Summary of Product Characteristics

1. NAME OF THE MEDICINAL PRODUCT

NITYR 2mg, 5mg, 10mg tablets.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 2 mg, 5mg, 10mg nitisinone.
For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

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

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

4.2 Posology and method of administration

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

Posology
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 NITYR tablets treatment, a diet deficient in phenylalanine and tyrosine is required and should be followed by monitoring of plasma amino acids (see sections 4.4 and 4.8)

The recommended initial dose in the pediatric and adult population is 1mg/kg body weight administered orally. The dose of NITYR tablets should be adjusted individually. It is recommended to administer the dose once daily. However, due to the limited data in patients with body weight <20 kg, 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 4.4). If urine succinylacetone is still detectable one month after the start of NITYR tablets treatment, the NITYR tablets dose should be increased to 1.5 mg/kg body weight/day divided in 2 doses. 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 tests above, during the initiation of therapy, switch from twice daily to once daily dosing or if there is a deterioration, it may be necessary to follow more closely all available biochemical parameters (i.e. plasma succinylacetone, urine 5-aminolevulinate (ALA) and erythrocyte porphobilinogen (PBG)-synthase activity).

Special populations

There are no dosage adjustments provided in the manufacturer's labeling for renal or liver impaired patients

Pediatric population
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 <20 kg, it is recommended to divide the total daily dose into two daily administrations in this patient population.

Method of administration
Tablets may be disintegrated in water and administered using an oral syringe or crushed and mixed with applesauce

It is recommended that if NITYR tablets treatment is initiated with food, this should be maintained on a routine basis, see section 4.5.

- Maintain dietary restriction of tyrosine and phenylalanine when taking NITYR tablets.
- NITYR tablets can be taken with or without food.
- For patients, including pediatric patients, who have difficulty swallowing intact tablets, NITYR tablets can be disintegrated in water and administered using an oral syringe. If patients can swallow semi-solid foods, NITYR tablets can be crushed and mixed with applesauce. Administration of NITYR tablets with other liquids or foods has not been studied and is not recommended.

Preparation and Administration of NITYR 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 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 and ensuring the syringe is empty. If particles are still present in the syringe, repeat steps 9-10.

<u>Preparation and Administration of NITYR Mixed in Applesauce</u>
For patients who can swallow semi-solid food, NITYR tablets can be crushed and mixed with 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.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
Mothers receiving NITYR tablets must not breast-feed (see sections 4.6 and 5.3).

4.4 Special warnings and precautions for use

Monitoring of plasma tyrosine levels
It is recommended that a slit-lamp examination of the eyes is performed before initiation of NITYR tablets treatment and thereafter regularly, at least once a year. A patient displaying visual disorders during treatment with NITYR tablets should without delay be examined by an ophthalmologist. It should be established that the patient is adhering to his dietary regimen and the plasma tyrosine concentration should be measured. A more restricted tyrosine and phenylalanine diet should be implemented in case the plasma tyrosine level is above 500 micromol/l. It is not recommended to lower the plasma tyrosine concentration by reduction or discontinuation of NITYR tablets, since the metabolic defect may result in deterioration of the patient's clinical condition.

Liver monitoring
The liver function should be monitored regularly by liver function tests and liver imaging. It is recommended also to monitor serum alpha-fetoprotein concentration. Increase 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.

Platelet and white blood cell (WBC) monitoring
Leukopenia and/or thrombocytopenia have been reported; may improve with dose reduction. May be due to underlying liver disease rather than drug-related (McKiernan 2006). Monitor platelets and WBC regularly during therapy.

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
NITYR tablet is a moderate CYP2C9 inhibitor. NITYR tablets treatment may therefore result in increased plasma concentrations of co-administered medicinal products metabolized primarily via CYP2C9. NITYR tablets 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 4.5).

4.5 Interaction with other medicinal products and other forms of interaction

NITYR tablet is metabolized *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 4.4).
Nitisinoneis 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 5.2).No formal food interactions studies have been performed with NITYR tablets.
However, NITYR tablets has been co-administered with food during the generation of efficacy and safety data. Therefore, it is recommended that treatment with NITYR tablets is initiated with food, this should be maintained on a routine basis. See section 4.2.

4.6 Fertility, pregnancy and lactation

Pregnancy
There are no adequate data from the use of NITYR tablets in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). The potential risk for humans is unknown. NITYR tablets should not be used during pregnancy unless the clinical condition of the woman requires treatment with NITYR tablets.

Lactation
It is not known whether NITYR tablets is excreted in human breast milk. Animal studies have shown adverse postnatal effects via exposure of NITYR tablets in milk. Therefore, mothers receiving NITYR tablets must not breast-feed, since a risk to the suckling child cannot be excluded (see sections 4.3 and 5.3).

Fertility
There are no data on NITYR tablets affecting fertility.

4.7 Effects on ability to drive and use machines

NITYR tablets has minor influence on the ability to drive and use machines. Adverse reactions involving the eyes (see section 4.8) can affect the vision. If the vision is affected the patient should not drive or use machines until the event has subsided.

4.8 Undesirable effects

Summary of the safety profile
By its mode of action, nitisinone increases tyrosine levels in all nitisinone treated patients. Eye-related adverse reactions, such as conjunctivitis, corneal opacity, keratitis, photophobia, and eye pain, related to elevated tyrosine levels are therefore common. Other common adverse reactions include thrombocytopenia, leucopenia, and granulocytopenia. Exfoliative dermatitis may occur uncommonly.

Tabulated list of adverse reactions
The adverse reactions 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, adverse reactions are presented in order of decreasing seriousness.

MedDRA system organ class	Frequency	Adverse reaction
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

Description of selected adverse reactions
NITYR tablets treatment leads to elevated tyrosine levels. Elevated levels of tyrosine have been associated with eye-related adverse reactions, such as e.g. corneal opacities and hyperkeratotic lesions. Restriction of tyrosine and phenylalanine in the diet should limit the toxicity associated with this type of tyrosinemia by lowering tyrosine levels (see section 4.4). In clinical studies, granulocytopenia was only uncommonly severe ($<0.5x10^9$/L) and not associated with infections. Adverse reactions affecting the MedDRA system organ class 'Blood and lymphatic system disorders' subsided during continued NITYR tablets treatment.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form https://sideeffects.health.gov.il.

4.9 Overdose

No case of overdose has been reported. Accidental ingestion of NITYR tablets 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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other alimentary tract and metabolism products, Various alimentary tract and metabolism products, ATC code: A16A X04.

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. NITYR tablets 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, NITYR tablets 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.

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

Clinical efficacy and safety
The clinical study was open-labelled and uncontrolled. The dosing frequency in the study was twice daily. Survival probabilities after 2, 4 and 6 years of treatment with another oral formulation of nitisinone are summarized in the table below.

NTBC study (N=250)			
Age at start of treatment	2 years	4 years	6 years
< 2 months	93%	93%	93%
< 6 months	93%	93%	93%
> 6 months	96%	95%	95%
Overall	94%	94%	94%

Data from a study used as a historical control (van Spronsen et al., 1994) showed the following survival probability.

Age at onset of symptoms	1 year	2 years
< 2 months	38%	29%
> 2-6 months	74%	74%
> 6 months	96%	96%

Treatment with another oral formulation of nitisinone was also found to result in reduced risk for the development of hepatocellular carcinoma compared to historical data on treatment with dietary restriction alone. It was found that the early initiation of treatment resulted in a further reduced risk for the development of hepatocellular carcinoma.
The 2-, 4-, and 6-year probability of no occurrence of HCC during treatment for patients aged 24 months or younger at the start of treatment and for those older than 24 months at the start of treatment is shown in the following table:

NTBC study (N=250)							
	Number of patients at				Probability of no HCC (95% confidence interval) at		
	start	2 years	4 years	6 years	2 years	4 years	6 years
All patients	250	155	86	15	98% (95; 100)	94% (90; 98)	91% (81; 100)
Start age < 24 months	193	114	61	8	99% (98; 100)	99% (97; 100)	99% (94; 100)
Start age > 24 months	57	41	25	8	92% (84; 100)	82% (70; 95)	75% (56; 95)

In an international survey of patients with HT-1 on treatment with dietary restriction alone, it was found that HCC had been diagnosed in 18% of all patients aged 2 years and above.

A study to evaluate the PK, 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 AEs or other safety assessments between once and twice daily dosing. No patient had detectable succinylacetone (SA) 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.

5.2 Pharmacokinetic properties

Formal absorption, distribution, metabolism and elimination studies have not been performed with another oral formulation of nitisinone. In 10 healthy male volunteers, after administration of a single dose (1 mg/kg body weight) the terminal half-life (median) in plasma was 54 hours. Population pharmacokinetic analysis has been conducted on a group of 207 HT-1 patients. The clearance and half-life were determined to be 0.0956 l/kg body weight/day and 52.1 hours respectively.

In vitro studies using human liver microsomes and cDNA-expressed P450 enzymes have shown limited CYP 3A4-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 4.4 and 4.5).

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.

5.3 Preclinical safety data

Another oral formulation of nitisinone has shown embryo-foetal toxicity in the mouse and rabbit at clinically relevant dose levels. In the rabbit, it induced a dose-related increase in malformations (umbilical hernia and gastroschisis) from a dose level of 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 significant reduced pup survival and pup growth during the weaning period at dose levels of 125- and 25-fold higher, respectively, 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). It did not show carcinogenic potential in a 26- week carcinogenicity study in transgenic mice (TgrasH2).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Glycerol Dibehenate NF/Ph.Eur
Lactose monohydrate (Pharmatose 200M)
Lactose monohydrate (SuperTab 30GR)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life
The expiry date of the product is indicated on the packaging materials.

6.4 Special precautions for storage
Do not store above 25°C
Period after opening: 2 months

6.5 Nature and contents of container
High density polyethylene bottle with a tamper proof low density polyethylene snap -on caps, childproof cap, containing 60 capsules.

6.6 Special precautions for disposal
No special requirements.
Any unused product or waste material should be disposed of in accordance with local requirements.

7. MANUFACTURER
Cycle Pharmaceuticals Ltd,
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8. MARKETING AUTHORISATION HOLDER
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