

**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 less than 120 mg of lactose (as monohydrate).

For the full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Tablet.

White to beige, round (7 x 2.3 mm), flat tablets 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

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.

### 4.2 Posology and method of administration

Nitisinone 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 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).

The recommended initial 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 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).

#### *Special populations*

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

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

#### 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.

Breastfeeding (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 nitisinone treatment. A patient displaying visual disorders during treatment with nitisinone should without delay be examined by an ophthalmologist. 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.

#### Liver monitoring

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, as a few cases of reversible thrombocytopenia and leucopenia were observed during clinical evaluation.

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

#### Lactose

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

#### **4.5 Interaction with other medicinal products and other forms of interaction**

No formal interaction studies with other medicinal products have been 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 *in vitro* studies, nitisinone is not expected to inhibit CYP 1A2, 2C9, 2C19, 2D6, 2E1 or 3A4-mediated metabolism.

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.

##### 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. 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 ( $\geq 1/10$ ), common ( $\geq 1/100$  to  $< 1/10$ ), uncommon ( $\geq 1/1,000$  to  $< 1/100$ ), rare ( $\geq 1/10,000$  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

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.

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 ( $<0.5 \times 10^9/L$ ) 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 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

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

metabolites succinylacetone and succinylacetoacetate. Succinylacetone inhibits the porphyrin synthesis pathway leading to the accumulation of 5-aminolevulinate.

#### Pharmacodynamic effects

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 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 nitisinone are summarised 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 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:

NTBC study (N=250)							
	Numbers 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 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 CYP 3A4-mediated metabolism.

## **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 to protect from light.

For storage conditions after first opening of the medicinal product, see section 6.3.

#### **6.5 Nature and contents of container**

HDPE 75 mL square bottles 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 Ltd.  
Bailey Grundy Barrett Building  
Little St Mary's Lane,  
CB2 1RR, Cambridge,  
United Kingdom

### **8. MARKETING AUTHORISATION NUMBER(S)**

EU/1/18/1290/001

### **9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

### **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

Central Pharma (Contract Packing) Limited  
Caxton Road  
Elms Industrial Estate  
Bedford  
Bedfordshire  
MK41 0XZ  
UNITED KINGDOM

## **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**

The requirements for submission of periodic safety update reports 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 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**

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 Ltd.  
CB2 1RR, Cambridge,  
United Kingdom

**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 to protect from light.

Shelf life after first opening - 2 months

Open date:

Cycle Pharmaceuticals Ltd.

CB2 1RR, Cambridge, UK

**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. 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
2. What you need to know before you take Nityr
3. How to take Nityr
4. Possible side effects
5. How to store Nityr
6. Contents of the pack and other information

#### **1. What Nityr is and what it is used for**

The active ingredient of Nityr is nitisinone. This medicine is used for treatment of a rare disease called hereditary tyrosinemia type 1 in adults, adolescents and children.

In this disease 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.

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.

#### **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.

- 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. 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 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.

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

The recommended total daily dose is 1 mg/kg body administered orally weight. 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.

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. Common eye related side effects (may affect more than 1 in 10 people) 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).

##### 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.

#### **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 bottle and the carton 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 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 to 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**

The tablets are white to beige, round, flat which may display light yellow to brown speckles marked with “L” on one side and “10” on the other side.

The tablets are packaged in plastic square bottles with a tamper-evident child-resistant closure. Each bottle contains 60 tablets. Each carton contains 1 bottle.

**Marketing Authorisation Holder**

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

**Manufacturer**

Central Pharma Contract Packaging Limited  
MK41 0XZ, Bedford  
UK

**This leaflet was last revised in**

Detailed information on this medicine is available on the European Medicines Agency web site:

<http://www.ema.europa.eu>.