AUSTRALIAN PRODUCT INFORMATION – ORFADIN® nitisinone Capsule and Oral Suspension

1. NAME OF THE MEDICINE

Nitisinone

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Capsules: Each capsule contains 2 mg, 5 mg, 10 mg or 20 mg nitisinone.

Oral suspension: 1mL contains 4 mg of nitisinone.

Excipients with known effect: The oral suspension contains glycerol and sodium benzoate (see section 4.4 Special Warnings and Precautions for Use).

For the full list of excipients, see section 6.1 List of excipients.

3. PHARMACEUTICAL FORM

Capsules: white, opaque, hard gelatin capsules imprinted with “NTBC 2 mg”, “NTBC 5 mg”, “NTBC 10 mg” or “NTBC 20 mg” in black ink; and contain a white to off white powder.

Oral suspension: white, slightly viscous, opaque suspension.

4. CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

ORFADIN (nitisinone) is indicated for the treatment of patients with hereditary tyrosinaemia type 1 (HT-1) in combination with dietary restriction of tyrosine and phenylalanine.

4.2 DOSE AND METHOD OF ADMINISTRATION

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

Treatment of HT-1 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 mandatory. The patient should be provided with clear instructions on the restricted diet and on the importance of adherence to the restricted diet. The patient’s compliance to the diet should be checked regularly by monitoring plasma tyrosine levels.

The recommended initial dose is 1 mg/kg body weight /day divided in 2 doses administered orally. The dose of nitisinone should be adjusted individually. In patients who weigh 20 kg or more, and who have undetectable plasma and urine succinylacetone concentrations after a minimum of 4 weeks on a stable twice a day dosage of Orfadin, the total daily dose of Orfadin may be given once daily (i.e. 1 to 2 mg/kg 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.

ORFADIN capsules and oral suspension should be administered with food, see section 4.5 Interactions With Other Medicines And Other Forms Of Interactions).

ORFADIN is available in 2 mg, 5 mg, 10 mg and 20 mg capsules. In the case of paediatric patients, the capsules 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 adult patients who may have difficulty in swallowing capsules

The suspension is administered in the patient's mouth with an oral syringe without dilution. Three oral syringes (1 mL, 3 mL and 5 mL) are included in the pack to measure the dose in mL in accordance with the prescribed posology. It is recommended that the healthcare professional advises the patient or caregiver how to use the oral syringes to ensure that the correct volume is administered and that the prescription is given in mL.

The oral syringes are graduated in 0.01 mL, 0.1 mL and 0.2 mL increments respectively. Table 1 shows the dose conversion (mg/mL) for the three oral syringes sizes.

Table 1: ORFADIN dose conversion tables for the three oral syringe sizes

1-mL oral syringe *(0.01 mL graduation)*	
Dose ORFADIN	
mg	**mL**
1.00	0.25
1.25	0.31
1.50	0.38
1.75	0.44
2.00	0.50
2.25	0.56
2.50	0.63
2.75	0.69
3.00	0.75
3.25	0.81
3.50	0.88
3.75	0.94
4.00	1.00

3-mL oral syringe *(0.1 mL graduation)*	
Dose ORFADIN	
mg	**mL**
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

5-mL oral syringe *(0.2 mL graduation)*	
Dose ORFADIN	
mg	**mL**
13.0	3.2
14.0	3.6
15.0	3.8
16.0	4.0
17.0	4.2
18.0	4.6
19.0	4.8
20.0	5.0

<u>Important information about instructions for use:</u>

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.

How to prepare a new bottle of medicine for first time use:

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.

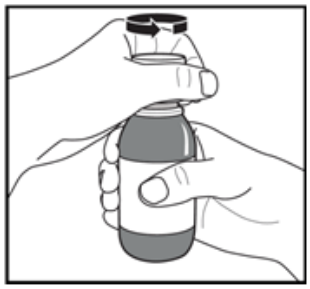


Figure B.

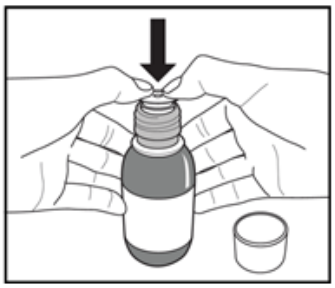


Figure C.

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 vigorously 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 on ‘How to prepare a dose of medicine’.

How to prepare a dose of medicine:

Figure D.

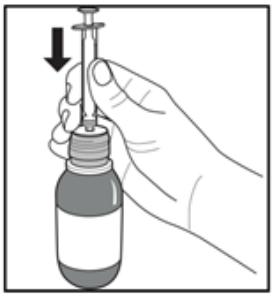


Figure E.

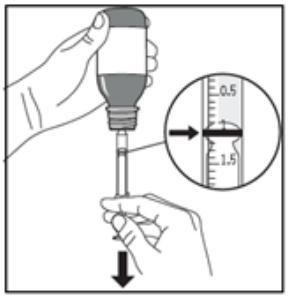


Figure F.

1. The bottle should be shaken vigorously 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 black ring 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 of the black ring 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 below 25°C or in the refrigerator.

Cleaning

Clean the oral syringe immediately with water. Separate barrel and plunger and rinse both with water. Shake off excess water and leave the disassembled oral syringe to dry until reassemble for next dosing occasion.

Dose adjustment

During regular monitoring, it is appropriate to follow urine succinylacetone, liver function test values and alpha-fetoprotein levels (see section 4.4 Special Warnings and Precautions for Use). If urine succinylacetone is still detectable one month after the start of ORFADIN treatment, the ORFADIN 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, a 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).

4.3 CONTRAINDICATIONS

Hypersensitivity to the active substance or to any of the excipients. Mothers receiving nitisinone should not breast-feed.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

High Plasma Tyrosine Concentrations and Associated Adverse Effects

There is a predictable increase in plasma tyrosine concentrations if nitisinone is administered without a diet restricted in tyrosine and phenylalanine content. Inadequate restriction of tyrosine and phenylalanine intake can result in elevations in plasma tyrosine. Plasma tyrosine levels should be kept below 500 micromole/L in order to avoid toxic effects to the eyes (corneal ulcers, corneal opacities, keratitis, conjunctivitis, eye pain, and photophobia), skin (painful hyperkeratotic plaques on the soles and palms) and nervous system (variable degrees of mental retardation and developmental delay). In a clinical study in a non HT-1 population without dietary restriction and reported tyrosine levels >500

micromole/L, both symptomatic and asymptomatic keratopathies have been observed in patients after receiving treatment with nitisinone.

Diet compliance and monitoring of plasma tyrosine levels

To avoid side effects that can occur due to high plasma tyrosine levels as described above, it is important to establish that the patient adheres to the dietary regimen and to monitor plasma tyrosine concentrations regularly. A more restricted tyrosine and phenylalanine diet should be implemented if the plasma tyrosine level goes above 500 micromole/L. It is not recommended to lower the plasma tyrosine concentration by reducing or discontinuing nitisinone, since the metabolic defect may result in deterioration of the patient's clinical condition.

General development

Cognitive and developmental disturbances have been observed in the patient population. On-going analysis has not yet identified whether these are caused by the disease itself, the medication or other contributing factors. In the view of the limited data on the long-term effects of nitisinone treatment, it is essential that all patients treated with nitisinone undergo regular and systematic developmental assessment, including neuro-cognitive development.

Eye monitoring

It is recommended that a slit-lamp examination of the eyes is performed before initiation of nitisinone treatment, and thereafter regularly. A patient displaying visual disorders during treatment with nitisinone should without delay be examined by an ophthalmologist.

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 WBC counts are monitored regularly, as a few cases of reversible thrombocytopenia and leucopenia were observed during clinical evaluation.

Monitoring visits should be performed every 6 months; shorter intervals between visits are recommended in case of adverse events.

Cytochrome P450
Nitisinone is a moderate CYP2C9 inhibitor. Nitisinone treated patients who are concomitantly treated with medicinal products primarily metabolized through CYP2C9, especially those with a narrow therapeutic window, should be monitored (see section 4.5 Interactions With Other Medicines And Other Forms Of Interactions).

Excipients with known effect – Oral Suspension

Glycerol

Each mL contains 500 mg glycerol. A dose of 20 mL oral suspension (10 g glycerol) or more may cause headache, stomach upset and diarrhoea. Consider switching patients who are unable to tolerate the oral suspension to ORFADIN capsules.

Sodium

Each ml contains 0.7 mg (0.03 mmol) of sodium. Consider switching patients on a sodium restricted diet to ORFADIN capsules.

Sodium benzoate

Each mL contains 1 mg sodium benzoate. 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 ORFADIN capsules should be considered instead of the oral suspension until the unconjugated bilirubin plasma levels are normalised.

Use in adult population

There is very limited data in the adult population and no information on the treatment of the elderly.

Use in the elderly
No data available.

Paediatric use
No data available.

Effects on laboratory tests
No data available.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

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, nitisinone is a moderate inhibitor of CYP2C9, a weak inducer of CYP2E1 and a weak inhibitor of OAT1, and OAT3, whereas nitisinone did not inhibit CYP2D6. Nitisinone treatment may therefore result in increased plasma concentrations of co-medications metabolized primarily via CYP2C9, such as warfarin and phenytoin (see section 4.4 Special Warnings and Precautions For Use).

The following AUC ratios, were observed for the probe drugs used in the clinical interaction study, when administered alone and together with nitisinone:

Table 2: AUC ratio for the probe drugs alone and co-administered with nitisinone

Enzyme/ transporter	Probe drug	Parameter (Unit)	n_1	n_2	LS Mean		AUC ratio*	90 % confidence interval for the ratio
					Probe drug	Orfadin + Probe drug		
CYP2C9	Tolbutamide	AUC_∞ (h·µg/mL)	18	16[1]	547.3	1264	2.31	[2.11, 2.53]
CYP2D6	Metoprolol	AUC_∞ (h.µg/mL)	18	18	245.0	232.3	0.95	[0.88, 1.03]
CYP2E1	Chlorzoxazone	AUC_∞ (h·µg/mL)	18	18	11.20	8.20	0.73	[0.67, 0.80]
OAT1/OAT3	Furosemide	AUC_∞ (h·µg/mL)	18	18	1928	3319	1.72	[1.63, 1.81]

*AUC ratio = $AUC_{probe+nitisinone}$ / AUC_{probe}
AUC = Area under the plasma concentration vs. time curve
AUC_∞ = Area under the plasma concentration-time curve from time 0 to infinity
LS Mean = Least square mean
n_1 = number of subjects with valid PK parameter Period 1
n_2 = number of subjects with valid PK parameter Period 2
[1] = two subjects were excluded due to residual AUC >30%

Based on *in vitro* studies, nitisinone is not expected to inhibit CYP 1A2, 2C9, 2C19, 2D6, 2E1 or 3A4- mediated metabolism or induce CYP 1A2, 2B6, or 3A4/5. Nitisinone is not expected to inhibit P-gp, BCRP, OATP1B1, OATP1B3 or OCT2-mediated transport.

Food does not influence the bioavailability (AUC) of Orfadin oral suspension, but intake together with food decreases the absorption rate, as shown in a study in healthy volunteers, and consequently leads to lower fluctuations in serum concentrations within a dosage interval. Cmax after administration with food was 81.5 % of Cmax in fasting subjects. Tmax increased from 0.5 h in fasting subjects to 8 h when the suspension was given with food.

No formal food interactions studies have been performed with Orfadin 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 capsules is initiated with food, this should be maintained on a routine basis.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

Prolonged mating period and increased post-implantation loss were observed following treatment of female mice prior to mating through early embryogenesis at 50 mg/kg/day orally (2 times the maximum clinical dose based on body surface area). No effects were observed at 5 mg/kg/day (less than the maximum clinical dose based on body surface area).

Use in pregnancy

PREGNANCY CATEGORY B3

There are no adequate data from the use of nitisinone in pregnant women. Nitisinone should not be used during pregnancy unless clearly necessary.

Gestation length was increased in pregnant mice given nitisinone at oral doses from 50 mg/kg/day (2 times the maximum clinical dose based on body surface area).

In pregnant mice and rabbits, embryotoxicity (decreased fetal weights, increased early intra-uterine deaths and increased post-implantation loss) and fetal abnormalities (incomplete skeletal ossification in mice, umbilical hernia, gastroschisis, reduced or absent lung, increased skeletal malformations and variations in rabbits) were observed at oral nitisinone doses from 5 mg/kg/day during organogenesis (less than the maximum clinical dose based on body surface area). In a preliminary study in pregnant rats, embryotoxicity (increased stillbirths, reduced live births, birth weights and survival after birth) and fetal abnormalities (increased skeletal variants) were observed at maternally toxic oral doses from 50 mg/kg/day (4 times the maximum clinical dose based on body surface area).

Use in lactation

It is not known whether nitisinone is excreted in human breast milk. Animal studies have shown adverse postnatal effects via exposure of nitisinone in milk (see below). Therefore, mothers receiving nitisinone should not breast-feed, since a risk to the suckling child cannot be excluded (sections 4.3 Contraindications and 5.3 Preclinical Safety Data).

Maternal treatment of mice at oral doses from 5 mg/kg/day (less than the maximum clinical dose based on body surface area) during organogenesis through weaning was associated with reduced pup survival, weight gain and developmental delays. In rats, lactational exposure of naïve pups to nitisinone from treated dams given 100 mg/kg/day orally was associated with reduced pup weight and the development of corneal opacities (9 times the maximum clinical dose based on body surface area).

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

No studies on the effects on the ability to drive and use machines have been performed.

Adverse reactions involving the eyes (see section 4.8 Adverse Effects) can affect the vision. If the vision is affected the patient should not drive or use machines until the event has subsided.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

ORFADIN was studied in one open-label, uncontrolled main study of 207 patients with HT - 1, from ages 0 to 21.7 years at enrolment (median age 9 months), who were diagnosed with HT-1 by the presence of succinylacetone in the urine or plasma. The starting dose of nitisinone was 0.6 to 1 mg/kg/day, and the dose was increased in some patients to 2 mg/kg/day based on weight, biochemical, and enzyme markers. Median duration of treatment was 22.2 months (range 0.1 to 80 months). A complementary analysis was performed on 250 patients.

Patients with HT-1 are at increased risk of developing porphyric crises, hepatic neoplasm, and liver failure requiring liver transplantation. Regular monitoring of these complications by hepatic imaging (ultrasound, computerized tomography, and magnetic resonance imaging) and laboratory tests, including serum alpha-fetoprotein concentration is recommended. Patients with increasing alpha-fetoprotein levels or development of liver nodules during treatment with nitisinone should be evaluated for hepatic malignancy.

Additional Adverse Events, **regardless of causality assessment**, reported in the complementary analysis of 250 patients, are presented in Table 3.

The adverse reactions considered at least possibly related to treatment are listed below, by body system organ class, and absolute frequency. Frequencies are defined as common (≥1/100, <1/10) or uncommon (≥1/1,000, <1/100). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Blood and lymphatic system disorders
Common: thrombocytopenia, leucopenia, granulocytopenia

Eye disorders
Common: conjunctivitis, corneal opacity, keratitis, photophobia, eye pain Uncommon: blepharitis

Skin and subcutaneous tissue disorders
Uncommon: exfoliative dermatitis, erythematous rash, pruritus

Nitisinone treatment is associated with elevated tyrosine levels. Elevated levels of tyrosine have been associated with corneal opacities and hyperkeratotic lesions. Restriction of tyrosine and phenylalanine in the diet should limit the toxicity associated with this type of tyrosinaemia by lowering tyrosine levels (see section 4.4 Special Warnings and Precautions for Use).

In clinical studies, granulocytopenia was only uncommonly severe (<0.5 x 10^9/L) and not associated with infections. Adverse reactions affecting the MedDRA system organ class 'Blood and lymphatic system disorders' subsided during continued nitisinone treatment.

Table 3: Adverse Events, <u>regardless of causality assessment</u>, reported in the complementary analysis of 250 patients

WHO Body System Class / Preferred Term	Total frequency (n=250)
Body as a whole, general disorders	
death	1.6%
elective transplantation	4.0%
Cardiovascular disorders, general	
cyanosis	0.4%
Central and peripheral nervous system disorders	
convulsions	0.8%
headache	0.8%
hyperkinesia	0.8%
hypokinesia	0.4%
Gastrointestinal system disorders	
abdominal pain	0.4%
constipation	0.4%
enanthema	0.4%
gastroenteritis	0.8%
gastrointestinal haemorrhage	0.8%
melaena	0.4%
tooth discolouration	0.4%

WHO Body System Class / Preferred Term	Total frequency (n=250)
Liver and biliary system disorders	
hepatic cirrhosis	0.8%
hepatic enzymes increased	0.8%
hepatic failure	6.4%
hepatic function abnormal	0.4%
hepatomegaly	0.4%
porphyria	0.8%
Metabolic and nutritional disorders	
dehydration	0.4%
Neoplasm	
hypoglycaemia	0.4%
brain neoplasm benign	0.4%
hepatic neoplasm	3.2%
hepatic neoplasm malignant	4.4%
lymphoma malignant	0.4%
Platelet, bleeding and clotting disorders	
epistaxis	0.4%
Psychiatric disorders	
nervousness	0.8%
Red blood cell disorders	
anaemia	0.4%
Reproductive disorders, female	
amenorrhea	0.4%
Resistance mechanism disorders	
infection	1.2%
otitis media	0.4%
Skin and appendages disorders	
alopecia	0.8%
skin dry	0.4%
Urinary system disorders	
haematuria	0.4%
cataract	0.8%
retinal disorder	0.4%

Reporting of suspected adverse effects

Reporting suspected adverse reactions after registration 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 at http://www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

For information on the management of overdose, contact the Poison Information Centre on 13 11 26 (Australia).

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

5. PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic group: Other alimentary tract and metabolism products. ATC code: A16A X04.

Mechanism of action

The biochemical defect in hereditary tyrosinaemia type 1 (HT -1) is a deficiency of fumarylacetoacetate hydrolase, which is the final enzyme of the tyrosine catabolic pathway. Nitisinone is a competitive inhibitor of 4-hydroxyphenylpyruvate dioxygenase, an enzyme which precedes fumarylacetoacetate hydrolase in the tyrosine catabolic pathway. By inhibiting the normal catabolism of tyrosine in patients with HT -1, nitisinone prevents the accumulation of the toxic intermediates maleylacetoacetate and fumarylacetoacetate. In patients with HT-1, these intermediates are converted to the toxic metabolites succinylacetone and succinylacetoacetate. Succinylacetone inhibits the porphyrin synthesis pathway leading to the accumulation of 5-aminolevulinate.

Pharmacodynamic effects

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

Clinical trials

Effects on overall survival

When compared to data for historical controls treatment with nitisinone together with dietary restriction results in a better survival probability in all HT-1 phenotypes than dietary restriction alone. This is seen in the following tables from the main analysis, complementary analysis and the historical control group:

Table 4: Survival probability: Main analysis of the study conducted during 1991-1997 includes 207 patients

Patients	Number of patients				Probability of survival % Main analysis (N=207)		
	Start	1 year	2 years	4 years	1 year	2 years	4 years
All	207	149	95	35	96%	96%	93%
Start 0-2 m	16	12	7	3	88%	88%	88%
Start 0-6 m	80	55	30	11	94%	94%	94%
Start > 6 m	127	94	65	24	97%	97%	93%

Table 5: Survival probability: Complementary analysis of the same study conducted during 1993-2000 includes 250 patients and share approx 150 patients with the main analysis above

Patients	Number of patients				Probability of survival % Complementary analysis (N=250)		
	Start	2 years	4 years	6 years	2 years	4 years	6 years
All	250	158	88	16	94%	94%	94%
Start 0-2 m	60	32	16	2	93%	93%	93%
Start 0-6 m	128	75	38	6	93%	93%	93%
Start > 6 m	122	83	50	10	96%	95%	95%

Data from a study used as a historical control (van Spronsen et al 1994) showed the following survival probability when treated with dietary restriction alone:

Table 6: Survival probabilities after 1 and 2 years from historical control (N=108)

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.

An open-label study to evaluate the PK, efficacy and safety of once daily dosing compared to twice daily dosing was performed in 18 patients with HT 1. While 19 patients were initially enrolled in the study, one enrolled patient did not take the IMP due to withdrawal of consent. All study patients were on a stable Orfadin daily dosage (0.4 – 1.6 mg/kg/day) during both study dosing regimens. After at least 4 weeks of twice a day dosing with Orfadin, both the urine and/or blood succinylacetone concentrations were below the limit of quantification. Patients were switched to once a day dosing with the same total daily dose of Orfadin and blood and/or urine succinylacetone concentrations remained undetectable when measured following at least 4 weeks treatment with once a day dosing. There was insufficient support for the once a day dosing regimen in patients with body weight <20 kg.

5.2 PHARMACOKINETIC PROPERTIES

Formal absorption, distribution, metabolism and elimination studies have not been performed with nitisinone. In 10 healthy male volunteers, after administration of a single dose of nitisinone capsules (1 mg/kg body weight) the terminal half-life (median) of nitisinone in plasma was 52.0 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 a small study in 6 children with HT-1 the mean terminal half –life was 25 hours compared with 21 hours in one adult with HT-1. The mean volume of distribution was 0.3 L/kg in 3 children with HT-1 and 0.07 L/kg in one adult with HT-1.

The single-dose pharmacokinetics of nitisinone have been studied for both Orfadin capsules and Orfadin oral suspension in healthy adult subjects.

Absorption

The pharmacokinetic characteristics following single oral administration of Orfadin 30 mg under fasting conditions are shown in Table 7. Compared to Orfadin capsule, the median Tmax occurred about 3 hours earlier with ORFADIN oral suspension.

Table 7: Nitisinone Geometric Mean Pharmacokinetic Parameters in Healthy Subjects Following a Single Oral 30 mg Dose of ORFADIN Under Fasting Conditions

Treatment	C_{max} (micromol/L) [range]	t_{max}* (h) [range]	AUC_{0-72h} (micromol·h/L) [range]
ORFADIN capsule (n=12)	10.2 [8.0 to 18.0]	3.50 [0.75 to 8.00]	403 [315 to 500]
ORFADIN oral suspension (n=12)	9.7 [7.8 to 20.3]	0.38 [0.25 to 4.00]	346 [264 to 456]

* presented as median [range]

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

In vitro binding of nitisinone to human plasma proteins is greater than 95% at 50 micromole concentration.

Patients with a diagnosis of HT-1 verified by the presence of succinylacetone in the urine or plasma. The median age of patients at enrolment was 9 months (range birth to 21.7 years, see Table 8).

Table 8: Characteristics of the Study Population

	N	Treatment time in months (median)
Total population	207	22
Females	93	23
Males	114	21
Age at start of nitisinone therapy		
0 – 24 months	142	20
> 24 months	65	28

The median duration of treatment was 22 months with a range of 0.1 months to 78 months.

Biochemical effects of nitisinone treatment

The efficacy of nitisinone as an inhibitor of 4-hydroxy-phenylpyruvate dioxygenase was inferred by the effects of treatment on the following biochemical parameters: urine succinylacetone, plasma succinylacetone and erythrocyte porphobilinogen synthase (PBG) activity. For all 186 patients for whom data are available, the excretion of succinylacetone in urine was reduced to a level below the reference limit, which represents the sensitivity of the analytical procedure. The median time to normalization was 0.3 months. For most patients for whom data are available (150/172=87%) the plasma concentration of succinylacetone decreased to a level below the reference. The median time to normalization was 3.9 months. For all 180 patients for whom data are available, the porphobilinogen synthase activity of erythrocytes increased to within reference limits. The median time to normalization was 0.3 months. The differences in these indices compared to the start of nitisinone treatment were statistically significant ($p<0.001$).

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

There is limited evidence of genotoxic potential for nitisinone in vitro and in vivo. Nitisinone was not mutagenic in the bacterial reverse mutation test but was genotoxic in the mouse lymphoma cell forward mutation test in vitro. In vivo nitisinone was weakly positive in the mouse bone marrow micronucleus test but negative in the mouse liver unscheduled DNA synthesis (UDS) test.

Carcinogenicity

At oral doses up to 100 mg/kg/day, 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

pregelatinised maize starch

Capsule shell

gelatin
titanium dioxide

printing ink – either Capsugel Ink 10A1 Black or Capsugel Ink 10A2 Black (containing iron oxide black, shellac, propylene glycol, ammonium hydroxide)

Oral suspension

hypromellose
glycerol
polysorbate 80
sodium benzoate
citric acid monohydrate
sodium citrate
strawberry 501440 T (aroma)
purified water

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF-LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Capsules: Store at 2°C to 8°C (Refrigerate. Do not freeze).

During the shelf life for ORFADIN nitisinone 5 mg, 10 mg, and 20 mg strength capsules, the patient may store the finished product for a single period of 2 months at a temperature below 25°C, after which the product must be discarded.

Oral suspension: Store refrigerated at 2°C to 8°C. Do not freeze. Store upright.

After first opening, the in-use stability is a single period of 2 months at a temperature below 25°C, after which it must be discarded.

6.5 NATURE OF CONTENTS OF CONTAINER

Capsules: High density polyethylene (HDPE) bottle with a tamper proof low density polyethylene (LDPE) cap, containing 60 capsules.

Oral suspension: 100mL brown glass (type III) bottle with a white, child resistant HDPE screw cap with tamper-evident seal. Each bottle contains 90 mL oral suspension. Each pack contains one bottle, one LDPE bottle adapter and 3 polypropylene (PP) oral syringes (1 mL, 3 mL and 5 mL).

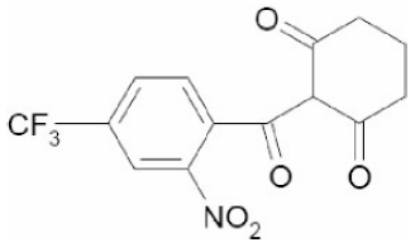
6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical name: nitisonone;
2-(2-nitro-4-trifluoromethylbenzoyl)cyclohexane- 1,3 -dione

Chemical structure:



Molecular formula: $C_{14}H_{10}F_3NO_5$

Molecular weight: 329.23

CAS Number: 104206-65-7

7. MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4 – Prescription Only Medicine

8. SPONSOR

A. Menarini Australia Pty Ltd
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Telephone 1800 644 542

9. DATE OF FIRST APPROVAL

22 November 2010

10. DATE OF REVISION

22 February 2019

SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
2, 3, 4.2, 6.1, 6.3, 6.4, 6.5	Includes information on new strength (20 mg capsules) and dosage form (oral suspension
4.2	Includes information on once-daily dosing
4.4	Warning & eye monitoring on potential keratopathies; monitoring of patients on concomitant medications with potential interactions. Information on interactions from clinical study.
4.5	Additional information on food interaction. Information on interactions from clinical study. Minor editorial change.
4.7	Additional statement on potential adverse effect on vision
4.8	Additional statement on granulocytopenia
5.1	Updated clinical trials information based on complementary analysis of completed study

5.2	Additional statement on human plasma protein binding
5.3	New statement on carcinogenicity study in mice
6.3	In-use stability information

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