

## **Nusinersen Stakeholder Meeting Statement**

**18 January 2018**

### **1. Welcome and Introductions**

The Pharmaceutical Benefits Advisory Committee (PBAC) Chair, Professor Andrew Wilson, welcomed all meeting participants. The Chair reminded non-departmental attendees that an Undertaking of Confidentiality declaration was required before attendance as discussions would include in-confidence material. All participants confirmed that confidential material would not be disclosed.

Participants were informed that a record of the meeting will be publically available on the PBS website.

Stakeholders in attendance included members of the Pharmaceutical Benefits Advisory Committee (PBAC), the CEO of SMA Australia, health practitioners with expertise in the treatment of SMA, a patient representative and representatives of Biogen Australia Pty Ltd and Biogen Global Corporate Headquarters.

Representatives of the Department of Health were also in attendance to facilitate the meeting and to support the Chair and members of the PBAC.

### **2. Background**

#### **Spinal muscular atrophy**

Spinal muscular atrophy (SMA) is an autosomal recessive neuromuscular disease caused by mutations or deletions in the SMN-1 gene. Alterations to this gene results in deficiency of SMN protein and in turn, loss of motor function and respiratory failure. Respiratory muscle failure is the major cause of morbidity and mortality for patients with SMA. An almost identical gene SMN-2, also produces SMN protein but at low levels. Approximately 10% of SMN-2 transcripts result in full-length SMN protein, however this is not sufficient to sustain survival of spinal motor neuron function. As SMN-2 copy number varies from patient to patient, there is a clinical spectrum of the disease where fewer SMN-2 gene copies are associated with earlier age of onset and increased symptom severity.

SMA is classified into infantile-onset (Type I), childhood-onset (Type II and III) and adult-onset (Type IV) based on age of onset of symptoms and maximum motor function achieved. Patients with Type I SMA have a maximum life expectancy of up to 2 years, while patients with Type II SMA typically survive into adulthood. Type III and Type IV SMA patients have normal lifespans.

#### **PBAC considerations of nusinersen (Spinraza®)**

At its November 2017 meeting, the PBAC did not recommend the listing of nusinersen for the treatment of patients with Infantile-onset (Type I) and childhood-onset (Types II and III) SMA due to uncertainty about the clinical effectiveness of nusinersen in terms of the extent and durability of response across the spectrum of

SMA for which subsidy was sought.

The PBAC acknowledged that there is a high and urgent clinical need for treatments for SMA, particularly for the most severe forms of the condition and noted that the consumer input was strongly supportive of a broad PBS listing across all forms of SMA, including adult onset disease. The PBAC considered that while the available evidence suggests patients may receive some benefit from nusinersen, the benefit needed to be better quantified.

The PBAC considered that further information on the cost-effectiveness of treatment with nusinersen is necessary in order for it to be able to form a view on the appropriate PBS subsidy price, but that based on the information already available it is likely that a substantial reduction in the proposed price will be required.

### **3. Summary of discussions**

The PBAC Chair outlined the goals of the stakeholder meeting as:

- i) to help inform the PBAC of clinical parameters which may be used to define a population of SMA patients (other than Type I) in high need of treatment;
- ii) to help inform the PBAC of clinical parameters which may be used to determine whether patients are responding to treatment (if appropriate);
- iii) to further inform the PBAC of SMA patient numbers in Australia and
- iv) to further inform the PBAC of the management of SMA through patient and clinical perspectives.

The stakeholders provided the following input to the PBAC in the discussion:

#### **i) Identifying high need SMA patients (other than Type I)**

- Young patients with early symptom onset (before 3 years of age) are those in highest need of new treatment options due to the severity of their condition relative to SMA patients with later symptom onset.
- It can be difficult to distinguish between Type I and Type II SMA as there is a large overlap in clinical presentations in these two patient groups.
- The burden of care for patients with early onset SMA is high, with these patients typically requiring full time care, physiotherapy, hospital stays and time in intensive care.
- The Biogen expanded access program was initiated to address the greatest urgency for Type I children. However, the greatest uptake will be expected for the Type II and Type IIIa children as they are the patients at greatest risk of losing function (and were not included in the Biogen expanded access program).
- Although adults with SMA are generally more clinically stable relative to younger patients, a deterioration in their condition can diminish opportunities to participate in society (e.g inability to work) and have significant psychological impact. Maintenance of function, or achieving small gains in function, which allow patients to maintain a level of independence are important outcomes for this patient population, and may lead some to seek treatment with nusinersen. Conversely, the burden of treatment (a 4

monthly intrathecal injection) may lower uptake in adult patients.

- In any case of SMA, SMN-2 gene copy number is less predictive of prognosis than age of onset and the achievement of functional abilities.
- Attendees agreed that entry criteria for the nusinersen program should not be too dogmatic, as specialists are already managing supportive care situations with families, and gauging disease progression and ventilation needs, up to permanent ventilation requirements. Some Type I patients would not benefit from nusinersen initiation or not be able to tolerate the procedures.

## **ii) Defining responders to treatment**

- The Hammersmith Functional Motor Scale-Expanded (HFMSSE) is not particularly sensitive to small changes in patient functioning, particularly at the lower end of the scale. Patients can demonstrate an improvement in function without a change in HFMSSE score.
- A stable HFMSSE score is clinically meaningful particularly in younger patients with progressive disease.
- For some younger patients, particularly those with poor function at diagnosis, the burden of treatment with nusinersen may outweigh the benefits leading them to stop treatment. Some families of Type I SMA patients elect not to commence treatment with nusinersen through the sponsors expanded access program.
- Attendees agreed that the response of patients to treatment would be strictly monitored, and that criteria for stopping treatment would be appropriate.
- It may be possible to develop a stopping rule for subsidy based on the requirement for permanent ventilation in the absence of a potentially reversible cause. Families of children with SMA currently make difficult decisions when a child's condition worsens and could be expected to continue to do so, although it was acknowledged that some families may find it difficult to stop treatment.
- Further work will be conducted to identify whether stopping rules are in place in any countries that currently subsidise nusinersen and what those rules are.

## **iii) Number of SMA patients in Australia**

- There are a limited number of hospital centres that deal with children with SMA.
- The estimates of the number of paediatric patients with SMA that were included in the November 2017 submission are reasonable, although need some refinement.
- It is difficult to estimate the number of adult patients with SMA, particularly as many adult patients are not currently under active care. More adults may seek care as new treatments become available.
- SMA Australia has a database with information on patients with SMA, and have been collecting this information since 2005. SMA provided a handout showing their current tally of numbers of Type I and Type II patients and

information by age, and location. SMA noted that not all patients with SMA in Australia are members so the data base is incomplete.

- A registry of patients would be very useful, drawn from all of the current Australian specialist sites, both from clinical and funding perspectives.

**iv) Clinical and patient perspectives on the management of SMA**

- These are recorded under sections i) to iii) above.

**Concluding remarks and next steps**

The PBAC Chair summarised the meeting discussions and reiterated the Committee's acknowledgement of the high clinical need for treatments for patients with SMA particularly for young patients with the severest forms of the condition.

The PBAC Chair indicated that the PBAC will consider the information provided at the stakeholder meeting in its consideration of nusinersen at the upcoming March 2018 meeting. The PBAC Chair anticipated that this information would also be helpful to Biogen in developing subsidy proposals for PBAC consideration.

The PBAC chair thanked all attendees for their time and contributions to the discussions, and requested the company representatives remain for a separate discussion relating to their proposed PBAC submission to the March 2018 meeting.