

# **PBAC STAKEHOLDER MEETING OUTCOME STATEMENT**

## **NITISINONE FOR TYROSINAEMIA TYPE 1**

**4 February 2015**

**Department of Health, Canberra**

### **Attendees**

Members of the Pharmaceutical Benefits Advisory Committee (PBAC), clinicians with experience in managing patients with hereditary tyrosinaemia type 1 (HT-1) and expertise in screening for the condition, representatives of the Metabolic Dietary Disorders Association (MDDA), Rare Voices Australia, the Australasian Society of Inborn Errors of Metabolism, the Therapeutic Goods Administration (TGA), A.Menarini Australia Pty Ltd, and the Department of Health were in attendance.

### **Purpose of stakeholder meeting**

To provide clarity about the clinical effectiveness of nitisinone for HT-1 with respect to current and future screening programs, as well as providing an opportunity to consider the need for progressive neurocognitive monitoring and assessment program and a proposed restriction for the sponsor's use in a resubmission to the PBAC.

### **Background**

The PBAC considered a submission for the Pharmaceutical Benefits Scheme (PBS) listing of nitisinone for HT-1 in November 2014. The PBAC deferred making a recommendation regarding the proposed Authority Required listing for nitisinone under Section 100 (Highly Specialised Drugs Program) for treatment of HT-1 due to a lack of clarity regarding current and future screening practices for detecting HT-1 and the potential impact on the significant survival advantage and adverse effects observed during treatment with nitisinone.

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 progressive neurocognitive monitoring and assessment program, and to propose an appropriate restriction arrangement.

A Public Summary Document on the PBAC's consideration of nitisinone for HT-1 at its November 2014 meeting will be published on the PBS website on 20 March 2015.

The Guidelines for Initiation of PBAC Stakeholder Meetings are available on the PBS website at <http://www.pbs.gov.au/info/industry/listing/elements/initiation-of-stakeholder-meetings>.

## **Discussion and outcomes**

### ***Current and future screening practices***

#### Current practice

The PBAC noted the lack of clarity regarding current and future screening practices for detecting HT-1. Clinical experts at the stakeholder meeting agreed that the current newborn screening practice for HT-1 is to measure a newborn's tyrosine levels. This is done by analysing a newborn's blood spot sample 24-48 hours after birth using tandem mass spectrometry and a tyrosine marker. Newborns with high tyrosine levels undergo additional tests for succinylacetone, which is a specific marker for the condition. Clinicians estimated that around half of all newborns with HT-1 are identified using this approach.

Despite being a specific marker for HT-1, succinylacetone testing is currently not conducted for all newborns. The clinical experts explained that, as succinylacetone testing is an additional and costly test, it is currently hard to justify screening all newborns for a condition that is relatively rare ahead of screening for other more commonly diagnosed conditions.

#### Future practice

A newborn blood spot screening policy framework is currently in development which aims to standardise national screening practices. It was agreed that expansion of succinylacetone screening would increase the number of newborns diagnosed with HT-1 with an upper estimate of around twice as many cases being diagnosed. It was noted, however, that patients not diagnosed in infancy are usually diagnosed later in life, so a doubling of the number of diagnoses was unlikely to be observed in practice.

It was agreed that the expansion of succinylacetone screening is unlikely to come into effect for at least the next three years. It was noted that while a national framework is being developed, the decision to implement the framework and responsibility for funding is that of individual state and territory governments.

### ***Adverse events associated with nitisinone treatment***

The PBAC noted that adverse events such as eye disorders, haematological events and developmental and cognitive disorders had been associated with nitisinone. In considering this, both consumers and clinicians present at the meeting described their experience with nitisinone treatment and adverse events. A consumer provided a personal perspective, and clinicians described their collective experience with the drug, noting that it had been available as a therapeutic option since the late 1990's. They suggested that the adverse events reported in nitisinone trials were possibly confounded by ascertainment bias, and likely due to the disease itself, rather than the drug. The TGA also confirmed it had not identified any safety issues associated with nitisinone since its registration in Australia.

In light of the continuing uncertainty about nitisinone related adverse events, it was agreed that neurocognitive assessments over time would be helpful in monitoring children's development while taking nitisinone to highlight any as yet unidentified risks. The challenges of performing neuropsychiatric assessments in very young children, and in repeating assessments more frequently than two years, were noted. The stakeholders agreed that the TGA, sponsor (A. Menarini), relevant clinicians and patient representatives should discuss

and agree on a limited and targeted set of risks to monitor via systematic post-market surveillance. In particular, this group would agree on the type of neurocognitive assessment to be provided, the relevant population to assess, and frequency of conducting the assessment. Consumers expressed that they were comfortable providing post listing data as long as appropriate safeguards were in place, and stressed that they would require access to the data. It was noted that safety data from post marketing surveillance would be relevant to the PBAC where it influences the cost-effectiveness of nitisinone.

### **PBS Restriction**

The following PBS restriction was proposed. It should be noted that this restriction is indicative only and is based on the clinical advice and discussions at the stakeholder meeting. A restriction would be finalised following a positive recommendation by the PBAC.

Category / Program	Section 100 – Highly Specialised Drugs Program
Prescriber type:	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
Condition:	Tyrosinaemia type I
PBS Indication	Tyrosinaemia type I
Treatment phase:	Initial
Restriction:	<input type="checkbox"/> Restricted benefit <input checked="" type="checkbox"/> Authority Required - In Writing <input type="checkbox"/> Authority Required - Telephone <input type="checkbox"/> Authority Required – Emergency <input type="checkbox"/> Authority Required - Electronic <input type="checkbox"/> 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.

<b>Administrative Advice:</b>	<p>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.</p> <p>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).</p> <p>Prescribing information (including Authority Application forms and other relevant documentation as applicable) is available on the Department of Human Services website at <a href="http://www.humanservices.gov.au">www.humanservices.gov.au</a></p> <p>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</p>
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<b>Condition:</b>	Tyrosinaemia type I
<b>PBS Indication</b>	Tyrosinaemia type I
<b>Treatment phase:</b>	Continuing
<b>Restriction Level / Method:</b>	<input type="checkbox"/> Restricted benefit <input checked="" type="checkbox"/> Authority Required - In Writing <input checked="" type="checkbox"/> Authority Required - Telephone <input checked="" type="checkbox"/> Authority Required – Emergency <input checked="" type="checkbox"/> Authority Required - Electronic <input type="checkbox"/> Streamlined
<b>Treatment criteria:</b>	<p>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.</p> <p>AND</p> <p>Must be treated by, or in consultation with, a paediatrician or specialist physician with experience in the management of patients with tyrosinaemia type I or other inherited metabolic diseases.</p>
<b>Clinical criteria:</b>	<p>Patient must have previously received PBS-subsidised therapy with this drug for this condition.</p> <p>AND</p> <p>The treatment must be administered in combination with dietary restriction of tyrosine and phenylalanine.</p>
<b>Prescriber Instructions:</b>	At the time of Authority application, prescribers should document the weight of the patient in the patient's record.
<b>Administrative Advice:</b>	<p>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.</p> <p>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).</p>

The following restriction changes were agreed to at the Stakeholder meeting:

- The clinical criteria specifying clinical suspicion of HT-1 was removed, as it would be inappropriate in the context of a neonatal screening program for succinylacetone.
- “and/or blood” was added in the clinical criteria as blood spot testing is a common screen for succinylacetone.
- The clinical criteria specifying that patients must not have had a liver transplant was removed.
- It was raised that the initial restriction’s Authority Required (in writing) requirement may be detrimental to patients who are in immediate need of the drug.
- It was agreed that it would be preferable for patients to be treated by a paediatrician or specialist physician with experience in the management of patients with HT-1 or other metabolic diseases. However, “in consultation with” was added to the continuing treatment criteria with the intention of ensuring equity of access for patients living in rural and regional areas.

Further notes on the restriction:

- Prescribers will need to document the weight of the patient when giving the prescription (as required in Prescriber Instructions), as the dose is determined based on patient weight.
- The continuing authority by telephone is intended to reduce the burden on prescribers, as nitisinone is a life-long therapy.
- In time, when technically possible, it would be preferred that continuing supplies be obtained under a Streamlined listing.

## **Conclusion**

Representatives of the sponsor of nitisinone, A.Menarini Australia Pty Ltd, were present and involved with the discussions at this meeting. The representatives indicated their intention to resubmit the request to list nitisinone for HT-1 under Section 100 (Highly Specialised Drug Program) to the PBAC.

The PBAC Chair thanked participants for their time in attending the stakeholder meeting and the advice provided. The meeting closed at 3:40pm.