Date: 21 March 2022
Swissmedic, Swiss Agency for Therapeutic Products

Swiss Public Assessment Report

Nityr

International non-proprietary name: nitisinone
Pharmaceutical form: tablet
Dosage strengths: 2 mg, 5 mg, 10 mg
Route(s) of administration: oral
Marketing Authorisation Holder: Curatis AG
Marketing Authorisation No.: 67970
Decision and Decision date: approved on 24.01.2022

Note:

Assessment Report as adopted by Swissmedic with all information of a commercially confidential nature deleted.

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About Swissmedic

Swissmedic is the Swiss authority responsible for the authorisation and supervision of therapeutic products. Swissmedic's activities are based on the Federal Act of 15 December 2000 (Status as of 1 January 2020) on Medicinal Products and Medical Devices (TPA, SR 812.21). The agency ensures that only high-quality, safe and effective drugs are available in Switzerland, thus making an important contribution to the protection of human health.

About the Swiss Public Assessment Report (SwissPAR)

- The SwissPAR is referred to in Article 67 para. 1 of the Therapeutic Products Act and the implementing provisions of Art. 68 para. 1 let. e of the Ordinance of 21 September 2018 on Therapeutic Products (TPO, SR 812.212.21).
- The SwissPAR provides information about the evaluation of a prescription medicine and the considerations that led Swissmedic to approve or not approve a prescription medicine submission. The report focuses on the transparent presentation of the benefit-risk profile of the medicinal product.
- A SwissPAR is produced for all human medicinal products with a new active substance and transplant products for which a decision to approve or reject an authorisation application has been issued.
- A supplementary report will be published for approved or rejected applications for an additional indication for a human medicinal product for which a SwissPAR has been published following the initial authorisation.
- The SwissPAR is written by Swissmedic and is published on the Swissmedic website. Information from the application documentation is not published if publication would disclose commercial or manufacturing secrets.
- The SwissPAR is a “final” document, which provides information relating to a submission at a particular point in time and will not be updated after publication.
- In addition to the actual SwissPAR, a concise version of the SwissPAR that is more comprehensible to lay persons (Public Summary SwissPAR) is also published.

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1 Terms, Definitions, Abbreviations

ADA	Anti-drug antibody
ADME	Absorption, Distribution, Metabolism, Elimination
ALT	Alanine aminotransferase
API	Active pharmaceutical ingredient
ATC	Anatomical Therapeutic Chemical Classification System
AUC	Area under the plasma concentration-time curve
AUC0-24h	Area under the plasma concentration-time curve for the 24-hour dosing interval
Cmax	Maximum observed plasma/serum concentration of drug
CYP	Cytochrome P450
ERA	Environmental Risk Assessment
GLP	Good Laboratory Practice
ICH	International Council for Harmonisation
Ig	Immunoglobulin
INN	International Nonproprietary Name
LoQ	List of Questions
MAH	Marketing Authorisation Holder
Max	Maximum
Min	Minimum
N/A	Not applicable
NO(A)EL	No Observed (Adverse) Effect Level
PD	Pharmacodynamics
PIP	Paediatric Investigation Plan (EMA)
PK	Pharmacokinetics
PopPK	Population PK
PSP	Pediatric Study Plan (US-FDA)
RMP	Risk Management Plan
SwissPAR	Swiss Public Assessment Report
TPA	Federal Act of 15 December 2000 (Status as of 1 January 2020 on Medicinal Products and Medical Devices (SR 812.21)
TPO	Ordinance of 21 September 2018 (Status as of 1 April 2020) on Therapeutic Products (SR 812.212.21)

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2 Background Information on the Procedure

2.1 Applicant's Request(s)

New Active Substance status
The applicant requested the status of a new active entity for the active substance nitisinone of the medicinal product mentioned above.

Orphan drug status
The applicant requested Orphan Drug Status in accordance with Article 4 a^{decies} no. 1 of the TPA. Orphan Drug Status was granted on 15 July 2020.

Authorisation in accordance with Art. 14 para. 1 a^{bis} TPA
The applicant requested a simplified authorisation in accordance with Art. 14 para. 1 a^{bis} TPA.

2.2 Indication and Dosage

2.2.1 Requested Indication

Treatment of adult and paediatric (in any age range) patients with confirmed diagnosis of hereditary tyrosinemia type 1 (HT-1) in combination with dietary restriction of tyrosine and phenylalanine.

2.2.2 Approved Indication

Nityr is used in addition to appropriate dietary measures, including restriction of tyrosine and phenylalanine intake, in children, adolescents, and adults with hereditary tyrosinemia type 1 (HT-1).

2.2.3 Requested Dosage

The recommended initial daily dose in the paediatric and adult population is 1 mg/kg body weight administered orally. The dose of nitisinone should be adjusted individually. Administration of the dose once daily is recommended. However, due to the limited data in patients with body weight <20 kg, division of the total daily dose into two daily administrations is recommended in this patient population.
If urine succinylacetone is still detectable one month after the start of nitisinone treatment, the nitisinone dose should be increased to 1.5 mg/kg body weight/day. A dose of 2 mg/kg body weight/day may be needed based on the evaluation of all biochemical parameters. This dose should be considered as a maximum dose for all patients.
If the biochemical response is satisfactory, the dose should be adjusted only according to body weight gain.

2.2.4 Approved Dosage

(see appendix)

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2.3 Regulatory History (Milestones)

Application	1 September 2020
Formal control completed	25 November 2020
List of Questions (LoQ)	18 March 2021
Answers to LoQ	15 June 2021
Predecision	16 September 2021
Answers to Predecision	14 November 2021
Final Decision	24 January 2022
Decision	approval

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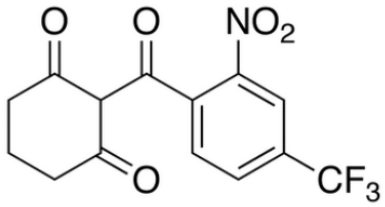
3 Quality Aspects

3.1 Drug Substance

INN: Nitisinone
Chemical name: 2-(2-nitro-4-trifluoromethylbenzoyl) cyclohexane-1,3-dione
Molecular formula: $C_{14}H_{10}F_3NO_5$
Molecular mass: 329.23
Molecular structure:



Nitisinone is a white to light brown, crystalline powder. It is practically insoluble in water; above pH 6, solubility of nitisinone increases significantly. No polymorphic forms of nitisinone have been observed.

The drug substance is manufactured by multiple-step chemical synthesis with final isolation by crystallisation.

The specification includes tests relating to identification, assay, impurities, residual solvents and particle size. The proposed specifications and analytical methods were considered appropriate for quality control of the drug substance.

Appropriate stability data have been presented for three batches.

3.2 Drug Product

Nityr is an immediate release tablet for oral administration with the dose strengths 2 mg, 5 mg and 10 mg. The tablets are white to beige, round, flat, may display light yellow to brown speckles and are marked with the tablet strength on one side and “L” on the other side.

The manufacturing process consists of dry blending and direct compression. The manufacturing process is sufficiently described including batch formula, process parameters and in-process controls. The commercial manufacturing process has been validated.

Adequate specifications at release and shelf life have been described for the drug product including appearance, identification, uniformity of dosage units, water content, assay, related substance, dissolution and microbial purity.

The tablets are packed in HDPE (high-density polyethylene) plastic bottles with childproof caps.

The drug product stability studies were conducted with three batches for each dose strength (2 mg, 5 mg and 10 mg) according to the recommendations of the relevant ICH guidelines.

3.3 Quality Conclusions

Satisfactory and consistent quality of the drug substance and drug product has been demonstrated.

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4 Nonclinical Aspects

In accordance with Art. 14 para. 1 a^{bis} TPA, Swissmedic has only reviewed the nonclinical overview for the authorisation of Nityr, tablets. The approval of Nityr, tablets, is based on the medicinal product Orfadin, hard capsules, which contains the same active substance and has been authorised in Germany for more than 10 years.

5 Clinical and Clinical Pharmacology Aspects

Swissmedic has not assessed the primary data relating to clinical aspects of this application and is taking over the results of the assessment of the foreign reference authority, the EMA. The current SwissPAR relating to clinical aspects refers to the publicly available Assessment Report Orfadin, hard capsules issued by the EMA.

5.1 Approved Indication and Dosage

See information for healthcare professionals in the Appendix.

6 Risk Management Plan Summary

The RMP summaries contain information on the medicinal products' safety profiles and explain the measures that are taken in order to further investigate and monitor the risks as well as to prevent or minimise them.
The RMP summaries are published separately on the Swissmedic website. Marketing Authorisation Holders are responsible for the accuracy and correctness of the content of the published RMP summaries. As the RMPs are international documents, their summaries might differ from the content in the information for healthcare professionals / product information approved and published in Switzerland, e.g. by mentioning risks occurring in populations or indications not included in the Swiss authorisations.

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7 Appendix

7.1 Approved Information for Healthcare Professionals

Please be aware that the following version of the information for healthcare professionals relating to Nytir was approved with the submission described in the SwissPAR. This information for healthcare professionals may have been updated since the SwissPAR was published.

Please note that the reference document, which is valid and relevant for the effective and safe use of medicinal products in Switzerland, is the information for healthcare professionals approved and authorised by Swissmedic (see www.swissmedicinfo.ch).

Note:
The following information for healthcare professionals has been translated by the MAH. The Authorisation Holder is responsible for the correct translation of the text. Only the information for healthcare professionals approved in one of the official Swiss languages is binding and legally valid.

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Nityr, tablets

The efficacy and safety of Nityr, tablets have only been summarily assessed by Swissmedic. The approval of Nityr, tablets is based on Orfadin, capsules as of February 2020, which contains the same active ingredient(s) and is approved in Germany.

Composition

Active substances

Nitisinone

Excipients

1 tablet of 2 mg contains:

Lactose monohydrate (116.4 mg), Glycerol dibehenate

1 tablet of 5 mg contains:

Lactose monohydrate (113.4 mg), Glycerol dibehenate

1 tablet of 10 mg contains:

Lactose monohydrate (108.4 mg), Glycerol dibehenate

Pharmaceutical form and active substance quantity per unit

1 tablet contains 2 mg, 5 mg or 10 mg nitisinone.

Indications/Use

Nityr is used in addition to appropriate dietary measures, including restriction of tyrosine and phenylalanine intake, in children, adolescents, and adults with hereditary tyrosinemia type 1 (HT-1).

Dosage/Administration

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

Treatment of all genotypes of the disease should be initiated as early as possible to increase overall survival and avoid complications such as liver failure, liver cancer and renal disease.

Adjunct to the nitisinone treatment, a diet deficient in phenylalanine and tyrosine is required and should be monitored by routine control of plasma amino acids (see sections “Warnings and precautions” and “Undesirable effects”). For pediatric patients in particular, dietary counseling and support by appropriately trained and experienced specialists is also recommended.

Dosage

The recommended initial daily dose in the paediatric and adult population is 1 mg/kg body weight administered orally. The dose of nitisinone should be adjusted individually. It is recommended to administer the dose once daily. However, due to the limited data in patients with body weight <20kg, it is recommended to divide the total daily dose into two daily administrations in this patient population.

Dose adjustment

During regular monitoring, it is appropriate to follow urine succinylacetone, liver function test values and alpha-fetoprotein levels (see section “Warnings and precautions”). If urine succinylacetone is still detectable one month after the start of nitisinone treatment, the nitisinone dose should be increased to 1.5 mg/kg body weight/day. A dose of 2 mg/kg body weight/day may be needed based on the evaluation of all biochemical parameters. This dose should be considered as a maximal dose for all patients. If the biochemical response is satisfactory, the dose should be adjusted only according to body weight gain.
However, in addition to the above tests, closer monitoring of additional available biochemical parameters (in particular, plasma succinylacetone, urine-5-aminolaevulinate (ALA), and erythrocyte porphobilinogen (PBG)-synthase activity) may be required, for example during the initiation of therapy, switch from twice daily to once daily dosing or if there is a deterioration.

Special populations

There are no specific dose recommendations for elderly or patients that have renal or hepatic impairment.

Children and adolescents

The dose recommendation in mg/kg body weight is the same in children and adults.
However, due to the limited data in patients with body weight <20kg, it is recommended to divide the total daily dose into two daily administrations in this patient population.

Method of administration

Nityr tablets are taken with water.
When taking Nityr, a restricted intake of tyrosine and phenylalanine with food must be followed.
Nityr tablets can be taken during meals or independently of meals.

Nitisinone was given with meals during the generation of efficacy and safety study. Therefore, it is recommended that when nitisinone treatment is initiated with a meal, this practice be continued routinely.

For patients who can swallow semi-solid food, Nityr 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 Mixed in Applesauce

1. Measure around one teaspoon of applesauce and transfer it into a clean container (e.g., clean glass).
2. Always crush one tablet at a time. Position the tablet between two metal teaspoons and apply light pressure on the top spoon. The two teaspoons should overlap each other to form a fine powder.
3. Press and rotate the two teaspoons against each other repeatedly until all of the tablet is in a fine powder.
4. Carefully transfer the resulting powder to the applesauce container ensuring all the powder is transferred, and no powder residue remains on the teaspoons.
5. If more than one tablet is needed, repeat the procedure starting from Step 2 and collect all the resulting powder together in the applesauce container.
6. Mix the powder into the applesauce until the powder is well dispersed.
7. Administer the entire Nityr-applesauce mixture to the patient’s mouth using a teaspoon. Administer immediately. However, if this is not possible, 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 any mixture that has not been given within 2 hours.
8. To assure that any leftover applesauce mixture from the container is recovered, add around one teaspoon of applesauce to the same container and mix the fresh applesauce with the remaining mixture.
9. Administer the additional Nityr-applesauce mixture immediately to the patient’s mouth using a teaspoon.

Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section “Composition”.

Mothers receiving nitisinone must not breast-feed (see sections “Pregnancy, Lactation” and “Preclinical data”).

Warnings and precautions

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

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

- Ocular signs and symptoms including corneal ulcers, corneal opacities, keratitis, conjunctivitis, eye pain, and photophobia have been reported in patients treated with nitisinone (see section “Undesirable effects”). Therefore, a baseline ophthalmologic examination including slit-lamp examination should be considered prior to initiating Nityr treatment. Patients who develop photophobia, eye pain, or signs of inflammation such as redness, swelling, or burning of the eyes 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.

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

Leukopenia and Severe Thrombocytopenia

In clinical trials, patients treated with another oral formulation of nitisinone and dietary restriction developed transient leukopenia (3%), thrombocytopenia (3%), or both (1.5%) (see section “Undesirable effects”). No patients developed infections or bleeding as a result of the episodes of leukopenia and thrombocytopenia. Monitor platelet and white blood cell counts during therapy with Nityr.

Liver monitoring

The liver function should be monitored regularly by liver function tests and suitable imaging. It is recommended to also monitor serum alpha-fetoprotein concentrations. Increase in serum alpha-fetoprotein concentration may be a sign of inadequate treatment. Patients with

increasing alpha fetoprotein or signs of nodular changes of the liver parenchyma should always be evaluated for hepatic malignancy.
Monitoring visits should be performed every 6 months; shorter intervals between visits are recommended in case of adverse events.

Concomitant use with other medicinal products
Nitisinone is a moderate CYP2C9 inhibitor. Nitisinone treatment may therefore result in increased plasma concentrations of co-administered medicinal products metabolized primarily via CYP2C9. Nitisinone treated patients who are concomitantly treated with medicinal products with a narrow therapeutic window metabolized through CYP2C9, such as warfarin and phenytoin, should be carefully monitored. Dose-adjustment of these co-administered medicinal products may be needed (see section “Interaction”).

Nityr contains lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose galactose malabsorption should not take this medicinal product.

Interactions

No formal interaction studies were conducted.
Nitisinone is metabolised in vitro by CYP 3A4 and dose-adjustment may therefore be needed when nitisinone is co-administered with inhibitors or inducers of this enzyme.
Based on data from a clinical interaction study with 80 mg nitisinone at steady-state, nitisinone is a moderate inhibitor of CYP2C9 (2.3-fold increase in tolbutamide AUC), therefore nitisinone treatment may result in increased plasma concentrations of co-administered medicinal products metabolized primarily via CYP2C9 (see section “Warnings and precautions”).
Nitisinone is a weak inducer of CYP2E1 (30% decrease in chlorzoxazone AUC) and a weak inhibitor of OAT1 and OAT3 (1.7-fold increase in AUC of furosemide), whereas nitisinone did not inhibit CYP2D6 (see section “Pharmacokinetics”).
A food effect study has been conducted with Nityr. The study demonstrated that Nityr can be administered with or without food without affecting its bioavailability.

Pregnancy, Lactation

Pregnancy
There are no adequate data from the use of nitisinone in pregnant women. Studies in animals have shown reproductive toxicity (see section “Preclinical data”). The potential risk for humans is unknown. Nityr should not be used during pregnancy unless the clinical condition of the woman requires treatment with nitisinone.

Breast-feeding

It is unknown whether nitisinone is excreted in human breast milk. Animal studies have shown adverse postnatal effects via exposure of nitisinone in milk. Therefore, mothers receiving nitisinone must not breast-feed, since a risk to the suckling child cannot be excluded (see sections “Contraindications” and “Preclinical data”).

Fertility

There are no data on nitisinone affecting fertility.

Effects on ability to drive and use machines

Nityr has minor influence on the ability to drive and use machines. Adverse reactions involving the eyes (see section “Undesirable effects”) can affect the vision. If the vision is affected the patient should not drive or use machines while this impairment exists.

Undesirable Effects

Summary of the safety profile

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 section “Dosage and Administration”). 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 section “Warnings and Precautions”). Fourteen patients experienced ocular/visual events. The duration of the symptoms varied from 5 days to 2 years. Six patients had thrombocytopenia, three of which had platelet counts 30,000/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 undesirable effects listed below by MedDRA system organ class and absolute frequency, are based on data from a clinical trial and post-marketing use. Frequency is defined as very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000), not known (cannot be estimated from the available data). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Blood and lymphatic system disorders
Common: Thrombocytopenia, leucopenia, granulocytopenia
Uncommon: Leukocytosis

Eye disorders
Common: Conjunctivitis, corneal opacity, keratitis, photophobia, eye pain
Uncommon: Blepharitis

Skin and subcutaneous tissue disorders
Uncommon Exfoliative dermatitis, erythematous rash, pruritus

Investigations
Very common: Elevated tyrosine levels

Children and adolescents
The safety profile is mainly based on the paediatric population since nitisinone treatment should be started as soon as the diagnosis of hereditary tyrosinemia type 1 (HT-1) has been established. From clinical study and post marketing data there are no indications that the safety profile is different in different subsets of the paediatric population or different from the one in adult patients.

Reporting suspected adverse reactions after authorisation of the medicinal product is of great importantance. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspicion of a new or serious adverse reaction via the online portal ElViS (Electronic Vigilance System). Information can be found at www.swissmedic.ch.

Overdose

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. 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.

Properties/Effects

ATC-Code

Pharmacotherapeutic group: Other alimentary tract and metabolism products, Various alimentary tract and metabolism products, ATC code: A16AX04.

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 leading to the accumulation of 5-aminolevulinate.

Pharmacodynamic

Nitisinone treatment leads to normalised porphyrin metabolism with normal erythrocyte porphobilinogen synthase activity and urine 5-aminolevulinate, decreased urinary excretion of succinylacetone, increased plasma tyrosine concentration and increased urinary excretion of phenolic acids. Available data from a clinical study indicates that in more than 90% of the patients urine succinylacetone was normalised during the first week of treatment. Succinylacetone should not be detectable in urine or plasma when the nitisinone dose is properly adjusted.

Clinical efficacy

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 twice daily. 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.

In this clinical study, for patients presenting with HT-1 younger than 2 months of age who were treated with dietary restriction and nitisinone, 2- and 4-year survival probabilities were 88% and 88%, respectively. Data from historical controls showed that patients 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 on urine and plasma succinylacetone, porphyrin metabolism, and urinary alpha-1-microglobulin were also assessed in this clinical study. Urine succinylacetone was measured in 186 patients. In all 186 patients, urinary succinylacetone level decreased to less than 1 mmol/mol creatinine. The median time to normalization was 0.3 months. The probability of recurrence of abnormal values of urine succinylacetone was 1% at a nitisinone concentration of 37 micromol/L (95% confidence interval: 23, 51 micromol/L). Plasma succinylacetone was measured in 172 patients. In 150 patients (87%), plasma succinylacetone decreased to less than 0.1 micromol/L. The median time to normalization was 3.9 months.

Porphyria-like crisis were reported in 3 patients (0.3% of cases per year) during the clinical study. This compares to an incidence of 5 to 20% of cases per year expected as part of the natural history of the disorder.

An assessment of porphyria-like crises was performed because these events are commonly reported in patients with HT-1 who are not treated with nitisinone.

Urinary alpha-1-microglobulin, a proposed marker of proximal tubular dysfunction, was measured in 100 patients at baseline. The overall median pretreatment level was 4.3 grams/mol creatinine. After one year of treatment in a subgroup of patients (N=100), overall median alpha-1-microglobulin decreased by 1.5 grams/mol creatinine. In patients 24 months of age and younger in whom multiple values were available (N=65), median alpha-1-microglobulin levels decreased from 5 to 3 grams/mol creatinine (reference value for age less than or equal to12 grams/mol creatinine). In patients older than 24 months in whom multiple values were available (N=35), median alpha-1-microglobulin levels decreased from

2.8 to 2 grams/mol creatinine (reference for age less than or equal to 6 grams/mol creatinine).
The long term effect of nitisinone on hepatic function was not assessed.

A study to evaluate the pharmacokinetic, efficacy and safety of once daily dosing compared to twice daily dosing was performed in 19 patients with HT-1. There were no clinically important differences in undesirable effects or other safety assessments between once and twice daily dosing. No patient had detectable succinylacetone levels at the end of the once-daily treatment period. The study indicates that once daily administration is safe and efficacious across all ages of patients. Data is, however, limited in patients with body weight <20 kg.

Pharmacokinetics

Absorption
Formal absorption, distribution, metabolism and elimination studies have not been performed with nitisinone.
In 23 healthy volunteers, after administration of a single dose of Nityr tablets (10 mg) the terminal half-life (median) of nitisinone in plasma was 59 hours (ranging from 41 to 74 hours).

Distribution
See under Absorption

Metabolism
In vitro studies using human liver microsomes and cDNA-expressed P450 enzymes have shown limited CYP3A4-mediated metabolism.
Based on data from a clinical interaction study with 80 mg nitisinone at steady-state, nitisinone caused a 2.3-fold increase in AUC∞ of the CYP2C9 substrate tolbutamide, which is indicative of a moderate inhibition of CYP2C9. Nitisinone caused an approximate 30% decrease in chlorzoxazone AUC∞, indicative of a weak induction of CYP2E1. Nitisinone does not inhibit CYP2D6 since metoprolol AUC∞ was not affected by the administration of nitisinone. Furosemide AUC∞ was increased 1.7-fold, indicating a weak inhibition of OAT1/OAT3 (see sections “Warnings and precautions” and “Interactions”). Based on *in-vitro* studies, nitisinone is not expected to inhibit CYP1A2, 2C19 or 3A4-mediated metabolism or to induce CYP1A2, 2B6 or 3A4/5. Nitisinone is not expected to inhibit P-gp, BCRP or OCT2-mediated transport. Nitisinone plasma concentration reached in clinical setting is not expected to inhibit OATP1B1, OATP1B3 mediated transport.

Elimination
See under Absorption

Preclinical Data

Nitisinone has shown embryo-foetal toxicity in the mouse and rabbit at clinically relevant dose levels. In the rabbit, nitisinone induced a dose-related increase in malformations (umbilical hernia and gastroschisis) from a dose level 2.5-fold higher than the maximum recommended human dose (2 mg/kg/day).

A pre- and postnatal development study in the mouse showed statistically significantly reduced pup survival and pup growth during the weaning period at dose levels 125- and 25-fold higher, respectively, than the maximum recommended human dose, with a trend toward a negative effect on pup survival starting from the dose of 5 mg/kg/day. In rats, exposure via milk resulted in reduced mean pup weight and corneal lesions.

No mutagenic but a weak clastogenic activity was observed in *in vitro* studies. There was no evidence of *in vivo* genotoxicity (mouse micronucleus assay and mouse liver unscheduled DNA synthesis assay). Nitisinone did not show carcinogenic potential in a 26-week carcinogenicity study in transgenic mice (TgrasH2).

Other information

Incompatibilities
Not applicable.

Shelf life
Do not use this medicine after the expiry date ("EXP") stated on the container.

Special precautions for storage
Store at room temperature (15-25°C). Keep out of the reach of children.
Keep the container tightly closed in the outer carton to protect the content from light.

Marketing authorisation number

67970 (Swissmedic)

Packs

Tablets with 2 mg, 5 mg and 10 mg: 60 (B)

Marketing authorisation holder

Curatis AG, 4410 Liestal

Date of revision of the text

Foreign reference product: February 2020

With safety-relevant amendments of Swissmedic: January 2022