

Medicinal product no longer authorised

ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Nitisinone MDK 2 mg hard capsules
Nitisinone MDK 5 mg hard capsules
Nitisinone MDK 10 mg hard capsules
Nitisinone MDK 20 mg hard capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Nitisinone MDK 2 mg hard capsule

Each hard capsule contains 2 mg nitisinone.

Nitisinone MDK 5 mg hard capsule

Each hard capsule contains 5 mg nitisinone.

Nitisinone MDK 10 mg hard capsule

Each hard capsule contains 10 mg nitisinone.

Nitisinone MDK 20 mg hard capsule

Each hard capsule contains 20 mg nitisinone.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Hard capsule.

The capsules contain a white to off white powder.

Nitisinone MDK 2 mg hard capsule

White, opaque capsules of 15.7 mm imprinted with black ink “2 mg” on the cap and “Nitisinone” on the body.

Nitisinone MDK 5 mg hard capsule

White, opaque capsules of 15.7 mm imprinted with black ink “5 mg” on the cap and “Nitisinone” on the body.

Nitisinone MDK 10 mg hard capsule

White, opaque capsules of 15.7 mm imprinted with black ink “10 mg” on the cap and “Nitisinone” on the body.

Nitisinone MDK 20 mg hard capsule

White, opaque capsules of 15.7 mm imprinted with black ink “20 mg” on the cap and “Nitisinone” on the body.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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.

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 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

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

Method of administration

Oral use.

The capsule may be opened and the content suspended in a small amount of water or formula diet immediately before intake.

Other pharmaceutical forms are available for paediatric patients who have difficulties swallowing capsules.

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

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. 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.

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 metabolised primarily via CYP2C9. Nitisinone treated patients who are concomitantly treated with medicinal products with a narrow therapeutic window metabolised 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 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 metabolised 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).

No formal food interactions studies have been performed with Nitisinone MDK hard capsules. However, nitisinone has been co-administered with food during the generation of efficacy and safety data. Therefore, it is recommended that if nitisinone treatment with Nitisinone MDK hard capsules 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 nitisinone in pregnant women. Animal studies have shown reproductive toxicity (see section 5.3). The potential risk for humans is unknown. Nitisinone MDK 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

Nitisinone 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 within 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 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 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 HT1, these intermediates are converted to the toxic metabolites succinylacetone and succinylacetoacetate. Succinylacetone inhibits the porphyrin synthesis pathway leading to the accumulation of 5-aminolevulinic acid.

Pharmacodynamic effects

Nitisinone treatment leads to normalised porphyrin metabolism with normal erythrocyte porphobilinogen synthase activity and urine 5-aminolevulinic acid, 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 normalized 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 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 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)							
	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 nitisinone. In 10 healthy male volunteers, after administration of a single dose of nitisinone capsules (1 mg/kg body weight) the terminal half-life (median) of nitisinone in plasma was 54 hours (ranging from 39 to 86 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

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 significant reduced pup survival and pup growth during the weaning period at dose levels 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). Nitisinone did not show carcinogenic potential in a 26-week carcinogenicity study in transgenic mice (TgrasH2).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule content

Pregelatinised starch (maize)

Capsule shell

Gelatin

Titanium dioxide (E171)

Printing ink

Black iron oxide (E172)

Shellac

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Nitisinone MDK 2 mg, 5 mg and 10 mg hard capsules

2 years

Nitisinone MDK 20 mg hard capsules

3 years.

After first opening

Store in a refrigerator (2°C - 8°C).

Alternatively, the capsules may be stored for a single period of 2 months, at a temperature not above 25°C, after which the medicinal product must be discarded.

If capsule is opened

If the capsule is opened and the content suspended in a small amount of water or formula diet (see section 4.2), the suspended powder must be consumed immediately.

6.4 Special precautions for storage

Store in a refrigerator (2°C - 8°C). Store in the original bottle in order to protect from light.

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

6.5 Nature and contents of container

HDPE plastic bottle with LDPE plastic cap containing 60 hard capsules.

Each carton pack contains one 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

MendeliKABS Europe Limited
Unit 3D, North Point House
North Point Business Park
New Mallow Road
Cork, T23 AT2P, Ireland

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/17/1217/001
EU/1/17/1217/002
EU/1/17/1217/003
EU/1/17/1217/004

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 24 August 2017
Date of latest renewal:

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>.

Medicinal product no longer authorised

ANNEX II

- A. MANUFACTURER 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**

Medicinal product no longer authorised

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

Elara Pharmservices Europe Limited
239 Blanchardstown Corporate Park
Ballycoolin, Dublin
D15 KV21, Ireland

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.

Medicinal product no longer authorised

ANNEX III
LABELLING AND PACKAGE LEAFLET

Medicinal product no longer authorised

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

Nitisinone MDK 2 mg hard capsules
nitisinone

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each capsule contains 2 mg nitisinone.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Hard capsule

60 hard capsules

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

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

MendeliKABS Europe Limited
Unit 3D, North Point House
North Point Business Park
New Mallow Road
Cork, T23 AT2P, Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/17/1217/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Nitisinone MDK 2 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

BOTTLE LABEL

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

Nitisinone MDK 2 mg hard capsules
nitisinone
Oral use

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

After first opening, can be stored for a single period of 2 months at a temperature not above 25°C, after which it must be discarded.

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

60 hard capsules

6. OTHER

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

Date when removed from refrigerator:

MendeliKABS Europe Limited

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

Nitisinone MDK 5 mg hard capsules
nitisinone

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each capsule contains 5 mg nitisinone.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Hard capsule
60 hard capsules

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

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

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Unit 3D, North Point House
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New Mallow Road
Cork, T23 AT2P, Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/17/1217/002

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Nitisinone MDK 5 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

BOTTLE LABEL

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

Nitisinone MDK 5 mg hard capsules
nitisinone
Oral use

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

After first opening, can be stored for a single period of 2 months at a temperature not above 25°C, after which it must be discarded.

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

60 hard capsules

6. OTHER

Store in a refrigerator.
Store in the original bottle in order to protect from light.
Date when removed from refrigerator:

MendeliKABS Europe Limited

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

Nitisinone MDK 10 mg hard capsules
nitisinone

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each capsule contains 10 mg nitisinone.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Hard capsule
60 hard capsules

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

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

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12. MARKETING AUTHORISATION NUMBER(S)

EU/1/17/1217/003

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Nitisinone MDK 10 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

BOTTLE LABEL

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

Nitisinone MDK 10 mg hard capsules
nitisinone
Oral use

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

After first opening, can be stored for a single period of 2 months at a temperature not above 25°C, after which it must be discarded.

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

60 hard capsules

6. OTHER

Store in a refrigerator.
Store in the original bottle in order to protect from light.
Date when removed from refrigerator:

MendeliKABS Europe Limited

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

Nitisinone MDK 20 mg hard capsules
nitisinone

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each capsule contains 20 mg nitisinone.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Hard capsule
60 hard capsules

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

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

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13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Nitisinone MDK 20 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

BOTTLE LABEL

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

Nitisinone MDK 20 mg hard capsules
nitisinone
Oral use

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

After first opening, can be stored for a single period of 2 months at a temperature not above 25°C, after which it must be discarded.

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

60 hard capsules

6. OTHER

Store in a refrigerator.
Store in the original bottle in order to protect from light.
Date when removed from refrigerator:

MendeliKABS Europe Limited

Medicinal product no longer authorised

B. PACKAGE LEAFLET

Package leaflet: Information for the user

Nitisinone MDK 2 mg hard capsules
Nitisinone MDK 5 mg hard capsules
Nitisinone MDK 10 mg hard capsules
Nitisinone MDK 20 mg hard capsules

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 or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Nitisinone MDK is and what it is used for
2. What you need to know before you take Nitisinone MDK
3. How to take Nitisinone MDK
4. Possible side effects
5. How to store Nitisinone MDK
6. Contents of the pack and other information

1. What Nitisinone MDK is and what it is used for

Nitisinone MDK contains the active substance nitisinone. This medicine is used for treatment of a rare disease called hereditary tyrosinemia type I in adults, adolescents and children (in any age range).

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. Nitisinone MDK 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 Nitisinone MDK

Do not take Nitisinone MDK:

- 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 Nitisinone MDK.

- 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. 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 Nitisinone MDK

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.

Nitisinone may interfere with the effect of other medicines, such as:

- medicines for epilepsy (such as phenytoin)
- medicines against blood clotting (such as warfarin)

Nitisinone MDK with food

If you start nitisinone treatment by taking it with food, it is recommended that you carry on taking it with 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 Nitisinone MDK".

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").

3. How to take Nitisinone MDK

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 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.

If you have problems with swallowing the capsules, you may open the capsule and mix the powder with a small amount of water or formula diet just before you take it.

If you take more Nitisinone MDK 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 Nitisinone MDK

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 Nitisinone MDK

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) 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).

Other common side effects

- reduced number of platelets (thrombocytopenia) and white blood cells (leucopenia), 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 Nitisinone MDK

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 the bottle after "EXP". The expiry date refers to the last day of that month.

Store in a refrigerator (2°C - 8°C). Store in the original bottle in order to protect from light.

After first opening the bottle, the medicine can be stored for a single period of 2 months at a temperature not above 25°C, after which it must be discarded. Do not forget to mark the date on the bottle label, when removed from the refrigerator.

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 Nitisinone MDK contains

- The active substance is nitisinone.

Nitisinone MDK 2 mg: Each capsule contains 2 mg nitisinone.
Nitisinone MDK 5 mg: Each capsule contains 5 mg nitisinone.
Nitisinone MDK 10 mg: Each capsule contains 10 mg nitisinone.
Nitisinone MDK 20 mg: Each capsule contains 20 mg nitisinone.

- The other ingredients are:
 - Capsule content: pregelatinised maize starch
 - Capsule shell: gelatin, titanium dioxide (E171)
 - Printing ink: black iron oxide (E172), shellac glaze

What Nitisinone MDK looks like and contents of the pack

Nitisinone MDK hard capsules are 15.7 mm long, white, opaque, hard gelatin capsules, imprinted with “Nitisinone” on the body and the corresponding strength “2 mg”, “5 mg”, “10 mg” or “20 mg” on the cap, in black.

The capsule contains a white to off-white powder.

The capsules are packaged in plastic bottles. Each bottle contains 60 hard capsules. Each carton pack contains one bottle.

Marketing Authorisation Holder

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Manufacturer

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Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site:
<http://www.ema.europa.eu>