1 PRODUCT NAME

Nitisinone DiPharma 2 mg hard capsules
Nitisinone DiPharma 5 mg hard capsules
Nitisinone DiPharma 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.

3 PHARMACEUTICAL FORM

Hard capsule.
White, opaque capsules (shell size 3) imprinted “company logo” and “2” on the body of the capsule in dark blue ink.
White, opaque capsules (shell size 3) imprinted “company logo” and “5” on the body of the capsule in dark blue ink.
White, opaque capsules (shell size 2) 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

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 Dose and method of administration

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

Dosage

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.

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 medicines 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.

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 DiPharma 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

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 medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions at https://nzphvc.otago.ac.nz/reporting/

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.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

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 HT-1, these intermediates are converted to the toxic metabolites succinylacetone and succinylacetoacetate. Succinylacetone inhibits the porphyrin synthesis pathway leading to the accumulation of 5-aminolevulinate.

Pharmacodynamic effects

Nitisinone treatment leads to normalised porphyrin metabolism with normal erythrocyte porphobilinogen synthase activity and urine 5-aminolevulinate, decreased urinary excretion of succinylacetone, increased plasma tyrosine concentration and increased urinary excretion of phenolic

acids. Available data from a clinical study indicates that in more than 90% of the patients urine succinylacetone was 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). A population pharmacokinetic analysis has been conducted on a group of 207 HT-1 patients. The clearance and half-life were determined to be 0.0956 l/kg body weight/day and 52.1 hours respectively.

In vitro studies using human liver microsomes and cDNA-expressed P450 enzymes have shown limited CYP 3A4-mediated metabolism.

5.3 Preclinical safety data

Nitisinone has shown embryo-foetal toxicity in the mouse and rabbit at clinically relevant dose levels. In the rabbit, nitisinone induced a dose-related increase in malformations (umbilical hernia and gastroschisis) from a dose level 2.5-fold higher than the maximum recommended human dose (2 mg/kg/day).

A pre- and postnatal development study in the mouse showed statistically significantly reduced pup survival and pup growth during the weaning period at dose levels 125- and 25-fold higher, respectively, than the maximum recommended human dose, with a trend toward a negative effect on pup survival starting from the dose of 5 mg/kg/day. In rats, exposure via milk resulted in reduced mean pup weight and corneal lesions.

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

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule content

Starch, pregelatinised (Starch 1500)
Stearic acid

Capsule shell

Gelatin

Printing ink

Shellac

Propylene glycol
Strong ammonia solution
Indigotine FD&C blue aluminium lake (E132)

6.2 Incompatibilities
Not applicable.

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

6.4 Special precautions for storage
Store at or below 30°C.

6.5 Nature and contents of container
HDPE bottle with a tamper-proof closure of PP, containing 60 capsules.
Each pack contains 1 bottle.

6.6 Special precautions for disposal <and other handling>

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

7 MEDICINE SCHEDULE
Prescription Only Medicine

8 SPONSOR
Te Arai BioFarma Ltd
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0800 TEARAI (832724)

9 DATE OF FIRST APPROVAL
12 March 2020

10 DATE OF REVISION OF THE TEXT

SUMMARY TABLE OF CHANGES