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

Orfadin hard capsules 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 Orfadin hard capsules 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 dose in the paediatric and adult population is 1 mg/kg body weight administered orally. The dose of Orfadin hard capsules 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 Orfadin hard capsules treatment, the Orfadin hard capsules 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, 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 Orfadin hard capsules 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 Orfadin hard capsules 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 Orfadin hard capsules treatment and thereafter regularly, at least once a year. A patient displaying visual disorders during treatment with Orfadin hard capsules 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 Orfadin hard capsules, 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.

Concomitant use with other medicinal products

Orfadin hard capsules is a moderate CYP2C9 inhibitor. Orfadin hard capsules treatment may therefore result in increased plasma concentrations of co-administered medicinal products metabolized primarily via CYP2C9. Orfadin hard capsules 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

Orfadin hard capsules 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 metabolized primarily via CYP2C9 (see section 4.4).
Nitisinoneis 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 Orfadin hard capsules. However, Orfadin hard capsules has been co-administered with food during the generation of efficacy and safety data. Therefore, it is recommended that treatment with Orfadin 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 Orfadin hard capsules in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). The potential risk for humans is unknown. Orfadin hard capsules should not be used during pregnancy unless. the clinical condition of the woman requires treatment with Orfadin hard capsules.

Lactation
It is not known whether Orfadin hard capsules is excreted in human breast milk. Animal studies have shown adverse postnatal effects via exposure of Orfadin hard capsules in milk. Therefore, mothers receiving Orfadin hard capsules 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 Orfadin hard capsules affecting fertility.

4.7 Effects on ability to drive and use machines

Orfadin hard capsules 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
Orfadin hard capsules 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 Orfadin hard capsules treatment.

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. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form https://sideeffects.health.gov.il.

4.9 Overdose
No case of overdose has been reported. Accidental ingestion of Orfadin hard capsules 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. Orfadin hard capsules 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, Orfadin hard capsules 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.

Pharmacodynamics effects

Orfadin hard capsules 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 Orfadin hard capsules 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 Orfadin hard capsules 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 Orfadin hard capsules 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 Orfadin hard capsules 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 Orfadin hard capsules. In 10 healthy male volunteers, after administration of a single dose of Orfadin hard capsules (1 mg/kg body weight) the terminal half-life (median) of Orfadin hard capsules 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.

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

Orfadin hard capsules has shown embryo-foetal toxicity in the mouse and rabbit at clinically relevant dose levels. In the rabbit, Orfadin hard capsules 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 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). Orfadin hard capsules 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
Capsule shell
Gelatin
Titanium dioxide
Imprint
Black iron oxide (E 172),

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

The expiry date of the product is indicated on the packaging materials.

6.4 Special precautions for storage

Store in a refrigerator (2°C – 8°C).

Orfadin 2 mg hard capsules:

- The capsules can be kept out of the refrigerator in a temperature that does not exceed 25°C for up to 2 months. After this period, the packaging should be destroyed.
- After first opening it can be used for 2 months.

Orfadin 5 mg hard capsules:

- The capsules can be kept out of the refrigerator in a temperature that does not exceed 25°C for up to 3 months. After this period, the packaging should be destroyed.
- After first opening you can use for 2 months.

Orfadin 10 mg hard capsules:

- The capsules can be kept out of the refrigerator in a temperature that does not exceed 25°C for up to 3 months. After this period, the packaging should be destroyed.
- After first opening you can use for 2 months.

6.5 Nature and contents of container

High density polyethylene bottle with a tamper proof low density polyethylene snap –on caps, childproof 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.
P.O.B 519, Hod-Hasharon 4510501
Israel

9. Reviewed on Jun 2020