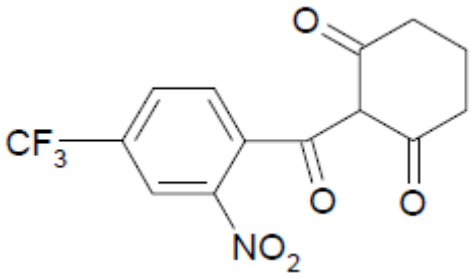
Common name nitisinone

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

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

Molecular mass: 329.228 g/mol

Structural formula:



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

CLINICAL TRIALS

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 *et al.*, 1994)	
Survival time	**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

Pharmacokinetics data

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

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

[Pr] MDK-Nitisinone
Nitisinone capsules

Read this carefully before you start taking MDK-Nitisinone 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 MDK-Nitisinone

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

How does MDK-Nitisinone work?
MDK-Nitisinone stops the build-up of toxic substances which cause the severe liver and kidney problems in patients with HT-1. By doing that, it also prevents the porphyric crises associated with HT-1.

What are the ingredients in MDK-Nitisinone?
Medicinal ingredient: nitisinone.
Non-medicinal ingredients: corn starch, gelatine, iron oxide, shellac glaze, titanium dioxide.

MDK-Nitisinone comes in the following dosage forms:

Capsules: 2 mg, 5 mg, 10 mg or 20 mg

Do not use MDK-Nitisinone if you:
- are allergic (hypersensitive) to nitisinone or any of the other ingredients in MDK-Nitisinone.
- are breast-feeding. Do not breast feed while taking MDK-Nitisinone.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take MDK-Nitisinone. 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 MDK-Nitisinone can cause high levels of tyrosine in your blood which can be toxic. As a result, while you are taking MDK-Nitisinone 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 MDK-Nitisinone. If you develop eye problems while taking MDK-Nitisinone, 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 MDK-Nitisinone:
- MDK-Nitisinone is usually taken twice a day.
- MDK-Nitisinone can be taken with or without food however, it should always be taken the same way. Therefore, if you start taking MDK-Nitisinone with food, you should always take it with food.
- For young children, MDK-Nitisinone capsules can be opened and the contents sprinkled into a small amount of water or formula immediately before use.

Usual dose:
Your healthcare professional will tell you how much MDK-Nitisinone to take and when to take it.

Overdose:

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

Missed Dose:
If you miss a dose by less than 12 hours, take it as soon as you remember.

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

MDK-Nitisinone can cause abnormal blood test results. While you are taking MDK-Nitisinone 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 **Low Platelets**: easy or unusual bruising. Bleeding into the skin causing a rash of pinpoint-sized reddish-purple spots, usually in the lower legs, prolonged bleeding from cuts, bleeding from your gums or nose, blood in urine or stools.		√	
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.

Reporting Side Effects

- You can report any suspected side effects associated with the use of health products to Health Canada by:Visiting the Web page on Adverse Reaction Reporting (http://www.hc-sc.gc.ca/dhp-mps/medeff/report-declaration/index-eng.php) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

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

Storage:

Store refrigerated between 2-8°C.
Opened bottles of 2 mg capsules can be stored for 1 month at room temperature (not above 25°C); then discarded.

Opened bottles of 5, 10 and 20 mg capsules can be stored for 3 months at room temperature (not above 25°C); then discarded.

Keep out of reach and sight of children.

If you want more information about MDK-Nitisinone:

- 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 (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html); the manufacturer's website www.mendelikabs.com, by calling 1-888-959-9987 or by sending an email to: contact@mendelikabs.com.

This leaflet was prepared by MendeliKABS Inc.

Last Revised: November 29, 2017