Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Nitisinone Dipharma 10 mg hard capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 10 mg nitisinone.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Hard capsule.
White, opaque capsules (shell size 2, length 18.0 mm) imprinted "company logo" on the cap and "10" on the body of the capsule in dark blue ink.
The capsules contain a white to off white powder.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Hereditary tyrosinemia type 1 (HT-1)
Nitisinone Dipharma is indicated for the 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.

Alkaptonuria (AKU)
Nitisinone Dipharma is indicated for the treatment of adult patients with alkaptonuria (AKU).

4.2 Posology and method of administration

Posology

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

Treatment of all genotypes of the disease should be initiated as early as possible to increase overall survival and avoid complications such as liver failure, liver cancer and renal disease. Adjunct to the nitisinone treatment, a diet deficient in phenylalanine and tyrosine is required and should be followed by monitoring of plasma amino acids (see sections 4.4 and 4.8).

Starting dose HT-1
The recommended initial daily dose in the paediatric and adult population is 1 mg/kg body weight administered orally. The dose of nitisinone should be adjusted individually. It is recommended to administer the dose once daily. However, due to the limited data in patients with body weight <20 kg, it is recommended to divide the total daily dose into two daily administrations in this patient population.

Dose adjustment HT-1
During regular monitoring, it is appropriate to follow urine succinylacetone, liver function test values and alpha-fetoprotein levels (see section 4.4). If urine succinylacetone is still detectable one month after the start of nitisinone treatment, the nitisinone dose should be increased to 1.5 mg/kg body weight/day. A dose of 2 mg/kg body weight/day may be needed based on the evaluation of all biochemical parameters.This dose should be considered as a maximal dose for all patients.
If the biochemical response is satisfactory, the dose should be adjusted only according to body weight gain.

However, in addition to the tests above, during the initiation of therapy, switch from twice daily to once daily dosing or if there is a deterioration, it may be necessary to follow more closely all available biochemical parameters (i.e. plasma succinylacetone, urine 5-aminolevulinate (ALA) and erythrocyte porphobilinogen (PBG)-synthase activity).

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

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

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

Paediatric population
HT-1: The dose recommendation in mg/kg body weight is the same in children and adults.
However, due to the limited data in patients with body weight <20 kg, it is recommended to divide the total daily dose into two daily administrations in this patient population.

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

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

Nitisinone is also available as a 4 mg/ml oral suspension 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.

HT-1: It should be established that the patient is adhering to his/her dietary regimen and the plasma tyrosine concentration should be measured. A more restricted tyrosine and phenylalanine diet should be implemented in case the plasma tyrosine level is above 500 micromol/l. It is not recommended to lower the plasma tyrosine concentration by reduction or discontinuation of nitisinone, since the metabolic defect may result in deterioration of the patient's clinical condition.

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

Liver monitoring
HT-1: The liver function should be monitored regularly by liver function tests and liver imaging. It is recommended to also monitor serum alpha-fetoprotein concentrations. Increase in serum alpha-fetoprotein concentration may be a sign of inadequate treatment. Patients with increasing alpha-fetoprotein or signs of nodules in the liver should always be evaluated for hepatic malignancy.

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

Concomitant use with other medicinal products

Nitisinone is a moderate CYP2C9 inhibitor. Nitisinone treatment may therefore result in increased plasma concentrations of co-administered medicinal products metabolized primarily via CYP2C9. Nitisinone-treated patients who are concomitantly treated with medicinal products with a narrow therapeutic window metabolized through CYP2C9, such as warfarin and phenytoin, should be carefully monitored. Dose-adjustment of these co-administered medicinal products may be needed (see section 4.5).

4.5 Interaction with other medicinal products and other forms of interaction

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 Dipharma 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 Dipharma 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 Dipharma 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 in both HT-1 and AKU patients. In the HT-1 population other common adverse reactions include thrombocytopenia, leucopenia, and granulocytopenia. Exfoliative dermatitis may occur uncommonly.

Tabulated list of adverse reactions

The adverse reactions listed below by MedDRA system organ class and absolute frequency, are based on data from clinical trials in patients with HT-1 and AKU and post-marketing use in HT-1. Frequency is defined as very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000), not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

MedDRAsystemorganclass	Frequency	Frequency in AKU[1]	Adversereaction
Infections and infestations		Common	Bronchitis, pneumonia
Blood and lymphatic system	Common		Thrombocytopenia,

Disorders			leucopenia, granulocytopenia
	Uncommon		Leukocytosis
Eye disorders	Common		Conjunctivitis, corneal opacity, keratitis, photophobia
		Very common[2]	Keratopathy
	Common	Very common[2]	Eye pain
	Uncommon		Blepharitis
Skin and subcutaneous tissue Disorders	Uncommon		Exfoliative dermatitis, erythematous rash
	Uncommon	Common	Pruritus, rash
Investigations	Very common	Very common	Elevated tyrosine levels

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

Description of selected adverse reactions
Nitisinone treatment leads to elevated tyrosine levels. Elevated levels of tyrosine have been associated with eye-related adverse reactions, such as e.g. corneal opacities and hyperkeratotic lesions in HT-1 and AKU patients. Restriction of tyrosine and phenylalanine in the diet should limit the toxicity associated with this type of tyrosinemia by lowering tyrosine levels (see section 4.4).
In clinical studies of HT-1, granulocytopenia was only uncommonly severe ($<0.5x10^9$/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 in HT-1 is mainly based on the paediatric population since nitisinone treatment should be started as soon as the diagnosis of hereditary tyrosinemia type 1 (HT-1) has been established. From clinical study and post marketing data there are no indications that the safety profile is different in different subsets of the paediatric population or different from the safety profile in adult patients.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance, Website: www.hpra.ie; E-mail: medsafety@hpra.ie.

4.9 Overdose

Accidental ingestion of nitisinone by individuals eating normal diets not restricted in tyrosine and phenylalanine will result in elevated tyrosine levels. Elevated tyrosine levels have been associated with toxicity to eyes, skin, and the nervous system. Restriction of tyrosine and phenylalanine in the diet should limit toxicity associated with this type of tyrosinemia. No information about specific treatment of overdose is available.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

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

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

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

Pharmacodynamic effects

In patients with HT-1, nitisinone treatment leads to normalised porphyrin metabolism with normal erythrocyte porphobilinogen synthase activity and urine 5-aminolevulinate, decreased urinary excretion of succinylacetone, increased plasma tyrosine concentration and increased urinary excretion of phenolic acids. Available data from a clinical study indicates that in more than 90% of the patients urine succinylacetone was normalized during the first week of treatment. Succinylacetone should not be detectable in urine or plasma when the nitisinone dose is properly adjusted.

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

Clinical efficacy and safety

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.

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

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

No data is available for patients > 70 years.

5.2 Pharmacokinetic properties

Formal absorption, distribution, metabolism and elimination studies have not been performed with nitisinone. In 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). 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.

Based on data from a clinical interaction study with 80 mg nitisinone at steady-state, nitisinone caused a 2.3-fold increase in AUC_{∞} of the CYP2C9 substrate tolbutamide, which is indicative of a moderate inhibition of CYP2C9. Nitisinone caused an approximate 30% decrease in chlorzoxazone AUC_{∞}, indicative of a weak induction of CYP2E1. Nitisinone does not inhibit CYP2D6 since metoprolol AUC_{∞} was not affected by the administration of nitisinone. Furosemide AUC∞ was increased 1.7-fold, indicating a weak inhibition of OAT1/OAT3 (see sections 4.4 and 4.5).

Based on *in vitro* studies, nitisinone is not expected to inhibit CYP1A2, 2C19 or 3A4-mediated metabolism or to induce CYP1A2, 2B6 or 3A4/5. Nitisinone is not expected to inhibit P-gp, BCRP or OCT2-mediated transport. Nitisinone plasma concentration reached in clinical setting is not expected to inhibit OATP1B1, OATP1B3 mediated transport.

5.3 Preclinical safety data

Nitisinone has shown embryo-foetal toxicity in the mouse and rabbit at clinically relevant dose levels. In the rabbit, nitisinone induced a dose-related increase in malformations (umbilical hernia and gastroschisis) from a dose level 2.5-fold higher than the maximum recommended human dose (2 mg/kg/day).
A pre- and postnatal development study in the mouse showed statistically significantly reduced pup survival and pup growth during the weaning period at dose levels 125- and 25-fold higher, respectively, than the maximum recommended human dose, with a trend toward a negative effect on pup survival starting from the dose of 5 mg/kg/day. In rats, exposure via milk resulted in reduced mean pup weight and corneal lesions.

No mutagenic but a weak clastogenic activity was observed in in vitro studies. There was no evidence of *in vivo* genotoxicity (mouse micronucleus assay and mouse liver unscheduled DNA synthesis assay). Nitisinone did not show carcinogenic potential in a 26-week carcinogenicity study in transgenic mice (TgrasH2).

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule content
Starch, pregelatinised
Stearic acid

Capsule shell
Gelatin
Titanium dioxide (E 171)

Printing ink
Shellac
Propylene glycol
Indigotine aluminium lake (E 132)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Store below 30°C.

6.5 Nature and contents of container

HDPE bottle with a childproof closure in PP, containing 60 capsules. Each pack contains 1 bottle.
OPA/Alu/PVC – Alu perforated unit dose blisters. Each pack contains 60 capsules.

Not all pack sizes may be marketed.

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

Dipharma Arzneimittel GmbH
Offheimer Weg 33
Limburg a.d. Lahn
65549
Germany

8 MARKETING AUTHORISATION NUMBER

PA23449/001/002

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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Date of last renewal: 13th July 2022

10 DATE OF REVISION OF THE TEXT

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