**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

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

## 3. PHARMACEUTICAL FORM

Hard capsule.
White, opaque capsules of 15.7 mm imprinted with black ink “2 mg” on the cap and “Nitisinone” on the body.
White, opaque capsules of 15.7 mm imprinted with black ink “5 mg” on the cap and “Nitisinone” on the body.
White, opaque capsules of 15.7 mm imprinted with black ink “10 mg” on the cap and “Nitisinone” on the body.
The capsules contain a white to off white powder.

## 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
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 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.

## 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.

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. Studies in animals 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.

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 (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000), not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

| MedDRA system organ class | Frequency | Adverse reaction |
|---|---|---|

| | | |
|---|---|---|
| Blood and lymphatic system disorders | Common | Thrombocytopenia, leucopenia, granulocytopenia |
| | Uncommon | Leukocytosis |
| Eye disorders | Common | Conjunctivitis, corneal opacity, keratitis, photophobia, eye pain |
| | Uncommon | Blepharitis |
| Skin and subcutaneous tissue disorders | Uncommon | Exfoliative dermatitis, erythematous rash, pruritus |
| Investigations | Very common | Elevated tyrosine levels |

Description of selected adverse reactions
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 ($<0.5x10^9$/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: A16A X04.

Mechanism of action
The biochemical defect in hereditary tyrosinemia type 1 (HT-1) is a deficiency of fumarylacetoacetate hydrolase, which is the final enzyme of the tyrosine catabolic pathway. 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-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 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.

### 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)

Imprint
- Black iron oxide (E172)
- Shellac

### 6.2 Incompatibilities

Not applicable.

### 6.3 Shelf life

24 months.

### 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.

### 6.5 Nature and contents of container

HDPE plastic bottle with LDPE plastic cap containing 60 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
The Light Box
111 Power Rd, Unit G.07, Chiswick
London, W4 5PY, United Kingdom

## 8. MARKETING AUTHORISATION NUMBER(S)

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

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

Date of first authorisation: 24 August 2017

## 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

Elara Pharmaservices Limited
Iron Farm
7 Grimes Gate, Diseworth
Leicestershire, DE74 2QD
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**

**CARTON**

## 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

## 2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each capsule contains 2 mg nitisinone.
Each capsule contains 5 mg nitisinone.
Each capsule contains 10 mg nitisinone.

## 3. LIST OF EXCIPIENTS

## 4. PHARMACEUTICAL FORM AND CONTENTS

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.

## 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
The Light Box
111 Power Rd, Unit G.07, Chiswick
London, W4 5PY, United Kingdom

## 12. MARKETING AUTHORISATION NUMBER(S)

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

## 13. BATCH NUMBER

Lot:

## 14. GENERAL CLASSIFICATION FOR SUPPLY

## 15. INSTRUCTIONS ON USE

## 16. INFORMATION IN BRAILLE

Nitisinone MDK 2 mg
Nitisinone MDK 5 mg
Nitisinone MDK 10 mg

## 17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included

## 18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC: {number}
SN: {number}
NN: {number}

**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 MDK 5 mg hard capsules
Nitisinone MDK 10 mg hard capsules
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 capsules

## 6. OTHER

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

MendeliKABS Europe Limited

# 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

**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

The active ingredient of Nitisinone MDK is nitisinone. This medicine is used for treatment of a rare disease called hereditary tyrosinemia type 1 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.

- 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 MDK with food and drink**
If you start Nitisinone MDK 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 or pharmacist.

## 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 (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 or pharmacist. 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.

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.

- 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 capsules are 15.7 mm long, white, opaque, hard gelatin capsules, imprinted with "Nitisinone" and the strength "2 mg", "5 mg" or "10 mg", in black. The capsule contains a white to off-white powder.

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

**Marketing Authorisation Holder**
MendeliKABS Europe Limited
The Light Box
111 Power Rd, Unit G.07, Chiswick
London, W4 5PY, United Kingdom

**Manufacturer**
Elara Pharmaservices Limited
Iron Farm
7 Grimes Gate, Diseworth
Leicestershire, DE74 2QD
United Kingdom

This leaflet was last revised in

**Other sources of information**
Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu.