

SMA Stakeholder Meeting

Outcome Statement

Monday 7 December 2020

Attendees

Members of the Pharmaceutical Benefits Advisory Committee (PBAC), representatives from SMA Australia, clinicians with expertise in the management of SMA, patients, carers and representatives of Biogen, Novartis, Roche, and the Department of Health were in attendance.

Non-departmental attendees undertook confidentiality declarations and provided conflict of interest statements.

Purpose of meeting

The PBAC chair outlined that the objective of the meeting was to discuss the treatment algorithm for spinal muscular atrophy (SMA) and a decision support analysis that takes into account all the currently available clinical data and informs a “whole of disease” economic and financial analysis.

Background

a) Review of recent developments

The PBAC chair noted that the SMA diagnosis and testing landscape is changing rapidly. The PBAC chair noted that newborn screening programs for SMA are a state responsibility and are not currently routine in all states. However, SMA Australia has submitted an application to the national body responsible for facilitating a co-ordinated national approach. The PBAC chair noted the potential impact of preconception and early pregnancy parental carrier testing on the future incidence of SMA (MSAC application 1573).

The PBAC chair also noted the new/recent treatments for SMA undergoing regulatory and subsidy consideration, as outlined in the table below.

Therapy	Indication	TGA	Regulatory and subsidy status	Comments
Nusinersen (Spinraza®, Biogen)	Symptomatic types I, II and IIIa initiated up to and including 18 years	Registered	PBS 1 June 2018	Intrathecal injection, loading doses followed by one dose every 4 months
	Pre-symptomatic ≤ 2 copies of SMN2	Registered	PBS 1 December 2020	
	Symptomatic Types I to III, including paediatric Type IIIb patients, initiated regardless of age (including in adults over 18 years)	Registered	PBAC November 2020 (2nd time)	
Zolgensma® (onasemnogene abeparvovec, Novartis)	SMA Type I under 2 years of age	-	PBAC November 2020	Single tx gene therapy
Evrysdi® (risdiplam, Roche)	SMA all types, from 2 months of age	-	-	Oral therapy

b) Current approach to PBS subsidy

PBS submissions have been focussed on individual medicines and different segments of the SMA patient population:

- Pre-symptomatic (with defined SMN2 copy number);
- Symptomatic Type 0 – I;
- Symptomatic Type II and IIIa;
- Symptomatic Type IIIb (symptom onset > 3 years to 18 years, inclusive); and
- Prevalent adults with Types I – III.

The PBAC chair noted that, with the exception of the sponsor hearing provided for the November 2020 consideration of nusinersen, the PBAC had not yet had the opportunity to hear from clinicians experienced in treating adult patients with SMA.

c) Need for a decision support analysis

In its November 2020 consideration of two therapies to treat SMA - onasemnogene abeparvovec and nusinersen - the PBAC considered an overall and holistic approach to consideration of the entire treatment algorithm and the strength of all available evidence for SMA therapies would better support its decision making.

The PBAC chair noted the need to make decisions based on the limited evidence available for each SMA treatment, recognising that this is likely to evolve as additional evidence becomes available.

Discussion

Pre-symptomatic patients

SMN2 copy number

- Clinicians considered that patients with 1 to 3 copies of SMN2 should be eligible to initiate pre-symptomatic treatment, as these patients would have the most potential to experience the most benefit in gaining and/or maintaining motor function. Clinicians noted that patients with 1-2 copies of SMN2 are most likely to be symptomatic early in life, but also noted that patients with 3 copies of SMN2 are likely to significantly benefit from early treatment, based on outcomes seen in trials.

Should antenatal diagnosis be confirmed with postnatal testing (when accessing treatments based on genotype alone)?

- Clinicians considered that where a patient is diagnosed with SMA through antenatal testing there is no need to retest to confirm this diagnosis. Clinicians noted that SMA is not always detected through antenatal testing, so postnatal testing may be reasonable to confirm a negative antenatal result.

Lines of treatment

The PBAC chair noted that the intent of the discussion was not to prescribe a treatment pathway, but rather to understand the likely use in practice.

- Clinicians noted it is difficult to establish a clear treatment algorithm given the absence of head to head trials of active treatments. Clinicians noted that post-hoc analyses of onasemnogene abeparvovec versus nusinersen have been presented in various fora and do not show a clear efficacy advantage for either treatment. However, clinicians noted that the evidence for onasemnogene abeparvovec is in fewer patients and as a new treatment, has limited long-term follow-up in terms of both safety and effectiveness. Risdiplam is behind both onasemnogene abeparvovec and nusinersen in terms of its stage of clinical development.

- Clinicians noted the mode of administration is also a factor in considering the most appropriate treatment for particular patients. Risdiplam has the advantage of oral administration, and the once-off administration of onasemnogene abeparvovec has advantages over the ongoing intrathecal administration of nusinersen.
- Clinicians and consumers considered that patient preferences should also be taken into account when selecting a treatment, with consumers emphasising the importance of having choices. Contraindications also need to be taken into account. For some families, onasemnogene was preferred on the basis it is a single replacement treatment, whereas other families indicated a preference for risdiplam stating “it provides what my child needs on ongoing daily basis”.
- Clinicians considered that initiation of treatment as early as possible, ideally pre-symptomatically, is a more important factor than which of the available treatments are selected.
- Access to pre-symptomatic treatment relies on early diagnosis and newborn screening, access to which is inconsistent between states and territories. Consumers and clinicians expressed frustration that there is no standard pathway for diagnosis across Australia.
- Clinicians stated that in considering which treatment to use, a whole of health approach is necessary, including consideration of the availability of newborn screening, family preferences and access to services and diagnosis.
- Overall, consumers and clinicians agreed that rather than accessing treatments in a cascade, it would be preferable to have early access to all treatments and the ability to choose the most suitable treatment based on individual preferences and circumstances.

Treatment failure

The PBAC chair requested advice regarding the approach to treatment following deterioration in the patient’s condition, or clear failure to respond to treatment.

- Clinicians considered that while patients are continuing to make progress (e.g. in motor milestones, feeding, respiratory function), even where delayed, this should not be considered treatment failure.
- Clinicians noted that pre-symptomatic treatment of patients means that treatment failure is difficult to distinguish as patients may be responding to treatment despite motor milestones not being achieved at what would be considered a normal timeline. Clinicians considered that only regression in milestones should be considered treatment failure.
- Clinicians reported that patients may sometimes require temporary ventilation for an extended time following viral illness, but that this should not be considered a treatment failure.
- In the event of treatment failure, consumers expressed a preference to have the option of adding a second treatment, but noted that decision would need to be based on evidence.
- Clinicians noted that there is no evidence that concomitant therapy (whether in sequence or in combination) is associated with additional benefits, and considered that concomitant therapy may be associated with safety concerns. Clinicians noted that there is only very limited evidence in patients who received multiple SMA treatments and the onus is on sponsors to provide such evidence.

Symptomatic patients

- Consumers and representatives from SMA Australia outlined the high demand for treatments for adults with SMA.

- The current restriction for nusinersen requires patients to have experienced symptom onset prior to 3 years of age and to commence treatment up to and including 18 years of age. Clinicians treating adult patients considered the requirement to have symptoms before age 3 arbitrary, and that the duration of symptoms would be a better predictor of treatment outcomes for adult patients.
- Clinicians noted that the critical need is in patients with Type 3a and 3b SMA, with the most clinically meaningful improvements likely to be in patients with Type 3b SMA.
- Consumers and clinicians outlined that adults have different treatment goals than paediatric patients. Major factors for adults include: the ability to continue in employment, ability to continue caring for dependents, maintaining independence and maintaining respiratory function. It was also noted that measurement of treatment outcomes is different in adults compared with paediatric patients. Treatment in adults is focused on preventing progression rather than achievement of milestones. Researchers are working to include measurement of patient reported outcomes in addition to motor assessments in future assessments of SMA therapies.
- Knowledge that the disease is progressive results in a high and ongoing burden on patient mental health.
- Clinicians stated that longer-term data regarding the effectiveness and durability of the effect of nusinersen in adults is becoming available from international registries and observational studies.
- Clinicians noted that there is an SMA registry currently collecting data on around 60 adult patients with SMA in Australia. This is part of an international registry aiming to provide aggregate post-market data. Long-term registries may better demonstrate the gradual changes in strength and function that occur in adults with SMA, which may not be shown in trials of shorter duration.

Of the three therapy sponsors, Biogen, Novartis and Roche, who attended the meeting, only Biogen made a statement and that was to request PBAC to support the funding of its therapy for adult patients. Biogen acknowledged the potential challenges of taking the “whole of disease” approach, however the Sponsor was supportive of an evidence based review of the therapies in SMA. The therapy sponsors made no other contribution to the discussion.

Conclusion

The PBAC Chair thanked stakeholders for their time and helpful inputs into the discussion.

The Chair also thanked the consumer representatives for their personal contributions, and appreciated their perspectives being articulated in this forum.