Summary of Product Characteristics

1. NAME OF THE MEDICINAL PRODUCT

Orfadin 2 mg, 5mg, 10mg Hard capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

3. PHARMACEUTICAL FORM

Hard capsule.
White, opaque capsules imprinted “NTBC 2mg”/ “NTBC 5mg”/ “NTBC 10mg” in black on the body of the capsule.
The capsules contain a white to off white powder.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of 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

Posology

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).

The dose of nitisinone should be adjusted individually.

The recommended initial dose in the paediatric and adult population is 1 mg/kg body weight/day divided in 2 doses administered orally.

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 divided in 2 doses. 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 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 safety and effect of nitisinone have been studied in the paediatric population. The dose recommendation in mg/kg body weight is the same in children and adults.

Method of administration

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

4.3 Contraindications
Hypersensitivity to the active substance or to any of the excipients.
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 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 also to monitor serum alpha-fetoprotein concentration. 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 white cell counts are monitored regularly, as a few cases of reversible trombocytopenia 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. However, nitisinone has been co-administered with food during the generation of efficacy and safety data. Therefore, it is recommended that if nitisinone treatment is initiated with food, this should be maintained on a routine basis.

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 should not be used during pregnancy unless clearly necessary.

Lactation

It is not known 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).

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. If the patient experiences adverse reactions affecting the vision, the ability to drive and use machines should be considered.

4.8 Undesirable effects

The adverse reactions considered at least possibly related to treatment are listed below, by body system, organ class, and absolute frequency. 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.

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

Nitisinone treatment is associated with elevated tyrosine levels. Elevated levels of tyrosine have been associated with corneal opacities and hyperkeratotic lesions. Restriction of tyrosine and phenylalanine in the diet should limit the toxicity associated with this type of tyrosinemia (see section 4.4).

4.9 Overdose

No case of overdose has been reported. 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.

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.

Nitisinone treatment leads to normalised porphyrin metabolism with normal erythrocyte PBG-synthase activity and urine 5-ALA, 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.

Effects on overall survival
When compared to data for historical controls, it can be seen that treatment with nitisinone together with dietary restriction results in a better survival probability in all HT-1 phenotypes. This is seen in the following table:

Age at start of treatment or diagnosis	**Survival probability**			
	Nitisinone treatment		**Dietary control ***	
	5 years	10 years	5 years	10 years
< 2 months	82	--	28	--
> 2-6 months	95	95	51	34
> 6 months	92	86	93	59

* From Figure 1,Van Spronsen et al., 1994.

Treatment with nitisinone was also found to result in reduced risk for the development of hepatocellular carcinoma (2.3 to 3.7-fold) 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 (13.5-fold when initiated prior to the age of 12 months).

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. 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 of 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 of 125- and 25-fold, respectively, the maximum recommended human dose, with a trend 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). Carcinogenicity studies have not been performed.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Capsule content
Starch, Pregelatinised
Capsule shell
Gelatin
Titanium dioxide
Imprint
Black iron oxide (E 172),

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
18 months.

6.4 Special precautions for storage
Store in a refrigerator (2°C – 8°C).
During the shelf life the patient may store the finished product for a single period of 2 months at a temperature not above 25°C, after which the product must be discarded.
Period after opening: 2 months

6.5 Nature and contents of container
High density polyethylene bottle with a tamper proof low density polyethylene cap, containing 60 capsules.

6.6 Special precautions for disposal
No special requirements.
Any unused product or waste material should be disposed of in accordance with local requirements.

7. MANUFACTURER
Apotek Produktion & Laboratorier AB, Kungens Kurva, Sweden **for** Swedish Orphan Biovitrum International AB (SOBI), Stockholm, Sweden

8. MARKETING AUTHORISATION HOLDER
Megapharm Ltd.
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