4.04 NITISINONE
2 mg capsule, 60
5 mg capsule, 60
10 mg capsule, 60
ORFADIN®, A. Menarini Pty Ltd

1 Purpose of Application

1.1 The minor re-submission sought to clarify the issues discussed at the nitisinone stakeholder meeting in order to assist the PBAC in making a decision to recommend listing of nitisinone on the PBS for the treatment of patients with hereditary tyrosinaemia type 1 (HT-1).

2 Requested listing

2.1 The submission requested the following new listing of nitisinone for the treatment of HT-1 on Section 100 (Highly Specialised Drugs).

Name, Restriction, Manner of administration and form	Max. Qty	№.of Rpts	Dispensed Price for Max. Qty (Public)	Dispensed Price for Max. Qty (Private)	Proprietary Name and Manufacturer
NITISINONE					
2 mg capsule, 60	1	5	$[redacted]	$[redacted]	ORFADIN® A. Menarini
5 mg capsule, 60	1	5	$[redacted]	$[redacted]	
10 mg capsule, 60	1	5	$[redacted]	$[redacted]	

Category / Program	Section 100 – Highly Specialised Drugs Program (Public) Section 100 – Highly Specialised Drugs Program (Private)
Prescriber type:	☐Dental ☒Medical Practitioners ☐Nurse practitioners ☐Optometrists ☐Midwives
Condition:	Tyrosinaemia type 1
PBS Indication:	Tyrosinaemia type 1
Treatment phase:	Initial
Restriction Level / Method:	☐Restricted benefit ☒Authority Required - In Writing ☐Authority Required - Telephone ☐Authority Required – Emergency ☐Authority Required - Electronic ☐Streamlined

Treatment criteria:	Must be treated in a centre with experience in metabolic disorders. AND Must be treated by a paediatrician or specialist physician with experience in the management of patients with tyrosinaemia type I or other inherited metabolic diseases.
Clinical criteria:	Patient must have a confirmed clinical diagnosis of tyrosinaemia type I based on detection of succinylacetone in the urine and/or blood by a National Association of Testing Authorities accredited laboratory. AND The treatment must be administered in combination with dietary restriction of tyrosine and phenylalanine.
Prescriber Instructions	At the time of Authority application, prescribers should advise the weight of the patient.
Administrative Advice	Increased maximum quantities may be requested from the Department of Human Services and should be based on a dosing regimen of 1 to 2 mg/kg/day. Any queries concerning the arrangements to prescribe may be directed to the Department of Human Services on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday). Prescribing information (including Authority Application forms and other relevant documentation as applicable) is available on the Department of Human Services website at www.humanservices.gov.au Applications for authority to prescribe should be forwarded to: Department of Human Services Prior Written Approval of Complex Drugs Reply Paid 9826 GPO Box 9826 HOBART TAS 7001

Category / Program	Section 100 – Highly Specialised Drugs Program (Public) Section 100 – Highly Specialised Drugs Program (Private)
Prescriber type:	☐Dental ☒Medical Practitioners ☐Nurse practitioners ☐Optometrists ☐Midwives
Condition:	Tyrosinaemia type 1
PBS Indication:	Tyrosinaemia type 1
Treatment phase:	Continuing
Restriction Level / Method:	☐Restricted benefit ☒Authority Required - In Writing ☒Authority Required - Telephone ☒Authority Required – Emergency ☒Authority Required - Electronic ☐Streamlined

Treatment criteria:	Must be treated in a centre with experience in metabolic disorders. If attendance at such a centre is not possible because of geographical isolation, management (including prescribing) may be in consultation with such a centre. AND Must be treated by, or in consultation with, a paediatrician or specialist physician with experience in the management of patients with tyrosinaemia type 1 or other inherited metabolic diseases.
Clinical criteria:	Patient must have previously received PBS-subsidised therapy with this drug for this condition. AND The treatment must be administered in combination with dietary restriction of tyrosine and phenylalanine.
Prescriber Instructions	At the time of Authority application, prescribers should advise the weight of the patient in the patient's record.
Administrative Advice	Increased maximum quantities may be requested from the Department of Human Services and should be based on a dosing regimen of 1 to 2 mg/kg/day. Authority applications for continuing treatment may be made by telephone to the Department of Human Services on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday).

3 Background

3.1 In November 2014 the PBAC considered a submission requesting Authority required Section 100 (Highly Specialised Drugs Program) listing of nitisinone for HT-1. The submission requested the PBAC to consider listing on the basis of 'rule of rescue'.

3.2 While the PBAC considered the submission satisfactorily addressed and met the four criteria for listing under the 'rule of rescue', it deferred making a recommendation regarding the proposed listing. The PBAC considered there was a lack of clarity on both the impact of current and future HT-1 screening practices on patient survival, and the association between adverse events and nitisinone treatment.

3.3 Noting the clinical need for nitisinone, the PBAC recommended holding a stakeholder meeting with the sponsor, the Department, clinicians from applicable professional bodies, consumer representatives and PBAC members. The aims were to provide clarity about the clinical effectiveness of nitisinone for HT-1 with respect to current and future screening programs, to consider the need for a neuropsychological assessment and monitoring program, and to propose an appropriate restriction arrangement.

3.4 The stakeholder meeting was held on 4 February 2015.

For more detail on PBAC's view, see section 6 "PBAC outcome"

4 Comparator

4.1 The major submission for nitisinone nominated standard medical management without nitisinone (i.e. diet alone). This was accepted by the PBAC and remained unchanged in the minor submission.

For more detail on PBAC's view, see section 6 "PBAC outcome"

5 Consideration of the evidence

Sponsor hearing

5.1 There was no hearing for this item as it was a minor submission.

Consumer comments

5.2 The PBAC noted and welcomed the input from individuals (18) and an organisation (1) via the Consumer Comments facility on the PBS website. The comments described a range of benefits of treatment with nitisinone including the fact that it is a reliable and effective treatment which enables patients to live a longer life than would otherwise be possible. It was considered that availability on the PBS would provide more security with regards to continued treatment access.

5.3 The PBAC noted the advice received from the Metabolic Dietary Disorders Association clarifying the benefits of nitisinone including the ability to extend life, the opportunity for patients to manage their condition and the avoidance of costly and risky liver transplant. The advice 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. The PBAC noted that this advice was supportive of the evidence provided in the submission.

Comparative harms

5.4 At the November 2014 meeting the PBAC raised concerns that adverse events such as eye disorders, haematological events and developmental and cognitive disorders had been associated with nitisinone treatment.

5.5 It was agreed at the stakeholder meeting that neuropsychological assessment over time would be helpful in monitoring children's development while taking nitisinone to highlight any as yet unidentified risks.

5.6 The minor re-submission provided an overview of the literature on the relationship between developmental and cognitive disorders in patients with HT-1 who were treated with nitisinone in combination with diet therapy. It was noted that although neurocognitive disorders in patients with HT-1 treated with nitisinone in combination with diet therapy have been reported, none of the studies provided established causality between developmental and cognitive disorders, and treatment with nitisinone in combination with diet therapy. It was also highlighted that the majority of the patients reported in the publications had much higher than recommended plasma

tyrosine levels, and argued that this most likely represented poor compliance with diet therapy.

5.7 The minor re-submission advised the sponsor has approached the TGA to discuss the requirements for a risk management plan and is currently awaiting their response.

5.8 The pre-PBAC response provided an update on the sponsor's development of a systematic post-marketing surveillance program. The response advised that discussions between the TGA, sponsor and the Australasian Society for Inborn Errors of Metabolism (ASIEM) are ongoing and that TGA and ASIEM had agreed on a potential approach for the surveillance program. It also advised that the PBAC will be informed on the details of the approach once it is finalised.

5.9 The minor re-submission also highlighted advice from the ASIEM that neuropsychological assessments are currently undertaken as per good medical practice determined by the treating physicians in the metabolic centres. The submission stated that implementation of post-market surveillance will formalise what is already clinical practice.

Clinical claim

5.10 The PBAC recalled that the November 2014 submission described nitisinone plus diet therapy as superior in terms of comparative effectiveness and superior in terms of comparative safety over diet alone. At the July meeting the PBAC reiterated its consideration from November 2014 that this claim was reasonable in terms of effectiveness but not reasonable in terms of safety.

Economic analysis

5.11 In November 2014 the PBAC recommended that if treatment with nitisinone is commenced prior to the development of clinical symptoms (i.e. prior to 1 month of age), the results of the Larochelle 2012 study would be considered relevant. It was noted that such a scenario would occur if succinylacetone (SA) screening (a highly sensitive and specific test for HT-1) for all newborns were to be implemented. According to the Larochelle study, the introduction of SA testing would result in an incremental cost per life year-gained for early nitisinone treatment of $105,000 – $200,000 and $105,000 – $200,000 per quality adjusted life year (QALY) gained.

5.12 At the stakeholder meeting it was agreed that although SA testing may be introduced, a universal newborn screening program for SA is unlikely to come into effect in the next three years. In addition, it was noted that while a national framework for adding new tests is being developed, the decision to implement the framework and responsibility for funding is that of individual state and territory governments.

5.13 The minor re-submission noted the PBAC advice and accepted the $105,000 - $200,000 per QALY ICER for early nitisinone treatment based on the Larochelle trial. Given the outcomes of the stakeholder meeting, the PBAC considered that the ICER based on the Larochelle trial may not reflect current practice, but would be relevant in the event that a newborn SA screening program was introduced (which is unlikely to occur in the next three years). By comparison, the ICER presented in the pre-sub-

committee response for the major submission, which assumed the continuation of current screening practices and a time horizon of 22 years, was more than $200,000 per QALY.

Estimated PBS usage & financial implications

5.14 At the November 2014 meeting the PBAC expressed concern that the potential introduction of SA screening would substantially increase the number of newborns diagnosed with HT-1.

5.15 At the stakeholder meeting it was agreed that while SA screening could potentially double the number of newborn HT-1 diagnoses, this was unlikely to be observed in clinical practice since patients not diagnosed in infancy are usually diagnosed later in life. It was also reiterated that introduction of SA screening was unlikely to occur in the next 3 years.

5.16 The minor re-submission revised the incidence of HT-1 from 0.54/100,000 live births to 1.08/100,000 live births in years 4 and 5. This change was based on the assumption that SA screening would be introduced in year 4, thus doubling the number of infants diagnosed.

5.17 The minor re-submission also updated the prevalence of HT-1 on advice from ASIEM indicating that there are currently 19 HT-1 patients in Australia (compared with the 18 patients stated by the previous major submission).

5.18 The minor re-submission's revised financial estimates, incorporating the updated incidence and prevalence figures for HT-1, are presented in the following table.

Table 1: Revised financial estimates presented in the minor re-submission

	Year 1	Year 2	Year 3	Year 4	Year 5
Number of patients	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cost to the PBS/RPBS	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Patient copayments	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Net cost to the PBS/RPBS	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]

5.19 The redacted table above shows the minor re-submission estimated a net cost to the PBS of less than $10 million in year 5 of listing, with a total net cost to the PBS of $10-$20 million over the first 5 years of listing.

5.20 The minor re-submission referenced the fees for neuropsychological assessments, as advised by the Australian Psychological Society and Department of Veterans Affairs. According to these sources, tests ranged from 16 minutes to 4 hours and had an associated fee range from $129 to $595.65. The submission claimed that these costs would have little to no impact on the cost-effectiveness or net financial implications to Government health budgets.

5.21 The submission noted that the sponsor is willing to enter into a discussion with the PBAC on a Risk Sharing Agreement and the potential mechanisms to contain the risk associated with the cost of the drug to the PBS.

For more detail on PBAC's view, see section 6 "PBAC outcome"

6 PBAC Outcome

6.1 The PBAC rejected the request to list nitisinone on the PBS for the treatment of HT-1 on the basis of an uncertain and unacceptably high estimate of cost effectiveness.

6.2 The PBAC recalled that in November 2014, it noted the clinical need for nitisinone for the treatment of HT-1 and that patients are currently being treated with the drug through hospitals.

6.3 The PBAC accepted that standard medical management without nitisinone (i.e. diet alone) was the appropriate comparator.

6.4 The PBAC noted that the restriction requested in the minor re-submission was consistent with the agreed wording from the February 2015 stakeholder meeting.

6.5 The PBAC noted that no new clinical evidence was presented in the minor re-submission. The PBAC recalled that the previous major submission presented evidence based on non-randomised studies.

6.6 The PBAC recalled that the November 2014 submission described nitisinone plus diet therapy as superior in terms of comparative effectiveness and superior in terms of comparative safety over diet alone. The PBAC reiterated its consideration from November 2014 that this claim was reasonable in terms of effectiveness but not reasonable in terms of safety.

6.7 The PBAC also recalled that nitisinone had been associated with adverse events such as eye disorders, haematological events and developmental and cognitive disorders. The PBAC noted the advice received at the stakeholder meeting that adverse events reported in nitisinone trials were possibly confounded by ascertainment bias and likely due to the disease itself, rather than the drug. The PBAC also noted that the TGA had not identified any safety issues since registration of nitisinone in Australia in 2010. The PBAC noted the sponsor's argument that many of the adverse events could be due to non-compliance with diet therapy but did not accept that neurocognitive disorders were caused solely by non-compliance with diet therapy, considering that the relationship between diet and plasma levels of tyrosine was unclear. The PBAC agreed with the consensus at the stakeholder meeting that neuropsychological assessments over time would be helpful, noting that the product information for nitisinone recommends regular and systematic developmental assessment, including neuro-cognitive development. The PBAC noted the submission's assertion that this is already undertaken as per good medical practice, however reiterated its position that this monitoring is important and should be implemented in a systematic fashion.

6.8 The PBAC noted the submission's assertion that neuropsychological assessments would have little to no impact on the cost-effectiveness or net financial implications to Government health budgets. The PBAC agreed that the cost of these assessments would be small compared with the cost of the drug.

6.9 The PBAC considered that the ICERs presented were unacceptably high, regardless of SA screening status. The PBAC noted that this was primarily driven by the high cost of nitisinone. The PBAC recalled the major submission had requested listing under the 'rule of rescue' and that the PBAC had considered in November 2014 that it satisfied the four necessary criteria. In July 2015, the PBAC considered that a significantly lower price than that proposed by the sponsor in the current submission would be needed for a positive PBAC recommendation under 'rule of rescue'. The PBAC Guidelines (2013, v4.4) state that, unlike the Life Saving Drugs Programme criteria, the rule of rescue "supplements, rather than substitutes for the evidence-based consideration of comparative cost-effectiveness.

6.10 The PBAC recalled that the utilisation estimates are dependent on whether neonatal screening results in an increased incidence of HT-1 and noted the re-submission presented financial estimates based on a doubling of diagnoses upon the introduction of SA screening. The PBAC agreed with the stakeholder meeting consensus that this doubling of patients was unlikely to occur in practice. The PBAC also noted that the minor re-submission did not address the PBAC's concern from November 2014 that the cost per patient per year was underestimated. The PBAC maintained that as it was based on the current mean weight of Australian HT-1 patients (31.1 kg) this cost may increase as an increasing proportion of the HT-1 patient population survive through to adulthood.

6.11 The PBAC noted that this submission is eligible for an Independent Review.

Outcome:
Rejected

7 Context of 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.

8 Sponsor's Comment

A.Menarini Australia Pty Ltd is committed to partnering with the department to find a solution to allow nitisinone to be reimbursed for patients with tyrosinaemia type 1.