NEW ZEALAND DATA SHEET –
NITYR™ nitisinone tablets

1. NAME OF THE MEDICINE

NITYR

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 2 mg, 5 mg or 10 mg nitisinone.

Contains lactose.

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

3. PHARMACEUTICAL FORM

NITYR tablets are white to beige, round, flat tablets, which may display light yellow to brown speckles, marked with the strength “2”, “5” or “10” on one side and “L” on the other side.

4. CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

NITYR tablets (nitisinone) are indicated for the treatment of patients with hereditary tyrosinaemia type 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 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 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 dose of nitisinone should be adjusted individually.

The recommended initial dose is 1 mg/kg body weight/day divided in 2 doses administered orally.

NITYR tablets may be taken with or without food.

For infants, tablets may be crushed between two spoons and mixed with apple sauce for administration. Administration of NITYR tablets with other liquids or foods has not been studied and is not recommended. Tablets may also be disintegrated in water inside an oral syringe by following the instruction described below. Do not administer the suspension using a baby bottle.

<u>Preparation and Administration of NITYR tablets with water in an Oral Syringe:</u>

- A 5-mL oral syringe with a cap will be provided by a pharmacist.
- Follow the instructions below for one or two intact tablets, depending on the number of tablets needed to achieve the patient's individual dosage.
- Do not prepare more than two tablets at once within the same oral syringe.
- If patient's dosage requires more than two tablets, follow the steps below using multiple oral syringes to achieve the required dose.

One Tablet

1. Remove the plunger from the 5-mL oral syringe and insert a single, intact tablet.
2. Replace the plunger and draw up 2.6 mL of room temperature water.
3. Cap the oral syringe and leave it for at least 60 minutes.
4. After 60 minutes, turn the oral syringe up and down for at least 30 seconds to suspend the material.
5. Inspect the syringe to ensure the tablet has disintegrated prior to administration to the patient. Administer immediately. However, do not administer unless the tablet has fully disintegrated.
6. If the tablet is not fully disintegrated, leave the oral syringe for an additional 10 minutes. Before administration of the suspension to the patient, turn the oral syringe up and down for 30 seconds to re-suspend the particles. Inspect the syringe again to ensure the tablet has disintegrated prior to administration to the patient. Do not administer unless the tablet has fully disintegrated.
7. Administer immediately. However, if this is not possible, the suspension can be stored at room temperature in the capped oral syringe, protected from direct sunlight for up to 24 hours after adding water to the tablet. Discard after 24 hours.

8. Uncap the oral syringe and administer the suspension in the patient's mouth. To facilitate full administration, avoid pressing the plunger to the end of the oral syringe and leave a gap between the plunger and the oral syringe.
9. Rinse the oral syringe by drawing up 2 mL of water. Cap the oral syringe and shake it well for 10 seconds to suspend any remaining particles.
10. Uncap the oral syringe and administer the suspension into the patient's mouth, this time fully pressing the plunger and ensuring the syringe is empty and no particles are left in the tip of the syringe. If particles are still present in the syringe, repeat steps 9-10.

Two Tablets

1. Remove the plunger from the 5-mL oral syringe and insert two intact tablets.
2. Replace the plunger and draw up 5 mL of room temperature water.
3. Cap the oral syringe and leave it for at least 60 minutes.
4. After 60 minutes, turn the oral syringe up and down for at least 30 seconds to suspend the material.
5. Inspect the syringe to ensure the tablets have disintegrated prior to administration to the patient. Administer immediately. However, do not administer unless the tablet has fully disintegrated.
6. If the tablets are not fully disintegrated, leave the oral syringe for an additional 10 minutes. Before administration of the suspension to the patient, turn the oral syringe up and down for 30 seconds to re-suspend the particles. Inspect the syringe again to ensure the tablets have disintegrated prior to administration to the patient. Do not administer unless the tablets have fully disintegrated.
7. Administer immediately. However, if this is not possible, the suspension can be stored at room temperature in the capped oral syringe, protected from direct sunlight for up to 24 hours after adding water to the tablets. Discard after 24 hours.
8. Uncap the oral syringe and administer the suspension into the patient's mouth. To facilitate full administration, avoid depressing the plunger to the end of the oral syringe and leave a gap between the plunger and the oral syringe.
9. Rinse the oral syringe by drawing up 2 mL of water. Cap the oral syringe and shake it well for 10 seconds to suspend any remaining particles.
10. Uncap the oral syringe and administer the suspension into the patient's mouth, this time fully depressing the plunger and ensuring the syringe is empty and no particles are left in the tip of the syringe. If particles are still present in the syringe, repeat steps 9-10.

<u>Disposal</u>

In New Zealand, any unused medicinal product or waste material should be disposed of in accordance with local requirements.

Preparation and Administration of NITYR tablets Mixed in Applesauce

For patients who can swallow semi-solid food, NITYR tablets can be crushed and mixed with applesauce:

1. Measure around one teaspoon of applesauce and transfer it into a clean container (e.g., clean glass).
2. Always crush one tablet at a time. Position the tablet between two metal teaspoons and apply light pressure on the top spoon. The two teaspoons should overlap each other to form a fine powder.
3. Press and rotate the two teaspoons against each other repeatedly until all of the tablet is in a fine powder.
4. Carefully transfer the resulting powder to the applesauce container ensuring all the powder is transferred, and no powder residue remains on the teaspoons.
5. If more than one tablet is needed, repeat the procedure starting from Step 2 and collect all the resulting powder together in the applesauce container.
6. Mix the powder into the applesauce until the powder is well dispersed.
7. Administer the entire NITYR tablets -applesauce mixture to the patient's mouth using a teaspoon. Administer immediately. However, if this is not possible, the mixture can be stored at room temperature, out of direct sunlight, for up to 2 hours after adding the crushed tablets to the applesauce. Discard any mixture that has not been given within 2 hours.
8. To assure that any leftover applesauce mixture from the container is recovered, add around one teaspoon of applesauce to the same container and mix the fresh applesauce with the remaining mixture.
9. Administer the additional NITYR tablets applesauce mixture immediately to the patient's mouth using a teaspoon.

Dose adjustment

During regular monitoring, it is appropriate to follow urine succinylacetone, liver function test values and alpha-fetoprotein levels if urine succinylacetone is still detectable one month after the start of nitisinone treatment, the nitisinone dose should be increased to 1.5 mg/kg body weight/day divided in 2 doses. A dose of 2 mg/kg body weight/day may be needed based on the evaluation of all biochemical parameters. This dose should be considered as a maximal dose for all patients.

If the biochemical response is satisfactory, the dose should be adjusted only according to body weight gain.

However, in addition to the tests above, during the initiation of therapy or if there is a

deterioration, it may be necessary to follow more closely all available biochemical parameters (i.e. plasma succinylacetone, urine 5-aminolevulinate (ALA) and erythrocyte porphobilinogen (PBG)-synthase activity).

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

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 µmol/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).

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 micromoles/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.

General Development

Cognitive and developmental disturbances have been observed in the patient population. On-going analysis has yet not 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. 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) monitor

It is recommended that platelet and white cell 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.

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

No formal interaction studies with other medicinal products have been conducted.

Nitisinone is metabolised in vitro by CYP 3A4 and dose-adjustment may therefore be needed when nitisinone is co-administered with inhibitors or inducers of this enzyme. Based on in vitro studies, nitisinone is not expected to inhibit CYP 1A2, 2C9, 2C19, 2D6, 2E1 or 3A4-mediated metabolism.

No formal food interactions studies have been performed. However, nitisinone has been co- administered with food during the generation of efficacy and safety data. Therefore, it is recommended that if nitisinone treatment is initiated with food, this should be maintained on a routine basis.

4.6 FERTILITY, PREGNANCY AND LACTATION

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 per oral (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 (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.

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.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Nitisinone 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 1.

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, rash, pruritus

Other adverse reactions, reported in less than 1% of the patients, included encephalopathy, diarrhoea, septicaemia and bronchitis.

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.

Table 1. Adverse Events, regardless of causality assessment, reported in the complementary analysis of 250 patients.

WHO Body System Class	WHO 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%
Gastro-Intestinal system disorders	abdominal pain	0.4%
	constipation	0.4%
	enanthema	0.4%
	gastroenteritis	0.8%
	GI haemorrhage	0.8%
	melaena	0.4%
	tooth discoloration	0.4%
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	amenorrhoea	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 reactions

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

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 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.

5.2 PHARMACOKINETIC PROPERTIES

Formal absorption, distribution, metabolism and elimination studies have not been performed with nitisinone. In 23 healthy adult volunteers, after administration of a single dose of NITYR tablets (10 mg) the terminal half-life (median) of nitisinone in plasma was 60.4 hours, and the median time to maximal plasma concentrations (Tmax) was 3.5 hours (range 1.0-4.0 hours).

Administration of NITYR tablets with food resulted in delayed absorption of nitisinone compared to administration whilst fasting, with a median T_{max} of 6 h (range 2.0-10.0 h) in fed conditions, compared to 3 h (range 2.0-8.0 h) in fasting conditions. No clinically significant effect of food was seen on nitisinone AUC_{0-72h}, C_{max}, or $t_{½}$.

Population pharmacokinetic analysis of nitisinone 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.

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

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 2).

Table 2. 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 ($p<0.001$).

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:

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

Patients	Number of patients				Probability of survival % (95% CI) 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 %

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 % (95% CI) Main analysis (N= 207)		
	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 %

Survival probability in control group with dietary restriction alone. (From figure 1, Van Spronsen et al.,1994).

Age at onset of symptoms	Survival probability with dietary control (%)	
	5 years	10 years
0-2 months	28	---
2-6 months	51	34
> 6 months	93	59

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.

Treatment with nitisinone was also found to result in reduced risk for the development of hepatocellular carcinoma (2.3 to 3.7-fold) compared to historical data on treatment with

dietary restriction alone. It was found that the early initiation of treatment resulted in a further reduced risk for the development of hepatocellular carcinoma (13.5 -fold when initiated prior to the age of 12 months).

5.3 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

The carcinogenic potential of nitisinone has not been studied in animals.

6. PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Glyceryl dibehenate and lactose monohydrate.

6.2 INCOMPATIBILITIES

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

6.3 SHELF-LIFE

30 months from date of manufacture. The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 25°C.
Store in the original bottle. Protect from light.

6.5 NATURE OF CONTENTS OF CONTAINER

NITYR tablets are packed in High-density polyethylene (HDPE) square bottles with a child-resistant tamper-evident Polypropylene (PP) screw cap. Each bottle contains 60 tablets.

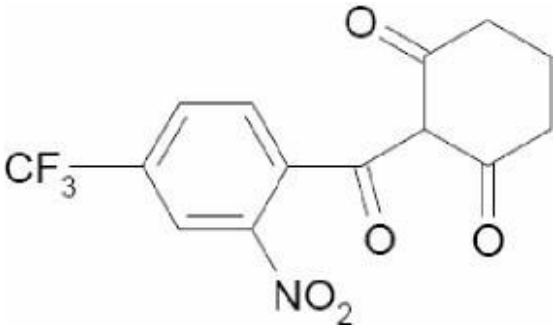
6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

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

6.7 PHYSICOCHEMICAL PROPERTIES

Nitisinone, 2-(2-nitro-4-trifluoromethylbenzoyl)cyclohexane- 1,3 -dione
Molecular Formula: $C_{14}H_{10}F_3NO_5$
Molecular Weight: 329.23

Chemical Structure



CAS Number

104206-65-7

The active substance is a weak acid and it is highly soluble in the pH range 4.5 - 7.2 according to the Biopharmaceutics classification system. Partition coefficient for nitisinone in octanol/water at pH 6.5 is 0.432.

7. MEDICINE SCHEDULE

Prescription

8. SPONSOR

Orpharma NZ Limited
c/o Staples Rodway Limited
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Email: medical@orpharma.com

Ph: +64 9 815 2664
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9. DATE OF FIRST APPROVAL

21 January 2021

10. DATE OF REVISION

SUMMARY TABLE OF CHANGES

Section changed	Summary of new information