**5.5 NITISINONE**

**2 mg capsule, 60; 5 mg capsule, 60; 10 mg capsule, 60; Orfadin®, A. Menarini Australia Pty Ltd.**

1. Purpose of Application
	1. Section 100 (Highly Specialised Drugs) listing for nitisinone for treatment of hereditary tyrosinaemia type 1 (HT-1).
2. Requested listing
	1. The submission requested that the PBAC consider listing on the basis of ‘rule of rescue’. The following table details the rule of rescue criteria and a summary of the response.

**Rule of Rescue Criteria**

| **Criterion** | **Summary of Response** |
| --- | --- |
| No alternative exists in Australia to treat patients with the specific circumstances of the medical condition meeting the criteria of the restriction. This means that there are no non-pharmacological or pharmacological interventions for these patients.  | Nitisinone is the only available pharmacological treatment for HT-1. A proportion of patients with HT-1 may undergo a liver transplant. However, current international treatment guidelines for HT-1 recommend that liver transplantation is only an alternative in patients who do not respond to nitisinone in combination with diet therapy or who present with very severe acute disease and liver failure.Nitisinone is the only available pharmacological treatment for HT-1. Liver transplantation is an alternative non-pharmacological treatment for some patients. |
| The medical condition defined by the requested restriction is severe, progressive and expected to lead to premature death. The more severe the condition, or the younger the age at which a person with the condition might die, or the closer a person with the condition is to death, the more influential the rule of rescue might be in the consideration by PBAC.  | With diet alone the 2 year survival for HT-1 patients with clinical onset at <2 months, 2-6 months and >6 months is 29%, 74% and 96%, respectively (van Spronsen 1994).The life expectancy for HT-1 patients, especially those with an early clinical onset, is substantially reduced. A proportion of patients undergo liver transplantation which is essentially a cure as the new liver allograft provides the fumarylacetoacetate hydrolase enzyme to metabolise dietary tyrosine.  |
| The medical condition defined by the requested restriction applies to only a very small number of patients. Again, the fewer the patients, the more influential the rule of rescue might be in the consideration by PBAC. However, PBAC is also mindful that the PBS is a community-based scheme and cannot cater for individual circumstances.  | In Australia a total of 17 patients have been diagnosed with HT-1 over the past 10 years. Based on this the incidence is estimated to be 0.54/100,000 live births. The current prevalence is 18.The patient numbers in the submission could not be verified but the incidence is consistent with that reported for other countries. It is stated in the submission that hospitals are currently funding nitisinone for all Australian HT-1 patients. |
| The proposed medicine provides a worthwhile clinical improvement sufficient to qualify as a rescue from the medical condition. The greater the rescue, the more influential the rule of rescue might be in the consideration by PBAC. | In the NTBC study, survival at 2, 4 and 6 years from the start of nitisinone treatment was 94%. The probability of no death or transplant due to liver failure was 94% at 2 and 4 years, and 92% at year 6. The probability of no occurrence of HCC was 98% at 2 years, 94% at 4 years and 91% at 6 years.The clinical improvement is substantial. For nitisinone treatment, survival was similar regardless of age of commencing treatment. For diet alone, survival was substantially reduced in patients with an early disease onset (overall 77% of patients in the diet study had an onset prior to 6 months of age compared with approximately two-thirds of patients in the nitisinone study). However, the estimated clinical improvement is based on a comparison of nonrandomised studies, and limited data prevents an assessment of the overall likelihood of confounding. |

* 1. Suggestions and additions proposed by the Secretariat to the requested listing are added in italics and suggested deletions are crossed out with strikethrough.

|  |  |  |  |
| --- | --- | --- | --- |
| Name, Restriction,Manner of administration and form | Max.Qty | №. ofRpts | Proprietary Name and Manufacturer |
| NITISINONE |  |  |  |  |
| nitisinone capsule 2mg, oral | 60 | 5 | ORFADIN® | A. Menarini |
| nitisinone capsule 5mg, oral | 60 | 5 |  |  |  |
| nitisinone capsule 10mg, oral | 60 | 5 |  |  |  |
|  |
| **Category /** **Program** | Section 100 – Highly Specialised Drugs Program (public and private) |
| **Prescriber type:** | [ ] Dental [x] Medical Practitioners [ ] Nurse practitioners [ ] Optometrists[ ] Midwives |
| **Condition:** | ~~Hereditary~~ Tyrosinaemia type I ~~(HT-1)~~ |
| **PBS Indication** | *Tyrosinaemia type I* |
| **Restriction:** | Authority required |
| **Treatment criteria:** | ~~The patient~~ Must be treated in a centre with experience in metabolic disorders.*AND*~~The prescriber~~ Must be *treated by* a paediatrician, physician or health care provider with experience in the management of patients with ~~HT-1~~ *tyrosinaemia type I* or other inherited metabolic diseases. |
| **Clinical criteria:** | Patient must have a confirmed clinical diagnosis of ~~HT-1~~ *tyrosinaemia type I* based on clinical suspicion and detection of succinylacetone in the urine by a ~~NATA~~ *National Association of Testing Authorities* accredited laboratory. *AND*Patient must not have had a ~~successful~~ liver transplant.*AND**The* treatment must be administered in combination with dietary restriction of tyrosine and phenylalanine. |
| **Administrative Advice** | Increased maximum quantities may be requested from ~~Medicare Australia~~ *the Department of Human Services* and should be based on a dosing regimen of 1 to 2 mg/kg/day. |

* 1. The Pre-Sub-Committee Response (PSCR) noted the issues raised regarding the proposed restriction in the Commentary and states that the sponsor will work with the Restrictions Working Group to refine the wording of the restriction.
	2. The PSCR clarified that succinylacetone is not detectable in patients who do not have HT-1 and therefore any level of detectable succinylacetone may be considered the result of fumarylacetoacetate deficiency and diagnostic of HT-1.
	3. The ESC considered that the meaning of a “successful” liver transplant is unclear in the wording of the clinical criteria of the restriction. Presumably it means that the new liver is functioning and produces fumarylacetoacetate hydrolase. Therefore, the patient may still benefit from treatment with nitisinone if a liver transplant is ‘unsuccessful’.
	4. Listing is requested based on cost-effectiveness versus standard medical management without nitisinone.

*For more detail on PBAC’s view, see section 7 “PBAC outcome”*

1. Background
	1. Nitisinone was TGA registered on 15 October 2010 for the treatment of patients with HT-1 in combination with dietary restriction of tyrosine and phenylalanine. It is currently supplied through hospitals with specialised units.
	2. Nitisinone had not been considered by the PBAC previously.
2. Clinical place for the proposed therapy
	1. HT-1 is a rare autosomal recessive inherited disease. The enzymatic defect in HT-1 is reduced activity of fumarylacetoacetate hydrolase in the liver, the last enzyme in the tyrosine degradation pathway. As a consequence, toxic metabolites upstream of the enzymatic block accumulate. The accumulation starts at birth and the severity of the phenotype is reflected in the age of onset of symptoms. The disease is characterised by severe liver dysfunction, impaired coagulation, painful neurological crises, renal tubular dysfunction and a high risk of hepatocellular carcinoma (HCC).
	2. HT-1 may be detected by neonatal screening using tyrosine or succinylacetone as the marker. Succinylacetone is a specific and sensitive marker for HT-1. An elevated tyrosine level is neither sensitive nor specific. Currently neonatal screening based on elevated tyrosine levels is funded by all Australian states and territories. Succinylacetone screening is reserved for second line confirmation following diagnosis based on presentation with clinical symptoms, elevated tyrosine and suspicion of HT‑1. Patients detected by screening start nitisinone treatment prior to the development of clinical symptoms, and potentially irreversible liver damage.
	3. The treatment of HT-1 includes dietary restriction of tyrosine and phenylalanine, and in the case of liver failure or malignancy, liver transplantation. Nitisinone is added to the restricted diet. The Australasian Society for Inborn Errors of Metabolism advised that there are currently 19 HT-1 patients in Australia and all are receiving treatment with nitisinone through hospitals. Of these patients, 4 (21%) were detected by screening (2 because of siblings with HT-1).
	4. The letter from the Australasian Society for Inborn Errors of Metabolism stated ‘newborn screening misses most cases of HT-1 currently, but an improved method for detecting the disorder has been published…. Median age of diagnosis was 1.5 months (range 0 to 18 months). Excluding those diagnosed by newborn screening or a previous affecting sibling, median age at diagnosis was 3 months…. There are no patients with HT-1 in adult metabolic services in Australia… It is not possible to comment on lifelong therapy with nitisinone as the age of the Australian patients treated with nitisinone is relatively young. The median age of the patients is 7.2 years (range 1-16 years) and the duration of treatment is a median of 6.6 years (range 0.92 to 15.5 years).’

*For more detail on PBAC’s view, see section 7 “PBAC outcome”*

1. Comparator
	1. Standard medical management without nitisinone (i.e. diet alone). The ESC considered that this is the appropriate comparator.

*For more detail on PBAC’s view, see section 7 “PBAC outcome”*

1. Consideration of the evidence

**Sponsor hearing**

* 1. There was no hearing for this item.

**Consumer comments**

* 1. The PBAC noted and welcomed the input from individuals (24) and organisations (3) via the Consumer Comments facility on the PBS website. The comments described a range of benefits of treatment with nitisinone including the ability to extend life, allow patients to manage their condition and avoidance of costly and risky liver transplant. The comments from organisations also noted current issues of equity and ease of access and security of supply due to this drug currently being funded and supplied through hospitals.

*For more detail on PBAC’s view, see section 7 “PBAC outcome”*

**Clinical trials**

* 1. The submission was based on a comparison of 2 single-arm studies (the NTBC nitisinone study and van Spronsen 1994 diet study), 3 supportive nitisinone single‑arm studies (Masurel-Paulet 2008, Raimann 2012, Couce 2011) and 1 supportive single-arm nitisinone study with historical controls (Larochelle 2012).
	2. Details of the studies presented in the submission are provided in the below table.

Trials and associated reports presented in the submission

|  |  |  |
| --- | --- | --- |
| **Trial ID** | **Protocol title/ Publication title** | **Publication citation** |
| **Proposed drug: Nitisinone, key study** |
| NTBC study | The NTBC study: NTBC treatment of hereditary tyrosinaemia type 1. Clinical Study Report. (Main analysis) | 5 November 1999 |
|  | Efficacy laboratory data, survival and safety analysis in patients enrolled in the NTBC Study between 1 July 1993 and 28 March 2000. Final Report. (Complementary analysis) | 15 February 2002 |
|  | Holme, E., Lindstedt, P. S., and Lock, E. A. Treatment of tyrosinemia type I with an enzyme inhibitor (NTBC)  | International Pediatrics 1995; 10 (1): 41-43 |
|  | Holme, E. and Lindstedt, S. Diagnosis and management of tyrosinemia type I | Current Opinion in Pediatrics 1995; 7 (6): 726-732 |
|  | Holme, E. and Lindstedt, S. Nontransplant treatment of tyrosinaemia  | Clinics in Liver Disease 2000; 4 (4): 805-814 |
|  | Lindstedt, S., Holme, E., Lock, E.A., Hjalmarson, O. and Strandvik, B. Treatment of hereditary tyrosinaemia type I by inhibition of 4-hydroxyphenylpyruvate dioxygenase  | Lancet 1992: 340, 813-17 |
|  | Holme, E. and Lindstedt, S. Tyrosinaemia type I and NTBC (2-(2-nitro-4-trifluoromethylbenzoyl)-1,3-cyclohexanedione) | Journal of Inherited Metabolic Disease 1998; 21: 507-517 |
| **Comparator: Diet alone, key study** |
| van Spronsen 1994 | van Spronsen, F. J., Thomasse, Y., Smit, G. P. A., Leonard, J. V., Clayton, P. T., Fidler, V., Berger, R., and Heymans, H. S. A. Hereditary tyrosinemia type I: A new clinical classification with difference in prognosis on dietary treatment  | Hepatology 1994; 20 (5): 1187-1191 |
| **Proposed drug: Nitisinone, supportive studies** |
| Masurel-Paulet 2008 | Masurel-Paulet, A., Poggi-Bach, J., Rolland, M. O., Bernard, O., Guffon, N., Dobbelaere, D., Sarles, J., Baulny, O. O. H., and Touati, G. NTBC treatment in tyrosinaemia type I: Long-term outcome in French patients  | Journal of Inherited Metabolic Disease 2008; 31 (1): 81-87 |
| Raimann 2012 | Raimann, E., Cornejo, V., Arias, C., Cabello, J. F., Castro, G., Fernandez, E., and de la Parra, A. Clinical follow up of Chilean patients with tyrosinemia type 1 treated with 2-(2-nitro-4-trifl uoromethylbenzoyl)- 1,3-ciclohexanedione (NTBC) | Revista Medica de Chile 2012; 140 (2): 169-175 |
| Couce 2011 | Couce, M. L., Dalmau, J., Del Toro, M., Pintos-Morell, G., and Aldamiz-Echevarria, L. Tyrosinemia type 1 in Spain: Mutational analysis, treatment and long-term outcome  | Pediatrics International 2011; 53 (6): 985-989 |
| Larochelle 2012 (single-arm study with historical cohort)  | Larochelle, J., Alvarez, F., Bussieres, J. F., Chevalier, I., Dallaire, L., Dubois, J., Faucher, F., Fenyves, D., Goodyer, P., Grenier, A., Holme, E., Laframboise, R., Lambert, M., Lindstedt, S., Maranda, B., Melancon, S., Merouani, A., Mitchell, J., Parizeault, G., Pelletier, L., Phan, V., Rinaldo, P., Scott, C. R., Scriver, C., and Mitchell, G. A. Effect of nitisinone (NTBC) treatment on the clinical course of hepatorenal tyrosinemia in Quebec  | Molecular Genetics and Metabolism 2012; 107 (1-2): 49-54 |

Source: Table B.2-3, p61 of the submission

* 1. The key features of the nonrandomised studies are summarised in the following table.

Key features of the included evidence

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Trial** | **N** | **Design/ duration** | **Risk of bias** | **Patient population** | **Outcome(s)** | **Use in modelled evaluation** |
| **Nitisinone key study** |  |  |  |  |  |  |
| NTBC study(Complementary analysis) | 250 | Single-arm, prospective, multinationalTmt duration: '''''''''''''''''''' years Median FU: between 2 and 4 yrs | High | Receiving nitisinone on compassionate useOnset <6 mo: '''''''''''a | OS, transplant, HCC, porphyria crises | Estimate survival and transplants for nitisinone |
| **Diet key study** |  |  |  |  |  |
| van Spronsen 1994 | 108 | Single-arm, retrospective, multinationalDuration of tmt and FU: NR | High | Clinical diagnosis of HT-1Onset <6 mo: 77% | OS, transplant, HCC | Estimate survival for diet |
| **Nitisinone supportive studies** |  |  |  |  |  |
| Masurel-Paulet 2008 | 46 | Single-arm, retrospectiveMean tmt duration: 4.75 years | High | HT-1 patients treated with nitisinone in France Onset <6 mo: 74% | OS, transplant, HCC, porphyria crises | Not used |
| Raimann 2012 | 12 | Single-arm, retrospectiveMedian FU: 6.6 years | High | Diagnosis of HT-1, treated in ChileOnset <6 mo: 58% | OS, transplant, HCC | Not used |
| Couce 2011 | 34 | Single-arm, retrospectiveMean tmt duration: 6.73 years | High | HT-1 patients treated with nitisinone in SpainMean age of onset: 4.3 mo | OS, transplant, HCC, porphyria crises | Not used |
| **Nitisinone single-arm study with historical controls** |  |  |  |  |  |
| Larochelle 2012, nitisinone | 50 | Tmt duration: mean 9.6 years | High | Diagnosis of HT-1 by neonatal | OS, transplant, | Not used |
| Larochelle 2012, control cohort | 28 | Single-arm, prospective with historical control cohort |  | screening in Quebec, Canada | porphyria crises | Estimate transplants for diet |

FU = follow-up; HCC = hepatocellular carcinoma; mo = months; NR = not reported; OS = overall survival; tmt = treatment.

Source: compiled during the evaluation

a Data based on subset of ''''''''' patients included in Main analysis

* 1. The risk of bias for the comparison based on the NTBC nitisinone study and the van Spronsen 1994 diet study is high. Lack of data on the comparability of people in the study prevents an assessment of the likely overall direction of the bias. For the van Spronsen 1994 diet study:
* Patients were selected retrospectively and the process for the selection of patients at each centre was not reported;
* Lack of reporting of patient demographic and disease characteristics prevents an assessment of the likelihood of confounding; and
* The extent and duration of follow-up is not reported.
	1. The PSCR acknowledged that “there is limited demographic data to assess whether the patient populations in the trials are similar. However neither study had specific inclusion or exclusion criteria other than patients having a clinical diagnosis of HT-1.”
	2. Larochelle 2012 was presented in the submission as supportive evidence. This study includes a cohort of historical controls and therefore enables a comparison of nitisinone and diet alone in patients treated in the same geographical region. This comparison is likely to be subject to less bias than the primary comparison presented in the submission as all participants came from the same geographical area (NTBC study vs van Spronsen 1994). Larochelle 2012 was conducted in Quebec, Canada, where there is a high prevalence of HT-1 due to the Founder effect and a universal neonatal HT-1 screening program. The applicability of the results of Larochelle 2012 is therefore dependent on the extent and type of HT‑1 screening in Australia. In Larochelle, those who commenced treatment at greater than 1 month of age had worse survival and more liver transplant than those who commenced less than or equal to 1 month of age. In the context of neonatal screening, it is not possible to determine whether patients would have had the acute, subacute or chronic subtypes as all patients would start treatment early.

*For more detail on PBAC’s view, see section 7 “PBAC outcome”*

**Comparative effectiveness**

* 1. For the NTBC study the results are presented for subgroups based on age at commencement of nitisinone. For van Spronsen 1994 the survival results are presented for subgroups based on age at onset of clinical symptoms. Increased survival with nitisinone compared with diet alone is not demonstrated for patients with a clinical onset after 6 months of age (defined as chronic) as overall survival at 2 years with diet alone is estimated to be 96%. However, the effect size on survival in people presenting clinically up to 6 months of age (acute/sub-acute disease) appears to be substantial. The proportion of patients with onset up to 6 months of age (acute/sub‑acute disease) was similar for the NTBC study and van Spronsen 1994 (''''''''''' vs 77%), although for the NTBC study this information is only available for a subset of patients (n =143/250, 57%).
	2. The PSCR argued that the clinical benefit of nitisinone for patients with a clinical onset after 6 months of age is a reduction in the risk of developing HCC. In the NTBC study, '''' of the ''''''' cases of HCC developed in patients who started nitisinone after 2 years of age. However, this group was heterogeneous and included patients with the acute, subacute and chronic forms, who may have been treated with diet for some time before starting nitisinone. Van Spronson demonstrated that patients with the chronic form remained at risk of HCC, and Holme and Lindstedt (1995) provide expert opinion that the chronic group rarely live beyond 20 years due to the risk of HCC and renal failure, but the effects of nitisinone on HCC in this subgroup are not known. In Larochelle 2012, the 7 liver transplants and 2 deaths in nitisinone treated patients occurred in patients who started nitisinone after 1 month of age (see the table outlining the results from Larochelle 2012 below).

Results of survival, liver transplantation, HCC and porphyria-crises in the nonrandomised studies

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Study** | **Mean follow-up** | **Survival** | **Liver transplant** | **HCC** | **Porphyria-crises** |
| **Primary comparison presented in submission: NTBC study vs van Spronsen 1994** |  |  |  |  |  |
| NTBC study, nitisinone | 2 years: 158 (63%)4 years: 88 (35%)6 years: 16 (6%) | Survival at 2 yearsNit started ≤2 months: 93% (n=32 at risk)Nit started ≤6 months: 93% (n=75 at risk)Nit started >6 months: 96% (n=83 at risk) | '''''''''''''''' ‘’’’’’’’’’ | '''''''''''''''''' '''''''''''Nit started ≤2 years'' '''''''''''''' '''''''''''''''''Nit started >2 years'' '''''''''' '''''''''''''''' | 2/250 (0.8%) |
| Van Spronsen 1994, diet | Not reported | Survival at 2 yearsaOnset <2 months: 29%Onset 2-6 months: 74%Onset >6 months: 96% | 26/108 (24%) | 10/108 (9%)Patients with ≥2 years survival: 18% | Not reported |
| **Supportive nitisinone single-arm studies** |  |  |  |  |  |
| Masurel-Paulet 2008  | 4.75 years | 45/46 (98%) | 4/46 (9%) | 2/46 (4%) | 0/46 (0%) |
| Raimann 2012 | 6.75 years | 10/12 (83%) | 2/12 (17%) | 2/12 (17%) | Not reported |
| Couce 2011 | 6.7 years | 34/34 (100%) | 1/34 (3%) | 0/34 (0%) | 0/34 (0%) |
| **Nitisinone single-arm study with historical controls** |  |  |  |  |  |
| Larochelle 2012, nitisinone | 9.6 years | 48/50 (96%) | 7/50 (14%) | Not reported | Hospitalisations for neurological crisis (months): 0/5731 |
| Larochelle 2012, controls | 2.3 years | 18/28 (64%)(P<0.001 vs nitisinone) | 20/28 (71%)(P<0.001 vs nitisinone) | Not reported | 71/777(P<0.001 vs nitisinone) |

Source: compiled during the evaluation

a n at risk at 2 years not reported, total n in each group: 39, 44 and 25 for patients with onset <2, 2-6 and >6 months, respectively

Results of survival and liver transplantation for Larochelle 2012 by age at starting nitisinone

| Outcome | Early nitisinone (start at ≤1 month of age) | Late nitisinone (start at >1 month of age) | No nitisinone |
| --- | --- | --- | --- |
|  | N=24 | N=26 | N=28 |
| Liver transplant | 0\*\*\* | 7 (27%)\*\*\* | 20 (71%) |
| Death | 0\*\*\* | 2 (8%)\*\* | 10 (36%) |
| Death before liver transplant | 0 | 0 | 8 (29%) |
| Death after liver transplant | 0 | 2 (8%) | 2 (7%) |

Source: Table B.6-19, p117 of the submission.

Note: \*\* P<0.01, \*\*\*P<0.001 versus no nitisinone group.

*For more detail on PBAC’s view, see section 7 “PBAC outcome”*

**Comparative harms**

* 1. In the NTBC study, the most commonly reported adverse events were visual disorders ''''''''''''''''''' of patients) including keratitis '''''''''''''''''' corneal opacity ''''''''''''''''' photophobia ''''''''''''''''' and conjunctivitis '''''''''''''''''' The probability of visual disorders increased with increasing plasma tyrosine levels. The second most commonly reported adverse events were disorders of the liver and biliary system '''''''''''''' including liver failure '''''''''''''''''' Leukopenia/granulocytopenia were also reported in the NTBC study '''''''''''''''''' ''''''''' and have been reported in the post-marketing setting. Developmental and cognitive disorders have been reported in the post-marketing setting in patients treated with nitisinone. The relationship of these events to nitisinone treatment is unknown. The nitisinone Product Information recommends regular and systematic developmental assessment, including assessment of neuro‑cognitive development.

**Benefits/harms**

* 1. A summary of the benefits and harms is presented in the table below.

Summary of comparative benefits and harms for nitisinone and diet alone (based on the non-randomised evidence)

| **Study** | **Nitisinone** | **Diet alone** |  |
| --- | --- | --- | --- |
| **Overall survival, at 2 years** |  |  |  |
| NTBC study | All patients: 94% (95% CI: '''''''''''' '''''''''''') (n=158)Nit started ≤2 months: 93% (n=32 at risk)Nit started ≤6 months: 93% (n=75 at risk)Nit started >6 months: 96% (n=83 at risk) | van Spronsen 1994 | Onset <2 months: 29%Onset 2-6 months: 74%Onset >6 months: 96% |
| **Deaths** |  |  |  |
| NTBC study | '''''''''''''''' '''''''''''Median follow-up: between 2 and 4 years | van Spronsen 1994 | 52/108 (48%)Follow-up not reported |
| Larochelle 2012, nitisinone | 2/50 (4%)Mean of 9.6 years follow-up | Larochelle 2012, controls | 10/28 (36%)Mean of 2.3 years follow-up |
| **Liver transplantation** |  |  |  |
| NTBC study | ''''''''''''''' ''''''''''''''Median follow-up: between 2 and 4 years | van Spronsen 1994 | 26/108 (24%)Follow-up not reported |
| Larochelle 2012, nitisinone | 7/50 (14%)Mean of 9.6 years follow-up | Larochelle 2012, controls | 20/28 (71%)Mean of 2.3 years follow-up |
| **Death or liver transplantation** |  |  |  |
| NTBC study | '''''''''''''''' ''''''''''''''Median follow-up: between 2 and 4 years | van Spronsen 1994 | 78/108 (72%)Follow-up not reported |
| Larochelle 2012, nitisinone | 7/50 (14%)Mean of 9.6 years follow-up | Larochelle 2012, controls | 28/28 (100%)Mean of 2.3 years follow-up |
| **Visual disorders** |  |  |  |
| NTBC study | '''''''''''''''' ''''''''''''''''Median follow-up: between 2 and 4 years | Not reported |  |
| **Cognitive disorders (memory and concentration difficulties, and slowness)** |  |  |  |
| Masurel-Paulet 2008 | 6/23 (26%)Mean of 4.75 years follow-up | Not reported |  |

Abbreviations: CI = confidence interval

Source: Compiled during the evaluation

* 1. An estimate of the incremental benefit based on the clinical studies was not presented in the submission. As it is unknown if the patient populations enrolled in the nitisinone and diet alone studies are similar, an estimate of the incremental benefit is also not presented here.
	2. On the basis of one single-arm study presented by the submission (NTBC study), for every 100 patients treated with nitisinone:
* Approximately 94 are alive after 2 years of treatment regardless of age of commencing nitisinone treatment, and with approximately two-thirds of patients having developed clinical symptoms of HT-1 before 6 months of age.
	1. On the basis of a second single-arm study presented by the submission (van Spronsen 1994), for every 100 patients not treated with nitisinone:
* Approximately 29 are alive after 2 years if clinical symptoms of HT-1 developed before 2 months of age;
* Approximately 74 are alive after 2 years if clinical symptoms of HT-1 developed between 2 and 6 months of age; and
* Approximately 96 are alive after 2 years if clinical symptoms of HT-1 developed after 6 months of age.
	1. On the basis of the third study, conducted in Quebec, Canada (Larochelle 2012), and where patients with HT-1 were identified through newborn screening:
* For every 100 patients treated with nitisinone, 96 are alive after an average of 9.6 years of treatment. Of the 96 *surviving* patients, 14 would have had a liver transplant.
* For every 100 patients treated in Quebec before nitisinone was available, 64 are alive an average of 2.3 years following liver transplant. A further 7 patients died following liver transplantation.
	1. On the basis of one single-arm study presented in the submission (NTBC study), for every 100 patients treated with nitisinone:
* Approximately 10 will develop eye disorders such as keratitis, corneal opacity, photophobia and conjunctivitis.
* The number of patients with HT-1 not treated with nitisinone that will develop eye disorders is unknown.
	1. Developmental and cognitive disorders have been reported in the post‑marketing setting in patients treated with nitisinone.

*For more detail on PBAC’s view, see section 7 “PBAC outcome”*

**Clinical claim**

* 1. The submission described nitisinone plus diet therapy as superior in terms of comparative effectiveness and superior in terms of comparative safety over diet therapy alone. This claim is reasonable in terms of effectiveness, although is based on a comparison of non-randomised studies. This claim is not reasonable in terms of safety. Nitisinone treatment may result in eye disorders, haematological events and cognitive dysfunction.
	2. The PSCR argued these adverse events are more likely due to non‑adherence to diet therapy rather than treatment with nitisinone. Accordingly, the PSCR claims that a non-inferior safety claim is an appropriate reflection of the clinical evidence. The ESC did not agree that these adverse events are not related to the safety of nitisinone. Rather, the adverse events related to non-compliance with diet are effects of how the drug may be used in a real life setting in which compliance is not perfect. Indeed, the ESC noted that these adverse effects are likely to increase with extrapolation as compliance is likely to be worse in teenagers than the infants and young children included in the studies. The extent to which diet non-compliance is an issue over the longer term is currently unknown.
	3. The PBAC considered that the claim of superior comparative effectiveness was reasonable.
	4. The PBAC considered that the claim of superior comparative safety was not adequately supported by the data.

**Economic analysis**

* 1. A cost-effectiveness analysis was presented. The submission models increased survival and a reduction in the number of liver transplants with nitisinone treatment compared to diet alone. The overall cost-effectiveness was calculated by weighting the costs and outcomes for patients with a clinical onset before 2 months, between 2 and 6 months and after 6 months of age by the proportion of patients in each subgroup.

Summary of model structure and rationale

| **Component** | **Summary** |
| --- | --- |
| Time horizon | 100 years in the model base case versus a median follow-up of <4 years in the nitisinone NTBC study. |
| Outcomes | LYG and QALYs |
| Methods used to generate results | Cohort expected value analysis |
| Health states | Treatment: patients remain in this state until transplantation or death.Transplantation: patients enter this state when undergoing a transplant. Treatment with nitisinone/diet is stopped. Patients remain in this state until death. Death |
| Cycle length | 3 months |
| Transition probabilities | Overall survival: NTBC study and van Spronsen 1994. Australian population rates for extrapolated period.Liver transplantation: NTBC study for nitisinone, with no transplants during extrapolated period. Larochelle 2012 for diet for study follow-up and extrapolated periods.Death following liver transplantation: Literature |
| Utility values | Treatment with nitisinone: 0.87 (based on chronic hepatitis B)Treatment with diet: 0.49-0.87 (depending on age of HT-1 onset; based on cirrhosis and hepatitis B)Post liver transplant: 0.72 (based on post liver transplant for hepatitis B patients) |

Source: compiled during the evaluation

* 1. The key drivers of the model are summarised in the table below.

Key drivers of the model

| **Description** | **Method/Value** | **Impact** |
| --- | --- | --- |
| Survival for nitisinone and diet | Sourced from non-randomised studies | High, direction unknown but likely to favour nitisinone |
| Nitisinone cost (unit cost, compliance and dose) | 100% compliance and dose of 1 mg/kg/day.Cost calculated assuming once daily rather than twice daily dosing. | HighCompliance: favours dietOnce daily dosing: favours nitisinone  |
| Time horizon and use of population death rates | 100 years; assumed from maximum follow-up of '''''''''' years in NTBC study | HighFor onset <6 months: favours dietFor onset >6 months: favours nitisinone |
| Liver transplantation | Nitisinone: no transplants assumed after 6 yearsDiet: high rate assumed for model duration | ModerateFavours diet |
| Utility values | Nitisinone: 0.87; Diet 0.49-0.87;Sourced from hepatitis B adult patients | HighDirection of impact unknown |
| Age of clinical onset | <2 months: '''''''''''; 2-6 months: ''''''''''; >6 months: ''''''''''' | High; Favours diet |

Source: compiled during the evaluation

* 1. The ESC noted the following concerns with components of the model:
* The proportion of patients with age of onset greater than 6 months (chronic form) used in the model (''''' ''''''''''') is an overestimate compared with the data provided for Australian patients in the PSCR ('''''''''''').
* A shorter time horizon than 100 years – for example, 22 years to coincide with the actual clinical experience of the drug – may be more appropriate to correspond to current clinical experience with the drug, given the lifetime effects of the drug are unclear.
* The applicability of utility values for adults with hepatitis B to children and adults with HT-1 is unknown. However, the ESC acknowledged the lack of available alternatives and considered that the utilities used in the model appeared to be a reasonable proxy.
* The costs associated with ongoing outpatient follow-up after liver transplantation and adverse events were not included in the model. However, it was acknowledged that the main cost driver in the model is the cost of nitisinone.
* The model does not consider the impact of neonatal screening on the costs and outcomes of treatment with nitisinone within an Australian setting. The PSCR argued that this was appropriate as it reflects current clinical practice. The ESC considered that changes in the extent and type of screening would increase the nitisinone treatment costs as patients commence treatment earlier, and would probably improve the outcome of treatment. The ESC noted that if neonatal screening detected most patients with HT-1 then the proportions of patients with acute, subacute and chronic disease could not be determined and the extent of the survival benefit of treatment would be unknown. The ESC noted that two tests were available in Australia, and that false positive and false negative tests would have important clinical and cost impacts.
	1. The results of the stepped economic evaluation are presented in the table below. In the subsequent table the results are presented by age of clinical onset.

Results of the stepped economic evaluation

|  |  |  |  |
| --- | --- | --- | --- |
| **Step and component** | **Nitisinone** | **Diet alone** | **Increment** |
| **Step 1: trial-based costs and outcomes** |  |  |  |
| Costs | ''''''''''''''''''''''' | '''''''''''''''''''' | '''''''''''''''''''''''' |
| LY | '''''''''' | '''''''''' | '''''''''''' |
| **Incremental cost/extra LY gained** |  |  | **''''''''''''''''** |
| **Step 2: trial results and pre-modelling (inclusion of liver transplants)** |  |  |  |
| Costs | ''''''''''''''''''''''' | '''''''''''''''''''' | ''''''''''''''''''''''' |
| LY | ''''''''''' | ''''''''''' | ''''''''''' |
| **Incremental cost/extra LY gained** |  |  | **''''''''''''''''** |
| **Step 3: trial results and pre-modelling (inclusion of monitoring costs)** |  |  |  |
| Costs | ''''''''''''''''''''''' | ''''''''''''''''''''' | ''''''''''''''''''''''' |
| LY | ''''''''''' | ''''''''''' | '''''''''' |
| **Incremental cost/extra LY gained** |  |  | **'''''''''''''''''** |
| **Step 4: trial results and pre-modelling (extrapolated to 100 year time horizon)** |  |  |  |
| Costs | '''''''''''''''''''''''''''' | ''''''''''''''''''''' | '''''''''''''''''''''''''' |
| LY | '''''''''''''' | '''''''''''' | ''''''''''' |
| **Incremental cost/extra LY gained** |  |  | **''''''''''''''''''** |
| **Step 5: modelled evaluation (quality weighting of survival)** |  |  |  |
| Costs | ''''''''''''''''''''''''''' | '''''''''''''''''''' | '''''''''''''''''''''''''' |
| QALY | '''''''''''' | '''''''''' | '''''''''''' |
| **Incremental cost/extra QALY gained** |  |  | **''''''''''''''''''** |

Source: Table D.5-1, p199; Table D.5-2, p200; Table D.5-3, p200; Table D.5-4, p201; Table D.5-5, p201 of the submission

LY = life year, QALY = quality adjusted life year

 The redacted table above shows the ICER to be more than $200,000/QALY

Results for model Steps 3 and 4 by age of clinical onset

| **Age at onset** | **Incremental cost** | **Incremental LYs** | **Incremental cost/LY gained** |
| --- | --- | --- | --- |
| **0-2 months** |  |  |  |
| 6.75 year time horizon (Step 3) | ''''''''''''''''''''' | '''''''''' | ''''''''''''''''''''''' |
| 100 year time horizon (Step 4) | '''''''''''''''''''''''' | '''''''''''''' | '''''''''''''''''''' |
| **2-6 months** |  |  |  |
| 6.75 year time horizon (Step 3) | ''''''''''''''''''''''' | '''''''''' | ''''''''''''''''''''''' |
| 100 year time horizon (Step 4) | '''''''''''''''''''''''  | ''''''''''' | '''''''''''''''''''''  |
| **>6 months** |  |  |  |
| 6.75 year time horizon (Step 3) | ''''''''''''''''''''' | ''''''''''' | '''''''''''''''''''''''''''' |
| 100 year time horizon (Step 4) | ''''''''''''''''''''''' | '''''''''' | '''''''''''''''''''''' |

Source: compiled during evaluation

LY = life year

* 1. The cost-effectiveness ratios are uncertain because the model is populated with data from non-randomised studies, the nitisinone data have been extrapolated from a median follow-up period of less than 4 years to 100 years by applying population death rates, and the utility values are from adult patients with hepatitis B. Applying population average death rates may result in an overestimate of the survival benefits (and costs) associated with nitisinone treatment. For all scenarios tested in the sensitivity analyses, the cost per QALY gained was more than $200,000.
	2. Using the proportions for age of clinical onset of Australian patients provided in the PSCR improves the ICER, to more than $200,000 per life year and more than $200,000 per QALY. Reducing the time horizon to 22 years improved the ICER further to more than $200,000 per QALY.
	3. The pre-PBAC response approximated a scenario that includes neonatal screening. In this scenario it was assumed that all patients treated with nitisinone are acute HT‑1 patients while the distribution of patients in the diet only arm across the acute, sub-acute and chronic sub-groups remains as per the distribution observed in the NTBC study. Over a 22-year time horizon, the cost per QALY is more than $200,000.
	4. If patients are detected by neonatal screening and nitisinone treatment is commenced prior to the development of clinical symptoms the results of Larochelle 2012 are relevant. A trial based analysis conducted during the evaluation using Larochelle 2012 suggests the cost per life year gained for early nitisinone treatment (before 1 month of age) is $105,000-$200,000 and for late nitisinone treatment (after 1 month of age) is more than $200,000. This estimate of cost per life year gained for early nitisinone treatment could translate to a cost per QALY of $105,000-$200,000.

*For more detail on PBAC’s view, see section 7 “PBAC outcome”*

**Drug cost/patient/year: '''''''''''''''''''''**

* 1. The initial recommended nitisinone dose is 1 mg/kg/day*,* divided into two doses. The mean weight of Australian HT-1 patients is currently ''''''''''' ''''''. The average per mg cost of nitisinone is ''''''''''''' (based on Australian 2013 sales of ''''''''''' for 2 mg, '''''''''''''''''' for 5 mg and '''''''''''''''''''' for 10 mg). The cost per month (30 days) is '''''''''''''''''' (30 x 31.1 x ''''''''''''). The cost per year is '''''''''''''''''''''''' (365 x 31.1 x '''''''''''''). Treatment is ongoing.

**Estimated PBS usage & financial implications**

* 1. This submission was not considered by DUSC.
	2. An epidemiological approach is taken in the submission to estimate the extent of use of nitisinone. The estimates are based on the incidence (0.54/100,000 live births; approximately 1.7 births per year) and prevalence (n=18) of HT-1 in Australia.

Estimated use and financial implications

|  | **Year 1** | **Year 2** | **Year 3** | **Year 4** | **Year 5** |
| --- | --- | --- | --- | --- | --- |
| **Estimated extent of use** |  |  |  |  |  |
| Number treated | ''''''''''''''' | ''''''''''''' | '''''''''''''' | '''''''''''''' | '''''''''''''' |
| **Packsa** |  |  |  |  |  |
| 60 x 2 mg capsules | '''''''''' | '''''''' | ''''''''' | '''''''''' | '''''''''' |
| 60 x 5 mg capsules | '''''''''' | '''''''''' | '''''''''' | '''''''''' | ''''''''' |
| 60 x 10 mg capsules | '''''''''' | ''''''''' | '''''''' | ''''''''' | '''''''''' |
| **Net cost to PBS/RPBS** | '''''''''''''''''''''''' | ''''''''''''''''''''''''' | ''''''''''''''''''''''''' | ''''''''''''''''''''''''''' | '''''''''''''''''''''''' |

a Assuming a dose of 1 mg/kg/day and pack distribution of '''''''''''' for 2 mg, ''''''''''''''''''' for 5 mg and '''''''''''''''''' for 10 mg capsules as estimated by the submission.

Source: Table E.2-1, p215; Table E.2-3, p216; Table E.2-4, p217 of the submission

* 1. Neonatal screening may result in an increased incidence of HT-1. If the incidence is increased from 0.54 to 2.48 per 100,000 births, the PBS cost in year 5 is less than $10 million. The ESC noted that the current prevalence in Australia is approximately 1:1,000,000 and given the low prevalence, that incidence may be lower than that stated in the submission. However, it was also noted that prevalence may increase with more sensitive screening.
	2. The PBAC was particularly concerned about the uncertain size of the patient population, particularly in the context of a sensitive neonatal screening program and the introduction of a new line of life-long therapy. Also the PBAC noted ongoing trials to investigating nitisinone treatment for alkaptonuria. The PBAC considered, among other matters, that its assessment of the cost-effectiveness of nitisinone would be more acceptable if a Risk Share Agreement (RSA) between the sponsor and the Government were implemented to contain risks associated with the cost of the drug to the PBS. A RSA should include a cap on total expenditure derived using the number of patients eligible to receive nitisinone.

*For more detail on PBAC’s view, see section 7 “PBAC outcome”*

1. PBAC Outcome
	1. The PBAC deferred making a recommendation regarding the proposed Authority Required listing for nitisinone under Section 100 for treatment of HT-1 due to a lack of clarity regarding current and future screening practices for detecting HT-1 and the subsequent impact on the significant survival advantage and adverse effects observed during treatment with nitisinone.
	2. The PBAC recommended a stakeholder meeting be held between the sponsor, the Department, clinicians from applicable professional bodies, consumer representatives and PBAC members. The aim of this meeting would be to provide clarity about the clinical effectiveness of nitisinone for HT-1 with respect to current and future screening programs. The meeting would also provide an opportunity to consider the need for a progressive neurocognitive monitoring and assessment program, as well as an appropriate restriction arrangement.
	3. While the PBAC deferred making a recommendation, it made the following comments regarding the proposed listing and restriction wording.
	* The PBAC considered that the wording of the suggested clinical criterion, that a patient must have a confirmed clinical diagnosis of HT-1 based on clinical suspicion and detection of succinylacetone, would be inappropriate if a neonatal screening program for succinylacetone was established. In this scenario, patients would be diagnosed through detection of succinylacetone prior to clinical suspicion of HT-1.
	* The PBAC also noted that the wording of the criterion with respect to whether the patient has had a liver transplant would require clarification with stakeholders.
	* The submission did not specify a method by which prescribing authority was to be sought. The PBAC considered that, given the small patient population and significant cost of the life-long treatment, it would be desirable for prescribers to provide written evidence that their patient satisfies the treatment and clinical criteria to the Department of Human Services.
	* As the daily dose of nitisinone is 1 mg/kg/day, the PBAC noted that the proposed maximum quantity of 60 capsules, at the maximum strength of 10 mg, would not be sufficient for patients weighing over 20 kg and that the mean weight of patients currently treated with nitisinone in Australia is ''''''' ''''''. The PBAC considered that allowing the Department of Human Services to increase the maximum quantity on request would be appropriate.
	1. The PBAC accepted that medical management without nitisinone (i.e., diet alone) is the appropriate comparator.
	2. The PBAC noted the clinical need for nitisinone for the treatment of HT-1 and that patients are currently being treated with the drug through hospitals. The PBAC welcomed input from individuals and organisations regarding the range of benefits of this treatment. In addition, the PBAC considered advice from the Australasian Society for Inborn Errors of Metabolism, as outlined in paragraphs 4.3 and 4.4.
	3. The PBAC noted the limitations of the available clinical evidence, including the lack of randomised trials and sources of bias. The PBAC acknowledged the difficulty of obtaining better quality clinical evidence given the small patient population for this rare condition. In this context, the PBAC considered that the evidence presented in the submission demonstrated that nitisinone provides a significant survival advantage for HT-1 patients over diet alone and, for some patients, may help avoid a costly and clinically risky liver transplant.
	4. The PBAC considered that the evidence provided by the supportive Larochelle study was important in understanding the impact a sensitive neonatal screening program would have on HT-1 patient outcomes from early treatment with nitisinone. It was noted that a neonatal screening program would most likely improve survival and result in a greater reduction in the need for liver transplants.
	5. The PBAC agreed with the ESC that the claim of superior comparative safety over diet alone was not reasonable, noting adverse events such as eye disorders, haematological events and developmental and cognitive disorders. While the PBAC noted the sponsor’s argument that these adverse events are more likely due to non‑adherence to diet therapy, rather than treatment with nitisinone, the PBAC considered it was difficult to separate the harms from HT-1 compared with treatment with nitisinone. The PBAC considered that it would be prudent to implement a program to closely monitor and assess the progressive neurocognitive and developmental impacts of nitisinone treatment.
	6. The PBAC considered that the cost effectiveness of nitisinone is highly uncertain due to the unreliable nature of the available clinical evidence and the uncertain impact screening would have on costs and outcomes. The PBAC considered that the presented base ICER of more than $200,000 per QALY is not acceptably cost effective, but noted that it did not take account of future changes in screening practices and the resulting increase in costs (as patients commence treatment earlier) and benefits of starting treatment within the first month of life. In this regard, the PBAC considered that an analysis conducted during the evaluation using results from Larochelle was more informative (see paragraph 6.30). This analysis indicated that in the context of an established sensitive and specific succinylacetone neonatal screening program, the ICER could be the order of $105,000-$200,000 per QALY.
	7. The PBAC noted that the utilisation estimates are dependent on whether neonatal screening results in an increased incidence of HT-1. In addition, the estimated drug cost per patient per year was considered to be an underestimate as it is based on the current mean weight of Australian HT-1 patients ('''''''''''' '''''') that may increase as an increasing proportion of the HT-1 patient population survive through to adulthood.
	8. The PBAC considered the submission satisfactorily addressed (see paragraph 2.1) and met the four criteria for listing under the “rule of rescue”.

**Outcome:**

Deferred

1. **Context for Decision**

The PBAC helps decide whether and, if so, how medicines should be subsidised in Australia. It considers submissions in this context. A PBAC decision not to recommend listing or not to recommend changing a listing does not represent a final PBAC view about the merits of the medicine. A company can resubmit to the PBAC or seek independent review of the PBAC decision.

1. **Sponsor’s Comment**

Menarini looks forward to working with the PBAC to make nitisinone available on the PBS for this high need patient group.