ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Orfadin 2 mg hard capsules
Orfadin 5 mg hard capsules
Orfadin 10 mg hard capsules
Orfadin 20 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.
Each capsule contains 20 mg nitisinone.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Hard capsule.
White, opaque capsules (6x16 mm) imprinted “NTBC 2mg” in black on the body of the capsule.
White, opaque capsules (6x16 mm) imprinted “NTBC 5mg” in black on the body of the capsule.
White, opaque capsules (6x16 mm) imprinted “NTBC 10mg” in black on the body of the capsule.
White, opaque capsules (6x16 mm) imprinted “NTBC 20mg” in black on the body of the capsule.
The capsules contain a white to off white powder.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Hereditary tyrosinemia type 1 (HT-1)
Orfadin 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)
Orfadin 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 Orfadin 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.

Orfadin is also available as a 4 mg/ml oral suspension for paediatric and other 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

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 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).
Nitisinone is 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, nitisinone has been co-administered with food during the generation of efficacy and safety data. Therefore, it is recommended that if nitisinone 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 nitisinone in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). The potential risk for humans is unknown. Orfadin 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

Orfadin 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.

MedDRA system organ class	**Frequency in HT-1**	**Frequency in AKU[1]**	**Adverse reaction**
Infections and infestations		Common	Bronchitis, pneumonia
Blood and lymphatic system disorders	Common		Thrombocytopenia, leucopenia, granulocytopenia
	Uncommon		Leukocytosis
Eye disorders	Common		Conjunctivitis, corneal opacity, keratitis, photophobia
		Very common[2]	Keratopathy
	Common	Very common[2]	Eye pain
	Uncommon		Blepharitis

MedDRA system organ class	Frequency in HT-1	Frequency in AKU[1]	Adverse reaction
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 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
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 in HT-1

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 CYP3A4-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 (maize)

Capsule shell
gelatin
titanium dioxide (E 171)

Printing ink
black iron oxide (E 172)
shellac
propylene glycol
ammonium hydroxide

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

During the shelf life, the patient may store the capsules for a single period of 2 months (for 2 mg capsules) or 3 months (for 5 mg, 10 mg and 20 mg capsules) at a temperature not above 25°C, after which the medicinal product must be discarded.

6.4 Special precautions for storage

Store in a refrigerator (2°C – 8°C).

6.5 Nature and contents of container

HDPE bottle with a tamper-proof closure of LDPE, containing 60 capsules.
Each pack contains 1 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

Swedish Orphan Biovitrum International AB
SE-112 76 Stockholm
Sweden

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/04/303/001
EU/1/04/303/002
EU/1/04/303/003
EU/1/04/303/004

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 21 February 2005
Date of latest renewal: 19 January 2010

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.

1. NAME OF THE MEDICINAL PRODUCT

Orfadin 4 mg/ml oral suspension

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 ml contains 4 mg of nitisinone.

Excipients with known effect:
Each ml contains:
sodium 0.7 mg (0.03 mmol)
glycerol 500 mg
sodium benzoate 1 mg

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Oral suspension.
White, slightly viscous opaque suspension.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Hereditary tyrosinemia type 1 (HT-1)
Orfadin 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)
Orfadin 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 Orfadin in children aged 0 to 18 years with AKU have not been established. No data are available.

Method of administration
The suspension is administered in the patient's mouth with an oral syringe without dilution. A 1.5 ml, 3 ml and 6 ml oral syringes are included in the pack to measure the dose in ml in accordance with the prescribed posology. The oral syringes are graduated in 0.05 ml, 0.1 ml and 0.25 ml steps respectively. The table below shows the dose conversion (mg/ml) for the three oral syringes sizes.

Dose conversion tables respectively for the three oral syringe sizes:

1.5-ml oral syringe (0.05 ml graduation)	Dose Orfadin	
	mg	ml
	1.00	0.25
	1.20	0.30
	1.40	0.35
	1.60	0.40
	1.80	0.45
	2.00	0.50
	2.20	0.55
	2.40	0.60
	2.60	0.65
	2.80	0.70
	3.00	0.75
	3.20	0.80
	3.40	0.85
	3.60	0.90
	3.80	0.95
	4.00	1.00

3-ml oral syringe (0.1 ml graduation)	Dose Orfadin	
	mg	ml
	4.0	1.0
	4.5	1.1
	5.0	1.3
	5.5	1.4
	6.0	1.5
	6.5	1.6
	7.0	1.8
	7.5	1.9
	8.0	2.0
	8.5	2.1
	9.0	2.3
	9.5	2.4
	10.0	2.5
	10.5	2.6
	11.0	2.8
	11.5	2.9
	12.0	3.0

6-ml oral syringe (0.25 ml graduation)	Dose Orfadin	
	mg	ml
	12.0	3.00
	13.0	3.25
	14.0	3.50
	15.0	3.75
	16.0	4.00
	17.0	4.25
	18.0	4.50
	19.0	4.75
	20.0	5.00
	21.0	5.25
	22.0	5.50
	23.0	5.75
	24.0	6.00

Important information about instructions for use:
Re-dispersing is required before each use by vigorous shaking. Before re-dispersion, the medicinal product may appear as a solid cake with a slightly opalescent supernatant. The dose should be withdrawn and administered immediately after re-dispersion.
It is important to carefully follow the instructions given in section 6.6 for preparation and administration of the dose, in order to ensure the dosing accuracy.
It is recommended that the healthcare professional advises the patient or care giver how to use the oral syringes to ensure that the correct volume is administered and that the prescription is given in ml.

Orfadin is also available in 2 mg, 5 mg, 10 mg and 20 mg capsules, if considered more suitable for the patient.

It is recommended that the oral suspension is taken with food, see section 4.5.

Precautions to be taken before handling or administering the medicinal product
No needle, intravenous tubing or any other device for parenteral administration should be attached to the oral syringe.
Orfadin is for oral use only.

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).

Excipients with known effect:
Glycerol
Each ml contains 500 mg. A dose of 20 ml oral suspension (10 g glycerol) or more may cause headache, stomach upset and diarrhoea.

Sodium
Each ml contains 0.7 mg (0.03 mmol).

Sodium benzoate
Each ml contains 1 mg. Increase in bilirubin following its displacement from albumin, caused by benzoic acid and its salts, may increase jaundice in pre-term and full-term jaundiced neonates and develop into kernicterus (unconjugated bilirubin deposits in the brain tissue). A close monitoring of the plasma levels of bilirubin in the newborn patient is therefore of great importance. Bilirubin levels should be measured before start of treatment: in case of markedly elevated plasma levels of bilirubin, especially in premature patients with risk factors as acidosis and low albumin level, treatment with an appropriately weighed portion of an Orfadin capsule should be considered instead of the oral suspension until the unconjugated bilirubin plasma levels are normalised.

4.5 Interaction with other medicinal products and other forms of interaction

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 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).
Nitisinone is 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).

Food does not influence the bioavailability of nitisinone oral suspension, but intake together with food decreases the absorption rate and consequently leads to lower fluctuations in serum concentrations within a dosage interval. Therefore, it is recommended that the oral suspension is taken with food, 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. Orfadin 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

Orfadin 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.

MedDRA system organ class	Frequency in HT-1	Frequency in AKU[1]	Adverse reaction
Infections and infestations		Common	Bronchitis, pneumonia
Blood and lymphatic system disorders	Common		Thrombocytopenia, 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 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
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 in HT-1
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 CYP3A4 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

Hydroxypropylmethylcellulose
Glycerol
Polysorbate 80
Sodium benzoate (E211)
Citric acid monohydrate
Sodium citrate
Strawberry aroma (artificial)
Purified water

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.
After first opening, the in-use stability is a single period of 2 months at a temperature not above 25°C, after which it must be discarded.

6.4 Special precautions for storage

Store in a refrigerator (2°C – 8°C). Do not freeze.
Store upright.

For storage conditions after first opening of the medicinal product, see section 6.3.

6.5 Nature and contents of container

100 ml brown glass bottle (type III) with a white child-resistant HDPE screw cap with sealing and tamper evidence. Each bottle contains 90 ml oral suspension.
Each pack contains one bottle, one LDPE bottle adapter and 3 polypropylene (PP) oral syringes (1.5 ml, 3 ml and 6 ml).

6.6 Special precautions for disposal and other handling

Re-dispersing is required before each use by vigorous shaking. Before re-dispersion, the medicinal product may appear as a solid cake with a slightly opalescent supernatant. The dose should be withdrawn and administered immediately after re-dispersion. It is important to carefully follow the instructions given below for preparation and administration of the dose, in order to ensure the dosing accuracy.

Three oral syringes (1.5 ml, 3 ml and 6 ml) are provided for accurate measurement of the prescribed dose. It is recommended that the healthcare professional advises the patient or carer giver how to use the oral syringes to ensure that the correct volume is administered.

<u>How to prepare a new bottle of medicine for first time use</u>:

Before taking the first dose, the bottle should be shaken vigorously since during long-term storage the particles will form a solid cake at the bottom of the bottle.


Figure A.

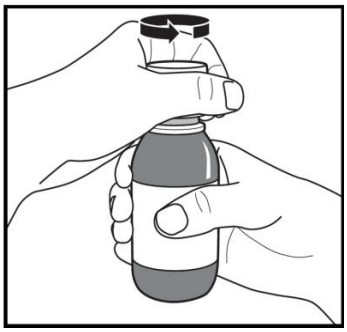
Figure B.

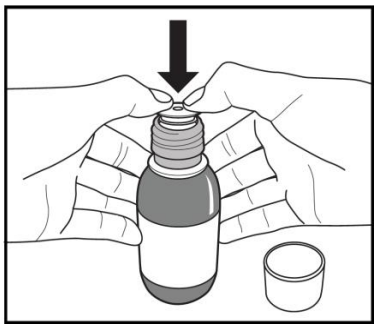
Figure C.

1. The bottle should be removed from the refrigerator, and the date when the bottle is removed from the refrigerator should be noted on the bottle label.
2. The bottle should be shaken vigourously for **at least 20 seconds** until the solid cake at the bottom of the bottle is completely dispersed (Figure A).

3. The child-resistant screw cap should be removed by pushing it down firmly and turning it anti-clockwise (Figure B).
4. The open bottle should be placed upright on a table, and the plastic adapter pushed firmly into the neck of the bottle as far as possible (Figure C). The bottle should be closed with the child resistant screw cap.

For subsequent dosing see the instructions below 'How to prepare a dose of medicine'

How to prepare a dose of medicine

Figure D.

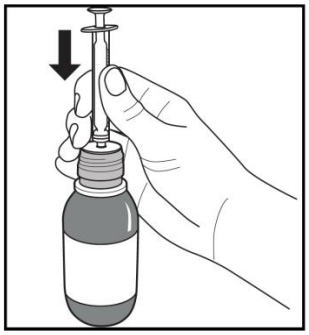

Figure E.

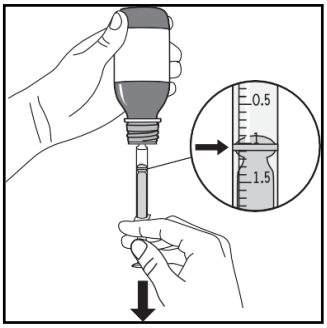

Figure F.

1. The bottle should be shaken vigourously for **at least 5 seconds** (Figure D).
2. Immediately thereafter, the bottle should be opened by removing the child-resistant screw cap.
3. The plunger inside the oral syringe should be pushed fully down.
4. The bottle should be kept in an upright position and the oral syringe inserted firmly into the hole of the adaptor, at the top of the bottle (Figure E).
5. The bottle should be turned carefully upside down with the oral syringe in place (Figure F).
6. In order to withdraw the prescribed dose (ml), the plunger should be pulled down **slowly** until the top edge of the plunger is exactly level with the line marking the dose (Figure F). If any air bubbles are observed inside the filled oral syringe, the plunger should be pushed back up until the air bubbles are expelled. Then the plunger should be pulled down again until the top edge is exactly level with the line marking the dose.
7. The bottle should be turned to an upright position again, and the oral syringe disconnected by gently twisting it out of the bottle.
8. The dose should be administered in the mouth immediately (without dilution) in order to avoid caking in the oral syringe. The oral syringe should be emptied **slowly** to allow swallowing; rapid squirting of the medicine may cause choking.
9. The child-resistant screw cap should be replaced directly after use. The bottle adapter should not be removed.
10. The bottle may be stored at a temperature not above 25°C or in the refrigerator.

Cleaning

Clean the oral syringe **immediately** with cold tap water only, and if necessary, move the plunger in and out. Shake off excess water and leave the oral syringe to dry until the next dosing occasion. Do not disassemble the oral syringe.

Disposal

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

7. MARKETING AUTHORISATION HOLDER

Swedish Orphan Biovitrum International AB
SE-112 76 Stockholm
Sweden

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/04/303/005

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 21 February 2005
Date of latest renewal: 19 January 2010

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. MANUFACTURERS RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTION 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. MANUFACTURERS RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturers responsible for batch release

2 mg, 5 mg, 10 mg and 20 mg hard capsules:
Apotek Produktion & Laboratorier AB
Prismavägen 2
SE-141 75 Kungens Kurva
Sweden

4 mg/ml oral suspension:
Apotek Produktion & Laboratorier AB
Celsiusgatan 43
SE-212 14 Malmö
Sweden

Apotek Produktion & Laboratorier AB
Prismavägen 2
SE-141 75 Kungens Kurva
Sweden

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

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

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Orfadin 2 mg hard capsules
Orfadin 5 mg hard capsules
Orfadin 10 mg hard capsules
Orfadin 20 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
Each capsule contains 20 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 PRODUCT OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Swedish Orphan Biovitrum International AB
SE-112 76 Stockholm
Sweden

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/04/303/001
EU/1/04/303/002
EU/1/04/303/003
EU/1/04/303/004

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Orfadin 2 mg
Orfadin 5 mg
Orfadin 10 mg
Orfadin 20 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}

PARTICULARS TO APPEAR ON IMMEDIATE PACKAGING UNITS

BOTTLE LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Orfadin 2 mg hard capsules
Orfadin 5 mg hard capsules
Orfadin 10 mg hard capsules
Orfadin 20 mg hard capsules
Nitisinone
Oral use

2. METHOD OF ADMINISTRATION

3. NAME OF THE MARKETING AUTHORISATION HOLDER

Swedish Orphan Biovitrum International AB

4. EXPIRY DATE

EXP

5. SPECIAL STORAGE CONDITIONS

2 mg: Store in a refrigerator. The product can be stored for a single period of 2 months at a temperature not above 25°C, after which it must be discarded.
Date when removed from refrigerator:

5 mg, 10 mg, 20 mg: Store in a refrigerator. The product can be stored for a single period of 3 months at a temperature not above 25°C, after which it must be discarded.
Date when removed from refrigerator:

6. BATCH NUMBER

Lot

7. CONTENTS BY UNIT

60 capsules

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Orfadin 4 mg/ml oral suspension
Nitisinone

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 ml contains 4 mg nitisinone.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Oral suspension
1 bottle of 90 ml, 1 bottle adaptor, 3 oral syringes (1.5 ml, 3 ml, 6 ml).

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet carefully before use.
Oral use only.

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.
Do not freeze.
Store upright.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCT OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Swedish Orphan Biovitrum International AB
SE-112 76 Stockholm
Sweden

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/04/303/005

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Orfadin 4 mg/ml

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

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

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

BOTTLE LABEL

1. NAME OF THE MEDICINAL PRODUCT

Orfadin 4 mg/ml oral suspension
Nitisinone

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 ml contains 4 mg nitisinone.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Oral suspension
90 ml

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet carefully before use.
Oral use only.

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.
Do not freeze.
Store upright.
The product can be stored for a single period of 2 months at a temperature not above 25°C, after which it must be discarded.
Date when removed from 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

Swedish Orphan Biovitrum International AB
SE-112 76 Stockholm
Sweden

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/04/303/005

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

B. PACKAGE LEAFLET

Package leaflet: Information for the user

Orfadin 2 mg hard capsules
Orfadin 5 mg hard capsules
Orfadin 10 mg hard capsules
Orfadin 20 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. 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, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Orfadin is and what it is used for

Orfadin contains the active substance nitisinone. Orfadin is used to treat:
- a rare disease called hereditary tyrosinemia type 1 in adults, adolescents and children (in any age range)
- a rare disease called alkaptonuria (AKU) in adults.

In these diseases 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. Orfadin blocks the breakdown of tyrosine and the harmful substances are not formed.

For the treatment of hereditary tyrosinemia type 1, 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.

For the treatment of AKU, your doctor may advise you to follow a special diet.

2. What you need to know before you take Orfadin

Do not take Orfadin
- 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 Orfadin.
- Your eyes will be checked by an ophthalmologist before and regularly during nitisinone treatment. 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.

If you receive Orfadin for treatment of hereditary tyrosinemia type 1, 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 Orfadin
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.
Orfadin may interfere with the effect of other medicines, such as:
- Medicines for epilepsy (such as phenytoin)
- Medicines against blood clotting (such as warfarin).

Orfadin with food
If you start 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 Orfadin”.

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 Orfadin

Always take this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure.

For hereditary tyrosinemia type 1, treatment with this medicine should be started and supervised by a doctor experienced in the treatment of the disease.

For 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.

For AKU, the recommended dose is 10 mg once daily.

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 Orfadin 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 Orfadin
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 Orfadin
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, pharmacist or nurse.

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. In patients with hereditary tyrosinemia type 1, commonly reported eye related side effects (may affect more than 1 in 100 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).
In AKU patients, eye irritation (keratopathy) and eye pain are very commonly reported side effects (may affect more than 1 in 10 people).

Other side effects reported in patients with hereditary tyrosinemia type 1 are listed below:

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.

Other side effects reported in patients with AKU are listed below:

Other common side effects
- bronchitis
- pneumonia
- itching (pruritus), rash.

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist or nurse. 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 Orfadin

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 bottle and the carton after "EXP". The expiry date refers to the last day of that month.

Store in a refrigerator (2°C – 8°C).
The medicine can be stored for a single period of 2 months (for 2 mg capsules) or 3 months (for 5 mg, 10 mg and 20 mg capsules) at a temperature not above 25°C, after which it must be discarded.

Do not forget to mark the date on the bottle, when removed from the refrigerator.

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 to protect the environment.

6. Contents of the pack and other information

What Orfadin contains

- The active substance is nitisinone.
  Orfadin 2 mg: Each capsule contains 2 mg nitisinone.
  Orfadin 5 mg: Each capsule contains 5 mg nitisinone.
  Orfadin 10 mg: Each capsule contains 10 mg nitisinone.
  Orfadin 20 mg: Each capsule contains 20 mg nitisinone.

- The other ingredients are
  Capsule content: starch, pregelatinised (maize).
  Capsule shell: gelatine, titanium dioxide (E 171).
  Printing ink: iron oxide (E 172), shellac, propylene glycol, ammonium hydroxide.

What Orfadin looks like and contents of the pack
The hard capsules are white, opaque, imprinted with "NTBC" and the strength "2 mg", "5 mg", "10 mg" or "20 mg", in black. The capsule contains a white to off-white powder.

The capsules are packaged in plastic bottles with tamper-proof closures. Each bottle contains 60 capsules.

Marketing Authorisation Holder
Swedish Orphan Biovitrum International AB
SE-112 76 Stockholm
Sweden

Manufacturer
Apotek Produktion & Laboratorier AB
Prismavägen 2
SE-141 75 Kungens Kurva
Sweden

This leaflet was last revised in .

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu. There are also links to other websites about rare diseases and treatments.

Package leaflet: Information for the user

Orfadin 4 mg/ml oral suspension
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. 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, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Orfadin is and what it is used for

Orfadin contains the active substance nitisinone. Orfadin is used to treat:
- a rare disease called hereditary tyrosinemia type 1 in adults, adolescents and children (in any age range)
- a rare disease called alkaptonuria (AKU) in adults.

In these diseases 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. Orfadin blocks the breakdown of tyrosine and the harmful substances are not formed.

For the treatment of hereditary tyrosinemia type 1, 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.

For the treatment of AKU, your doctor may advise you to follow a special diet.

2. What you need to know before you take Orfadin

Do not take Orfadin
- 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 Orfadin.
- Your eyes will be checked by an ophthalmologist before and regularly during nitisinone treatment. 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.

If you receive Orfadin for treatment of hereditary tyrosinemia type 1, 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 Orfadin
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.
Orfadin may interfere with the effect of other medicines, such as:
- Medicines for epilepsy (such as phenytoin)
- Medicines against blood clotting (such as warfarin).

Orfadin with food
It is recommended that the oral suspension is taken with food.

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 Orfadin".

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").

Orfadin contains sodium, glycerol and sodium benzoate
This medicinal product contains 0.7 mg (0.03 mmol) sodium per ml.
A dose of 20 ml oral suspension (10 g glycerol) or more may cause headache, stomach upset and diarrhoea.
Sodium benzoate may increase jaundice (yellowing of the skin and eyes) in pre-term and full-term jaundiced neonates and develop into kernicterus (brain damage due to deposits of bilirubin in the brain). The newborn baby's blood levels of bilirubin (a substance that causes the yellowing of the skin in high levels) will be closely monitored. If the levels are markedly higher than they should be, especially in premature babies with risk factors as acidosis (too low pH in the blood) and low albumin level (a protein in the blood) treatment with Orfadin capsules will be considered instead of the oral suspension until the bilirubin plasma levels are normalised.

3. How to take Orfadin

Always take this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure.

Follow the instructions given below for dose preparation and administration carefully, in order to ensure that the correct dose is administered.

For hereditary tyrosinemia type 1, treatment with this medicine should be started and supervised by a doctor experienced in the treatment of the disease.

For 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.

For AKU, the recommended dose is 10 mg once daily.

The oral suspension is taken with a oral syringe directly in the mouth without dilution.
Orfadin must not be injected. Do not attach a needle to the syringe.

How to prepare the dose to be administered
The dose that your doctor prescribes you should be given in **ml of suspension** and not in mg. This is because the oral syringe which is used to withdraw the correct dose from the bottle is marked in ml. **If your prescription is in mg, contact your pharmacist or doctor for advice.**

The pack contains a bottle of medicine with a cap, a bottle adaptor and three oral syringes (1.5 ml, 3 ml and 6 ml). Always use one of the oral syringes provided to take the medicine.

- The 1.5 ml oral syringe (the smallest oral syringe) is marked from 0.1 ml to 1.5 ml with minor 0.05-ml graduations. It is used for measuring doses of less than or up to 1.5 ml.
- The 3 ml oral syringe (the middle sized oral syringe) is marked from 1 ml to 3 ml with minor 0.1-ml graduations. It is used for measuring doses of more than 1.5 ml and up to 3 ml.
- The 6 ml oral syringe (the largest oral syringe) is marked from 1 ml to 6 ml with minor 0.25-ml graduations. It is used for measuring doses of more than 3 ml.

It is important that you use the correct oral syringe when taking the medicine. Your doctor, pharmacist or nurse will advise which oral syringe to use depending on the dose that has been prescribed.

<u>How to prepare a new bottle of medicine for first time use</u>:

Before you take the first dose, shake the bottle vigorously since during long-term storage the particles will form a solid cake at the bottom of the bottle. Follow the instructions below:


Figure A.

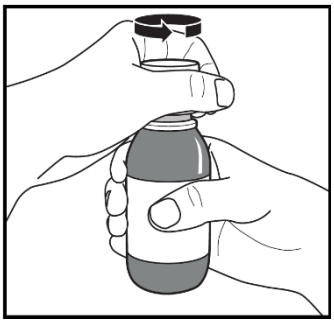
Figure B.

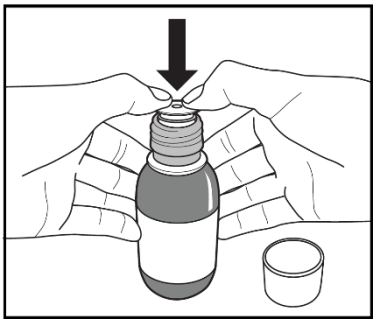
Figure C.

1. Remove the bottle from the refrigerator. Note the date when the bottle is removed from the refrigerator on the bottle label.
2. Shake the bottle vigorously for **at least 20 seconds** until the solid cake at the bottom of the bottle is completely dispersed (Figure A).
3. Remove the child resistant screw cap by pushing it down firmly and turning it anti-clockwise (Figure B).
4. Place the open bottle upright on a table. Push the plastic adapter firmly into the neck of the bottle as far as you can (Figure C) and close the bottle with the child resistant screw cap.

For subsequent dosing see the instructions below ‘How to prepare a dose of medicine’.

How to prepare a dose of medicine

Figure D.

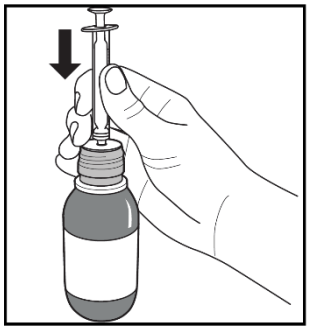

Figure E.

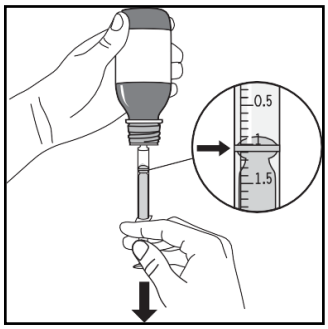

Figure F.

1. Shake the bottle vigorously for **at least 5 seconds** (Figure D).
2. Immediately thereafter, open the bottle by removing the child resistant screw cap.
3. Push the plunger inside the oral syringe fully down.
4. Keep the bottle in an upright position and insert the oral syringe firmly into the hole at the top of the bottle (Figure E).
5. Carefully turn the bottle upside down with the oral syringe in place (Figure F).
6. In order to withdraw the prescribed dose (ml), pull the plunger **slowly** down until the top edge of the plunger is exactly level with the line marking the dose (Figure F). If any air bubbles are observed inside the filled oral syringe, push the plunger back up until the air bubbles are expelled. Then pull the plunger down again until the top edge is exactly level with the line marking the dose.
7. Turn the bottle to an upright position again. Disconnect the oral syringe by gently twisting it out of the bottle.
8. The dose should be administered in the mouth immediately (without dilution) in order to avoid caking in the oral syringe. The oral syringe must be emptied **slowly** to allow swallowing; rapid squirting of the medicine may cause choking.
9. Replace the child resistant screw cap directly after use. The bottle adapter should not be removed.
10. The bottle may be stored at room temperature (not above 25°C).

Cleaning:
Clean the oral syringe **immediately** with cold tap water only, and if necessary, move the plunger in and out. Shake off excess water and leave the oral syringe to dry until the next dosing occasion. Do not disassemble the oral syringe.

If you take more Orfadin 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 Orfadin
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 Orfadin
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, pharmacist or nurse.

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. In patients with hereditary tyrosinemia type 1, commonly reported eye related side effects (may affect more than 1 in 100 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).
In AKU patients, eye irritation (keratopathy) and eye pain are very commonly reported side effects (may affect more than 1 in 10 people).

Other side effects reported in patients with hereditary tyrosinemia type 1 are listed below:

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.

Other side effects reported in patients with AKU are listed below:

Other common side effects
- bronchitis
- pneumonia
- itching (pruritus), rash.

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist or nurse. 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 Orfadin

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 bottle and carton after “EXP”. The expiry date refers to the last day of that month.

Store in a refrigerator (2°C – 8°C).
Do not freeze.
Store the bottle upright.

After first opening, the medicine can be stored for a single period of 2 months at a temperature not above 25°C, after which it must be discarded.

Do not forget to mark the date on the bottle, when removed from the refrigerator.

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 Orfadin contains
- The active substance is nitisinone. Each ml contains 4 mg nitisinone.
- The other ingredients are hydroxypropylmethylcellulose, glycerol (see section 2), polysorbate 80, sodium benzoate (E211) (see section 2), citric acid monohydrate, sodium citrate (see section 2), strawberry aroma (artificial) and purified water.

What Orfadin looks like and contents of the pack
The oral suspension is a white, slightly thicker opaque suspension. Before shaking the bottle, it may look like a solid cake in the bottom and a slightly opalescent liquid. It is provided in a 100 ml brown glass bottle with a white, child resistant screw cap. Each bottle contains 90 ml supension.
Each pack contains one bottle, one bottle adapter and three oral syringes.

Marketing Authorisation Holder
Swedish Orphan Biovitrum International AB
SE-112 76 Stockholm
Sweden

Manufacturer
Apotek Produktion & Laboratorier AB
Celsiusgatan 43
SE-212 14 Malmö
Sweden

Apotek Produktion & Laboratorier AB
Prismavägen 2
SE-141 75 Kungens Kurva
Sweden

This leaflet was last revised in .

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu. There are also links to other websites about rare diseases and treatments.