ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Nityr 10 mg tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 10 mg nitisinone.

Excipient with known effect

Each tablet contains 102.99 mg lactose (as monohydrate).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablet.

White to beige, round (7 mm), flat tablet, which may display light yellow to brown speckles, marked "10" on one side and "L" on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Hereditary tyrosinemia type 1 (HT-1)

Nityr is indicated for the treatment of adult and paediatric patients with confirmed diagnosis of hereditary tyrosinemia type 1 (HT-1) in combination with dietary restriction of tyrosine and phenylalanine.

Alkaptonuria (AKU)

Nityr is indicated for the treatment of adult patients with alkaptonuria (AKU).

4.2 Posology and method of administration

Posology

HT-1
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 followed by monitoring of plasma amino acids (see sections 4.4 and 4.8).

Starting dose HT-1

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 < 20 kg,

it is recommended to divide the total daily dose into two daily administrations in this patient population.

Dose adjustment HT-1

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 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 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).

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

The recommended dose in the adult AKU population is 10 mg once daily.

Special populations

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

Paediatric population

HT-1: 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.

AKU: The safety and efficacy of Nityr in children aged 0 to 18 years with AKU have not been established. No data are available.

Method of administration

The tablets may be taken with or without food. Tablets are not suitable for breaking to make up additional strengths.

For patients who require additional strengths (i.e. between multiples of 10 mg or lower than 10 mg) other medicinal products with lower strengths are available.

For paediatric patients who have difficulties swallowing tablets, other pharmaceutical forms are available.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Mothers receiving nitisinone must not breast-feed (see sections 4.6 and 5.3).

4.4 Special warnings and precautions for use

Monitoring visits should be performed every 6 months; shorter intervals between visits are recommended in case of adverse events.

Monitoring of plasma tyrosine levels

It is recommended that a slit-lamp examination of the eyes is performed before initiation of nitisinone treatment and thereafter regularly, at least once a year. A patient displaying visual disorders during treatment with nitisinone should without delay be examined by an ophthalmologist.

HT-1: It should be established that the patient is adhering to his/her 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 nitisinone, since the metabolic defect may result in deterioration of the patient's clinical condition.

AKU: In patients who develop keratopathies, plasma tyrosine levels should be monitored. A diet restricted in tyrosine and phenylalanine should be implemented to keep the plasma tyrosine level below 500 micromol/l. In addition, nitisinone should be temporarily discontinued and may be reintroduced when the symptoms have been resolved.

Liver monitoring

HT-1: The liver function should be monitored regularly by liver function tests and liver 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 nodules in the liver should always be evaluated for hepatic malignancy.

Platelet and white blood cell (WBC) monitoring

It is recommended that platelet and WBC counts are monitored regularly for both HT-1 and AKU, as a few cases of reversible thrombocytopenia and leucopenia were observed during clinical evaluation of HT-1.

Lactose

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

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 4.5).

4.5 Interaction with other medicinal products and other forms of interaction

Nitisinone is metabolised *in vitro* by CYP3A4 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).

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 5.2).

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.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no adequate data from the use of nitisinone in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). 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. Nitisinone crosses the human placenta.

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 4.3 and 5.3).

Fertility

There are no data on nitisinone affecting fertility.

4.7 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 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 in both HT-1 and AKU patients. In the HT-1 population 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 clinical studies in patients with HT-1 and AKU and post-marketing use in HT-1. 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.

Table 1. Summary of adverse reactions observed during clinical trials

MedDRA system organ class	Frequency in HT-1	Frequency in AKU[1]	Adverse reaction
Infections and infestations		Common	Bronchitis, pneumonia
Blood and lymphatic system disorders	Common		Thrombocytopenia, leucopenia, granulocytopenia
	Uncommon		Leukocytosis
Eye disorders	Common		Conjunctivitis, corneal opacity, keratitis, photophobia
		Very common[2]	Keratopathy
	Common	Very common[2]	Eye pain
	Uncommon		Blepharitis
Skin and subcutaneous tissue disorders	Uncommon		Exfoliative dermatitis, erythematous rash
	Uncommon	Common	Pruritus, rash
Investigations	Very common	Very common	Elevated tyrosine levels

[1]The frequency is based on one clinical study in AKU.
[2]Elevated tyrosine levels are associated with eye-related adverse reaction. Patients in the AKU study did not have a diet restricted in tyrosine and phenylalanine.

Description of selected adverse reactions

Nitisinone 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 in HT-1 and AKU patients. 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 of HT-1, granulocytopenia was only uncommonly severe ($< 0.5 \times 10^9$ /L) and not associated with infections. Adverse reactions affecting the MedDRA system organ class 'Blood and lymphatic system disorders' subsided during continued nitisinone treatment.

Paediatric population

The safety profile in HT-1 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 safety profile in adult patients.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

Mechanism of action

Nitisinone is a competitive inhibitor of 4-hydroxyphenylpyruvate dioxygenase, the second step in the tyrosine metabolism. By inhibiting the normal catabolism of tyrosine in patients with HT-1 and AKU, nitisinone prevents the accumulation of harmful metabolites downstream of 4-hydroxyphenylpyruvate dioxygenase.

The biochemical defect in HT-1 is a deficiency of fumarylacetoacetate hydrolase, which is the final enzyme of the tyrosine catabolic pathway. Nitisinone prevents the accumulation of the toxic intermediates maleylacetoacetate and fumarylacetoacetate. These intermediates are otherwise converted to the toxic metabolites succinylacetone and succinylacetoacetate. Succinylacetone inhibits the porphyrin synthesis pathway leading to the accumulation of 5-aminolevulinate.

The biochemical defect in AKU is a deficiency of homogentisate 1,2 dioxygenase, the third enzyme of the tyrosine catabolic pathway. Nitisinone prevents the accumulation of the harmful metabolite homogentisic acid (HGA), which otherwise leads to ochronosis of joints and cartilage and thereby the development of the clinical features of the disease.

Pharmacodynamic effects

In patients with HT-1, 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.

In patients with AKU, nitisinone treatment reduces the accumulation of HGA. Available data from a clinical study shows a 99.7 % reduction of urinary HGA, and a 98.8 % reduction of serum HGA, following nitisinone treatment compared to untreated control patients after 12 months of treatment.

Clinical efficacy and safety in HT-1

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 nitisinone are summarised in the table below.

Table 2. Probability of survival after treatment with nitisinone

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.

Table 3. Probability of survival based on historical control

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

Treatment with 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 nitisinone 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:

Table 4. Probability of HCC not developing during nitisinone treatment

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.

Clinical efficacy and safety in AKU

The efficacy and safety of 10 mg once daily nitisinone in the treatment of adult patients with AKU have been demonstrated in a randomized, evaluator-blinded, no-treatment controlled, parallel-group 48-months study in 138 patients (69 treated with nitisinone). The primary endpoint was the effect on urinary HGA levels; a 99.7 % reduction following nitisinone treatment compared to untreated control patients was seen after 12 months. Treatment with nitisinone was shown to have a statistically significant positive effect on cAKUSSI, eye pigmentation, ear pigmentation, osteopenia of the hip, and number of spinal regions with pain compared to the untreated control. cAKUSSI is a composite score including eye and ear pigmentation, kidney and prostate stones, aortic stenosis, osteopenia, bone fractures, tendon/ligament/muscle ruptures, kyphosis, scoliosis, joint replacements, and other manifestations of AKU. Thus, the lowered HGA levels in nitisinone-treated patients resulted in a reduction of the ochronotic process and reduced clinical manifestations, supporting a decreased disease progression.

Ocular events, such as keratopathy and eye pain, infections, headache and weight gain were reported with a higher incidence in nitisinone-treated than in untreated patients. Keratopathy led to temporary or permanent treatment discontinuation in 14 % of nitisinone-treated patients but was reversible upon withdrawal of nitisinone.

No data is available for patients > 70 years.

5.2 Pharmacokinetic properties

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).

A 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 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 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

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).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Glycerol dibehenate
Lactose monohydrate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

During the shelf life, the patient may store the bottle after first opening for a period of 2 months, after which the medicinal product must be discarded.

6.4 Special precautions for storage

This medicinal product does not require any special temperature storage conditions.
Store in the original bottle in order to protect from light.

6.5 Nature and contents of container

HDPE 75 mL square bottle with a tamper-evident child-resistant closure of polypropylene (PP). Each bottle contains 60 tablets. Each carton contains 1 bottle.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Cycle Pharmaceuticals (Europe) Limited
70 Sir John Rogerson's Quay
Dublin 2
D02 R296, Ireland

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/18/1290/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 26 July 2018
Date of latest renewal: 04 May 2023

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

ANNEX II

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer(s) responsible for batch release

Millmount Healthcare Limited
Block-7, City North Business Campus
Stamullen, Co. Meath,
K32 YD60, Ireland

Sciensus International B.V.
Bijsterhuizen 3142
6604 LV Wijchen
Netherlands

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- Periodic safety update reports (PSURs)

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- Risk management plan (RMP)

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Nityr 10 mg tablets
nitisinone

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 10 mg nitisinone.

3. LIST OF EXCIPIENTS

Contains lactose, see leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Tablet

60 tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in the original bottle in order to protect from light.
Shelf life after first opening: 2 months
Open date:

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Cycle Pharmaceuticals (Europe) Limited
70 Sir John Rogerson's Quay
Dublin 2
D02 R296, Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/18/1290/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Nityr 10 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

BOTTLE LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Nityr 10 mg tablets
nitisinone
Oral use

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

60 tablets

6. OTHER

Contains lactose.

Store in the original bottle in order to protect from light.

Shelf life after first opening: 2 months
Open date:

Cycle Pharmaceuticals (Europe) Limited
70 Sir John Rogerson's Quay
Dublin 2
D02 R296, Ireland

B. PACKAGE LEAFLET

Package leaflet: Information for the user

Nityr 10 mg tablets
nitisinone

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Nityr is and what it is used for

Nityr contains the active substance nitisinone.

Nityr is used to treat:
- A rare disease called hereditary tyrosinemia type 1 in adults, adolescents and children.
- A rare disease called alkaptonuria (AKU) in adults.

In these diseases your body is unable to completely break down the amino acid tyrosine (amino acids are building blocks of our proteins), forming harmful substances. These substances are accumulated in your body. Nityr blocks the breakdown of tyrosine and the harmful substances are not formed.

For the treatment of hereditary tyrosinemia type 1, you must follow a special diet while you are taking this medicine, because tyrosine will remain in your body. This special diet is based on low tyrosine and phenylalanine (another amino acid) content.

For the treatment of AKU, your doctor may advise you to follow a special diet.

2. What you need to know before you take Nityr

Do not take Nityr
- if you are allergic to nitisinone or any of the other ingredients of this medicine (listed in section 6).

Do not breast-feed while taking this medicine, see section “Pregnancy and breast-feeding”.

Warnings and precautions
Talk to your doctor or pharmacist before taking Nityr.
- Your eyes will be checked by an ophthalmologist before and regularly during nitisinone treatment. If you get red eyes or any other signs of effects on the eyes, contact your doctor immediately for an eye examination. Eye problems could be a sign of inadequate dietary control (see section 4).

During the treatment, blood samples will be drawn in order for your doctor to check whether the treatment is adequate and to make sure that there are no possible side effects causing blood disorders.

If you receive Nityr for treatment of hereditary tyrosinemia type 1, your liver will be checked at regular intervals because the disease affects the liver.

Follow-up by your doctor should be performed every 6 months. If you experience any side effects, shorter intervals are recommended.

Other medicines and Nityr
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.
Nityr may interfere with the effect of other medicines, such as:
- Medicines for epilepsy (such as phenytoin)
- Medicines against blood clotting (such as warfarin)

Nityr with food
Nityr can be taken with or without food throughout your course of treatment.

Pregnancy and breast-feeding
The safety of this medicine has not been studied in pregnant and breast-feeding women.
Please contact your doctor if you plan to become pregnant. If you become pregnant you should contact your doctor immediately.
Do not breast-feed while taking this medicine, see section “Do not take Nityr”.

Driving and using machines
This medicine has minor influence on the ability to drive and use machines. However, if you experience side effects affecting your vision you should not drive or use machines until your vision is back to normal (see section 4 “Possible side effects”).

Nityr contains lactose If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicine.

3. How to take Nityr

Always take this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure.

For hereditary tyrosinemia type 1, treatment with this medicine should be started and supervised by a doctor experienced in the treatment of the disease .

For hereditary tyrosinemia type 1, the recommended total daily dose is 1 mg/kg body weight administered orally. Your doctor will adjust the dose 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.

For AKU, the recommended dose is 10 mg once daily.

Patients who have problems swallowing Nityr tablets whole, are recommended to take alternative nitisinone formulations.

If you take more Nityr than you should
If you have taken more of this medicine than you should, contact your doctor or pharmacist as soon as possible.

If you forget to take Nityr
Do not take a double dose to make up for a forgotten dose. If you forget to take a dose, contact your doctor or pharmacist.

If you stop taking Nityr
If you have the impression that the medicine is not working properly, talk to your doctor. Do not change the dose or stop the treatment without talking to your doctor.

If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

If you notice any side effects relating to the eyes, talk to your doctor immediately to have an eye examination. Treatment with nitisinone leads to higher levels of tyrosine in the blood which can cause eye related symptoms. In patients with hereditary tyrosinemia type 1, commonly reported eye related side effects (may affect more than 1 in 100 people) caused by higher tyrosine levels are inflammation in the eye (conjunctivitis), opacity and inflammation in the cornea (keratitis), sensitivity to light (photophobia) and eye pain. Inflammation of the eyelid (blepharitis) is an uncommon side effect (may affect up to 1 in 100 people).

In AKU patients, eye irritation (keratopathy) and eye pain are very commonly reported side effects (may affect more than 1 in 10 people).

Other side effects reported in patients with hereditary tyrosinemia type 1 are listed below:
Other common side effects
- Reduced number of platelets (thrombocytopenia) and white blood cells (leukopenia), shortage of certain white blood cells (granulocytopenia).

Other uncommon side effects
- increased number of white blood cells (leucocytosis),
- itching (pruritus), skin inflammation (exfoliative dermatitis), rash.

Other side effects reported in patients with AKU are listed below:
Other common side effects
- bronchitis
- pneumonia
- itching (pruritus), rash

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Nityr

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and bottle label after EXP. The expiry date refers to the last day of that month.

This medicine does not require any special temperature storage conditions.
Store in the original bottle in order to protect from light.

Once the bottle is opened, the medicine can be stored for a period of 2 months, after which it must be discarded.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Nityr contains
- The active substance is nitisinone. Each tablet contains 10 mg nitisinone.
- The other ingredients are glycerol dibehenate and lactose monohydrate (see section 2 under 'Nityr contains lactose').

What Nityr looks like and contents of the pack
Nityr are white to beige, round, flat tablets, which may display light yellow to brown speckles, marked with "L" on one side and "10" on the other side.
Nityr is available in a bottle containing 60 tablets.

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Manufacturer
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Detailed information on this medicine is available on the European Medicines Agency website: http://www.ema.europa.eu. There are also links to other websites about rare diseases and treatments.