Nusinersen for spinal muscular atrophy: 24 month predicted versus actual analysis

Drug utilisation sub-committee (DUSC)

February 2021

Abstract

Purpose

To compare predicted and actual utilisation of nusinersen in Type I, II, and IIIa spinal muscular atrophy (SMA), as requested by DUSC at its October 2020 meeting.

Date of listing on the Pharmaceutical Benefits Scheme (PBS)

Nusinersen was PBS listed on 1 June 2018.

Data Source / methodology

Data extracted from the PBS and Authorities data maintained by Department of Health, processed by Services Australia was used for analyses.

Key Findings

- There were 140 and 160 patients treated with nusinersen during the first and second year of listing respectively, which was higher than estimated.
- There were 591 and 514 nusinersen prescriptions dispensed during the first and second year of listing respectively, which was higher than estimated.
- The most common age group in patients initiating nusinersen treatment were those aged between 0-4 years old (39.9% of patients) and overall, there was a similar gender ratio of female and male initiating patients.
- The data was too immature to analyse the time on nusinersen treatment, the median treatment duration was not reached by 30 September 2020.
- After age standardisation (0-18 years), the Australian Capital Territory (ACT) had the highest number of patients initiating nusinersen treatment relative to its population size.
- Type II SMA was the most common type of SMA in patients receiving nusinersen treatment. Similar patient numbers were observed for Type I and Type IIIa SMA.

Purpose of analysis

To compare predicted and actual utilisation of nusinersen for Type I, II and IIIa spinal muscular atrophy, as requested by DUSC at its October 2020 meeting. DUSC commented that nusinersen treats a rare disease with small patient numbers and the results of the review could inform future submissions for this disease.

Background

Clinical situation

Spinal muscular atrophy (SMA) is a genetic condition affecting skeletal motor neurons responsible for controlling muscle movement. These motor neurons degenerate, leading to muscle weakness, hypotonia and atrophy of skeletal muscles.[1] SMA is an autosomal recessive progressive neuromuscular disease due to mutations in chromosome 5q. It has a carrier frequency of one in 35 and an incidence of one in 10,000 live births in Australia.[2,3]

Most patients with SMA have low levels of survival-of-motor-neuron (SMN) protein in their spinal cord motor neurons.[4] The SMN protein is produced by survival motor neuron 1 (SMN1) and survival motor neuron 2 (SMN2) genes. SMA patients have no functioning copies of the SMN1 gene, due to a homozygous deletion of the SMN1 gene on chromosome 5q. Therefore, SMA patients are dependent on the SMN2 gene for production of SMN protein. The SMN2 gene is a pseudogene of SMN1, but differs in exon 7 where the 840th nucleotide is a C in SMN1 and T in SMN2. This difference results in splicing out of exon 7 in SMN2 messenger ribonucleic acid (mRNA) and the production of rapidly degrading SMN proteins.[5] Consequently, SMA patients have limited quantities of SMN protein. The phenotypic severity of SMA is associated with the number of SMN2 genes available. Fewer SMN2 gene copies are generally associated with an earlier age of onset and increased severity of symptoms.[6]

[1] Lunn M R, Wang CH. Spinal muscular atrophy. Lancet 2008; 371: 2120-33 https://doi.org/10.1016/S0140-6736(08)60921-6

[2] SMA Australia. SMA Information Guide. < https://smaaustralia.org.au/wp-content/uploads/SMA_2020_A4_Information_Guide-compressed.pdf> Accessed 9 December 2020.

[3] Farrar M.A, Park S.B, Vucic S, Carey K.A, Turner BJ, Gillingwater TH et al. Emerging therapies and Challenges in Spinal Muscular Atrophy. Annals of Neurology 2017; 81:355-368 doi: 10.1002/ana.24864

[4] Farrar M.A, Kiernan M.C. The Genetics of Spinal Muscular Atrophy: Progress and Challenges. Neurotherapeutics 2015; 12: 290-302

[5] Kolb S.J, Kissel J.T. Spinal Muscular Atrophy: A Timely Review. Archives of Neurology 2011; 68(8) doi:10.1001/archneurol.2011.74.

[6] Feldkötter M, Schwarzer V, Wirth R, Wienker T.F, Wirth B. Quantitative Analyses of SMN1 and SMN2 Based on Real-Time LightCycler PCR: Fast and Highly Reliable Carrier Testing and Prediction of Severity of Spinal Muscular Atrophy. The American Journal of Human Genetics; 70 (2): 358-368. https://doi.org/10.1086/338627.

There are several types of SMA: [4,7]

Table 1: Types of SMA

Type	Age of onset	Symptoms	Life span
Type I Infantile onset or Werdnig-Hoffmann disease)	Birth to 6 months	• Generalised muscle weakness • Weak cry • Trouble breathing, swallowing and sucking	Rarely survive beyond 2 years of age
Type II Childhood onset or Intermediate SMA	7 to 18 months	• Weakness in arms, legs, torso and respiratory muscles • Scoliosis • Can learn to sit unassisted but do not stand or walk independently	Young adulthood and longer
Type III Childhood onset or Kugelberg-Welander	<3 years (Type IIIa)	• Weakness in arms, legs, hips, shoulders and respiratory muscles • Can learn to stand and walk but some lose the ability to walk in adolescence	Normal
	>3 years (Type IIIb)		
	>12 to ≤18 years (Type IIIc)		
Type IV Adult onset SMA	18 to 50 years	• Mild muscle weakness • Tremors • Twitching	Normal

Pharmacology

Nusinersen is an antisense oligonucleotide (ASO) which increases the proportion of exon 7 inclusion in SMN2 mRNA transcripts by binding to an intronic splice silencing site (ISS-N1) in intron 7 or binding to SMN2 pre-mRNA. Exon 7 remains in SMN2 mRNA and can be translated to functional full length SMN protein.[8]

Therapeutic Goods Administration (TGA) approved indications

Nusinersen was ARTG approved 2 November 2017. Nusinersen is only indicated for the treatment of 5q Spinal Muscular Atrophy.

Dosage and administration

The recommended dosage of nusinersen is 12 mg (5 mL) per administration. Four loading doses are administered on days 0, 14, 28 and 63. A maintenance dose is administered once every four months thereafter.

[7] Muscular Dystrophy Australia. Spinal Muscular Atrophy- An Overview. https://www.mda.org.au/disorders/spinal-muscular-atrophy-an-overview/

[8] Spinraza (Nusinersen). Australian Approved Product Information. North Ryde: Biogen. Approved 3 November 2017, updated 2 January 2020. Available from < https://www.tga.gov.au/product-information-pi.>

If a loading dose is delayed or missed, nusinersen should be administered as soon as possible with at least 14 days between doses, and dosing continued at the prescribed dosing frequency. If a maintenance dose is delayed or missed, nusinersen should be administered as soon as possible and dosing continued at the prescribed dosing frequency.

Nusinersen is administered intrathecally by lumbar puncture. It should be administered by health care professionals experienced in performing lumbar punctures.

The current Product Information (PI) and Consumer Medicine Information (CMI) are available from the TGA (Product Information) and the TGA (Consumer Medicines Information).

PBS listing details (as at December 2020)

Nusinersen has Authority Required listings. Applications for authorisation of initial treatment must be made in writing and can be submitted online to Services Australia through the Health Professional Online Services (HPOS). Applications for authorisation of continuing or maintenance treatment can be made via the Online PBS Authorities system or by telephone.

No increase in the maximum quantity or number of units, or number of repeats, may be authorised.

Table 2: PBS listing of nusinersen

Item	Name, form & strength, pack size	Max. quant.	Rpts	DPMQ	Brand name and manufacturer
11363C S100 HSD Public	Nusinersen 12 mg/5 mL vial	1	3	$110,000.00	Spinraza Biogen Australia Pty Ltd
11378W S100 HSD Public	Nusinersen 12 mg/5 mL vial	1	0	$110,000.00	
11472T S100 HSD Private	Nusinersen 12 mg/5mL vial	1	3	$110,047.74	
11476B S100 HSD Private	Nusinersen 12 mg/5 mL vial	1	0	$110,047.74	
12176W S100 HSD Private	Nusinersen 12 mg/ 5 mL vial	1	3	$110,047.74	
12177X S100 HSD Public	Nusinersen 12 mg/5 mL vial	1	3	$110,000.00	

Source: the PBS website.
Note: Special Pricing Arrangements apply.

Restriction (Abridged)

The full restriction can be found in Appendix A.

Treatment criteria	Clinical criteria	Population criteria
Initial treatment: Loading dose		
Must be treated by a specialist medical practitioner experienced in the diagnosis and management of SMA associated with a neuromuscular clinic of a recognised hospital in the management of SMA; or in consultation with a specialist medical practitioner experienced in the diagnosis and management of SMA associated with a neuromuscular clinic of a recognised hospital in the management of SMA.	The condition must 5q homozygous deletion, mutation of, or compound heterozygous mutation in the SMN1 gene of type I, II or IIIa, **AND** Patient must have experienced at least two of the defined signs and symptoms of SMA type I, II or IIIa prior to 3 years of age, **AND** The treatment must be given concomitantly with standard of care for this condition, **AND** The treatment must not exceed four loading doses (at days 0, 14, 28 and 63) under this restriction.	Patient must be 18 years of age or under. Defined signs and symptoms of type I, type II, type IIIa SMA can be found in Appendix A.
Continuing treatment - Maintenance		
Must be treated by a specialist medical practitioner experienced in the diagnosis and management of SMA associated with a neuromuscular clinic of a recognised hospital in the management of SMA; or in consultation with a specialist medical practitioner experienced in the diagnosis and management of SMA associated with a neuromuscular clinic of a recognised hospital in the management of SMA; or initiated by a specialist medical practitioner experienced in the diagnosis and management of SMA associated with a neuromuscular clinic of a recognised hospital in the management of SMA.	Patient must have previously received PBS-subsidised treatment with this drug for this condition, **AND** The treatment must be given concomitantly with standard of care for this condition, **AND** The treatment must be ceased when invasive permanent assisted ventilation is required in the absence of a potentially reversible cause while being treated with this drug. Invasive permanent assisted ventilation means ventilation via tracheostomy tube for greater than or equal to 16 hours per day.	

For details of the current PBS listing refer to the PBS website.

Date of listing on PBS

Nusinersen was PBS listed in 1 June 2018.

Changes to listing

November 2018

The listing of nusinersen was extended from Section 100 (Highly Specialised Drugs Program) Public Hospitals to include Section 100 (Highly Specialised Drugs Program) Private Hospitals. The PBAC recommended this change in July 2018 following a request outlining a concern where private hospital patients would be placed at a higher risk as they would require an additional dose of general anaesthetic in order to receive nusinersen which was only listed on Section 100 (Highly Specialised Drugs Program) Public Hospitals.

December 2020

The listing of nusinersen was extended to include the pre-symptomatic initiation treatment of patients genetically diagnosed with SMA who have an SMN2 copy number of ≤2. In July 2020, the PBAC considered the pre-symptomatic initiation of treatment would provide an additional benefit for some patients compared with initiation upon development of symptoms.

Current PBS listing details are available from the PBS website.

Approach taken to estimate utilisation

November 2017 major submission

An epidemiological approach was used as nusinersen was the first treatment for SMA on the PBS. The submission undertook separate analyses for the three subtypes of SMA: infantile-onset SMA (Type I) and child-hood onset SMA (Type II and Type III). The incidence rate of each SMA subtype was applied to the number of live births each year in Australia. The patient survival of each SMA subtype was then applied to capture the number of prevalent patients of each SMA type at the time of nusinersen listing on the PBAC.

The PBAC considered the incidence of Type I SMA estimated based on Australian data to be reasonable. The PBAC considered the estimated number of patients with Type II and II SMA to be uncertain and likely underestimated as they were based on overseas data due to the lack of Australian data. The PBAC noted although the submission used the best available evidence to estimate the prevalence of SMA Type I-III, it was likely underestimated particularly regarding the number of patients over the age of 18 years.

Committee-in-confidence

[redacted]

End committee-in-confidence

March 2018 minor resubmission

The minor resubmission used new Australian data on the prevalence of SMA patients with Type I, II and IIIa SMA who are currently aged ≤18 years. The proposed patient population for this submission was narrower than what was proposed in the November 2017 major submission (Type I, II and III SMA patients). Type IIIb and c patients were not included in the minor resubmission as treatment with nusinersen must commence before a patient turns 19 years of age.

This data was derived from a survey of paediatric SMA treatment centres in Australia commissioned by the sponsor and survey data from the SMA Australia database. The SMA Australia data was based on known cases reported through the organisation. SMA Australia estimated the database captures 30-50% of the entire SMA community (including Type IV). The proportion of the requested high need population captured in this database is not known.

The pre-PBAC response presented revised financial estimates incorporating SMA Type II and IIIa Year 1 patient estimates based on the survey of paediatric neuromuscular centres and assumed uptake rate of 100% for all incident patients, increased uptake for SMA Type II and IIIa patients and increased continuation rates for SMA Type I patients.

Committee-in-confidence

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End committee-in-confidence

Relevant aspects of consideration by the Pharmaceutical Benefits Advisory Committee (PBAC)

November 2017 PBAC Meeting

The PBAC did not recommend the Section 100 (Highly Specialised Drugs Program) listing of nusinersen for the treatment of patients with infantile-onset (Type I) and childhood-onset (Types II & III) SMA because of uncertainty about its clinical effectiveness in terms of the extent and durability of response across the spectrum of SMA for which the submission has sought subsidy. The submission contained insufficient information for the PBAC to form a view on the cost-effectiveness of treatment across the spectrum of SMA.

The submission estimated the prevalence of SMA Type I-III to be less than 10,000 people in 2018. Despite using the best available evidence at the time, it was likely an underestimate, in particular with the number of patients over the age of 18 years. The incidence of Type I SMA was estimated based on Australian data which the PBAC considered reasonable. However, the number of patients with Type II and III SMA was based on overseas data due to the lack of Australian data, which PBAC considered to be likely underestimated.

The financial impact of listing was proposed to be $60-$100 million in Year 1 and increasing to more than $100 million per year by Year 6. The PBAC considered the financial impact would likely be higher than estimated due to the uncertainty of the size of the Type II and III SMA population, potential use outside the proposed indication and the likelihood of patients remaining on treatment long term given the lack of alternative treatments available and the progressive nature of the disease.

For further details refer to the Public Summary Document from the November 2017 PBAC meeting.

March 2018 PBAC Meeting

The PBAC recommended the Section 100 (Highly Specialised Drugs Program) listing of nusinersen for the treatment of paediatric patients with infantile-onset (Type I) or childhood onset SMA with onset of symptoms prior to 3 years of age (Types II & Type IIIa).

The PBAC was satisfied that based on the clinical evidence available, nusinersen provides a significant improvement in efficacy over standard of care for the proposed patient population. However, the PBAC considered there was remaining uncertainty around the extent and durability of treatment effect particularly in Type II/IIIa patients. The PBAC advised further negotiations with the sponsor were required to address these uncertainties through a combination of mechanisms including a reduction in price, increased rebates or lower financial caps.

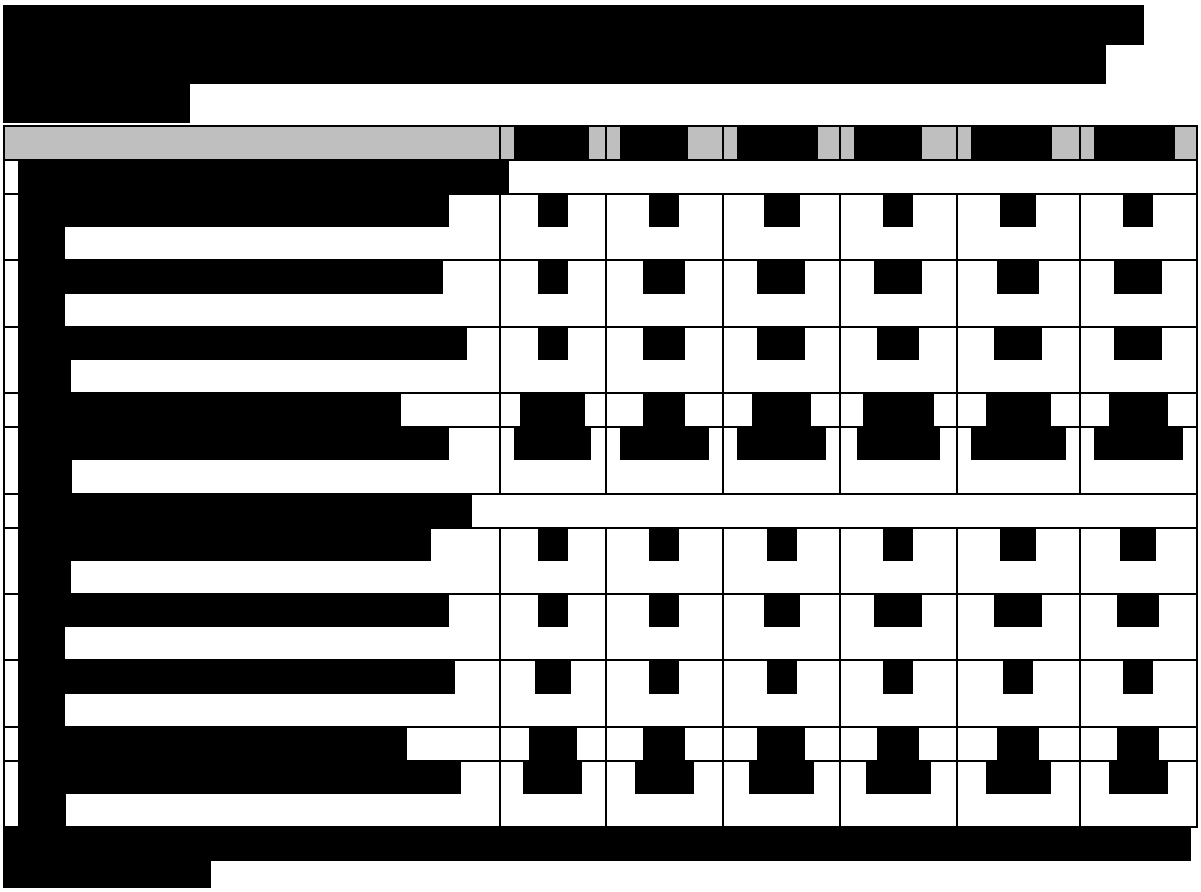
The PBAC considered the survey of paediatric neuromuscular centres in Australia was an appropriate source of data to base the estimated number of prevalent SMA Type II and IIIa patients given the limited number of these specialist centres in Australia. The PBAC noted although the submission did not estimate the prevalent number of SMA Type I patients based on the survey data, the estimated number of prevalent SMA Type I patients to be grandfathered (from the sponsor's expanded access program) aligned closely with the corresponding number of patients in the survey. The PBAC considered that the inclusion of additional patients to account for patients not treated at a paediatric neuromuscular centre was not justified given the nature of the disease.

PBAC recalled that DUSC previously considered the treatment uptake rates (80%, 100% and 80% incident uptake rate for Type I, II and III patients respectively) in the November 2017 major submission were underestimated given the nature of the disease and lack of alternative treatments. Based on the following information provided at the 18 January 2018 Stakeholder Meeting, the PBAC considered uptake may not reach 100% and the Sponsor's original uptake assumptions may be reasonable:

- Some Type I patients would not benefit from nusinersen initiation or not be able to tolerate the procedures
- Some families of Type I SMA patients elected not to commence treatment with nusinersen through the sponsor's Expanded Access Program
- 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
- The burden of treatment (a four monthly intrathecal injection) may lower uptake in adult patients

The PBAC noted that the financial impact of listing nusinersen of $30 - $60 million in Year 1 increasing to $30 - $60 million in Year 6 of listing to be significant albeit considerably less than the estimated financial impact of listing presented in the November 2017 major submission ($60 - $100 million in Year 1 increasing to more than $100 million in Year 6). The PBAC noted that these estimates would need to be revised following further negotiations with the sponsor in line with the PBAC recommendations.

Committee-in-confidence



End committee-in-confidence

For further details refer to the Public Summary Document from the March 2018 PBAC meeting.

Following the PBS listing of nusinersen for Type I, II and IIIa SMA in June 2018, a number of submissions were considered by the PBAC and are summarised in the table below:

Table 5: Summary of nusinersen submissions to the PBAC

PBAC meeting	PBAC Outcome
July 2018	Following the PBS listing of nusinersen on the Section 100 (Highly Specialised Drugs Program) for the Public Hospital setting only, the Department received a request to extend the listing to private hospitals due to risks associated with the administration of an additional dose of general anaesthetic. The PBAC recommended extending the listing to include Section 100 (Highly Specialised Drugs Program) Private Hospitals. For further details refer to the Public Summary Document from the July 2018 PBAC meeting.

PBAC meeting	PBAC Outcome
July 2019	The submission requested an extension of the nusinersen listing for the pre-symptomatic initiation of treatment for patients with SMA who have up to 3 copies of the SMN2 gene. The PBAC deferred making a final recommendation to extend the current listing of nusinersen pending advice from the Medical Services Advisory Committee (MSAC) on the prognostic value of SMN2 copy number for the severity of SMA to help determine eligibility for nusinersen in pre-symptomatic patients. The PBAC was of a mind not to recommend extending the current listing as there was insufficient evidence to demonstrate pre-symptomatic initiation of treatment with nusinersen would be effective than treatment with nusinersen following the onset of symptoms of SMA. For further details refer to the Public Summary Document from the July 2019 PBAC meeting.
November 2019	MSAC considered the SMN2 copy number to be the main source of prognostic information for SMA severity, however MSAC advised there are several other genetic components that may also modify the phenotype to some extent. The PBAC did not recommend extending the current listing to include pre-symptomatic initiation of treatment of patients genetically diagnosed with SMA. For further details refer to the Public Summary Document from the November 2019 PBAC meeting.
July 2020	The PBAC recommended the addition of pre-symptomatic initiation treatment of patients genetically diagnosed with SMA who have an SMN2 copy number of ≤2 to the current listing of nusinersen. The PBAC considered pre-symptomatic initiation of treatment with nusinersen would provide an additional benefit for some patients compared with initiation upon development of symptoms. The PBAC advised pre-symptomatic initiation of treatment should be limited to patients less than three years of age. For further details refer to the Public Summary Document from the July 2020 PBAC meeting.
November 2020	The PBAC did not recommend extending the listing of nusinersen to include the treatment of SMA in patients with symptom onset prior to 19 years of age, and removal of the age limit of 18 years for initiation of treatment. The PBAC recognised the high clinical need for effective treatments for adults with SMA. However, the PBAC considered the resubmission had not adequately defined the appropriate adult population for nusinersen and proposed convening a consultation with experts in the clinical management of adult SMA to help resolve the specific issues associated with use of nusinersen in adult patients.

Methods

Data extracted from the PBS data maintained by the Department of Health and processed by Services Australia was used for the analyses. Prescription data was extracted from when nusinersen was PBS listed from 1 June 2018 up to and including 30 September 2020. Data was extracted on 2 December 2020.

This data was used to determine the number of incident and prevalent patients, number of prescriptions supplied and to analyse patient demographics such as age and gender. Initiating and prevalent patients were counted by quarter of supply. An initiating patient was defined based on their first date of supply of nusinersen. The number of patients according to each phase (initial, continuing and grandfathered) and hospital setting (public or private) based on item codes were counted by listing year.

The Kaplan-Meier method was used to analyse treatment duration with nusinersen, censoring patients that were still continuing treatment at the analysis end date. Initiating patients were selected from 1 November 2018, to exclude grandfathered patients. These patients were followed until 30 September 2020. The median standard treatment days were 112 days. Patients were censored if they received a supply within two sets of standard treatment days before the analysis end date.

The number of initiating patients were extracted according to state and territory. Patient numbers were standardised in order to provide a more representative value relative to the population size of the respective state or territory. Population estimates for those aged between 0 and 18 years were extracted from the Australian Bureau of Statistics (ABS) for each state and territory.[9] Population estimates as at June 2019 were used, as it was approximately halfway between the analysis start and end date: June 2018 to September 2020. The number of initiating patients were divided by the population estimates for each state and territory. These figures were multiplied by 100,000 to generate the age standardised values for each state and territory.

As this analysis uses date of supply prescription data, there may be small differences compared with publicly available Department of Human Services (DHS) Medicare date of processing data.[10] The publicly available DHS Medicare data only includes subsidised R/PBS prescriptions with prescriptions under the patient co-payment not included. The DHS Medicare data used in this report includes under co-payment prescriptions from 1 April 2012.

Additional data was extracted from the Authorities database maintained by Department of Health and processed by Services Australia. Processed authorities data was extracted from when nusinersen was PBS listed from 1 June 2018 up to and including 30 September 2020. Data was extracted on 7 December 2020. Nusinersen requires a written authority

[9] Australian Bureau of Statistics. Quarterly Population Estimates (ERP), by State/Territory, Sex and Age. <http://stat.data.abs.gov.au/Index.aspx?DataSetCode=ERP_QUARTERLY#>. Accessed 9 December 2020.
[10] PBS statistics. Australian Government Department of Human Services Medicare. Canberra. Available from <http://www.medicareaustralia.gov.au/provider/pbs/stats.jsp>.

application where several questions regarding the patient's condition are answered by prescribing clinicians. Responses to these questions, such as the type of SMA a patient has, were analysed.

Data manipulation was undertaken using SAS.

Results

Analysis of drug utilisation

Overall utilisation

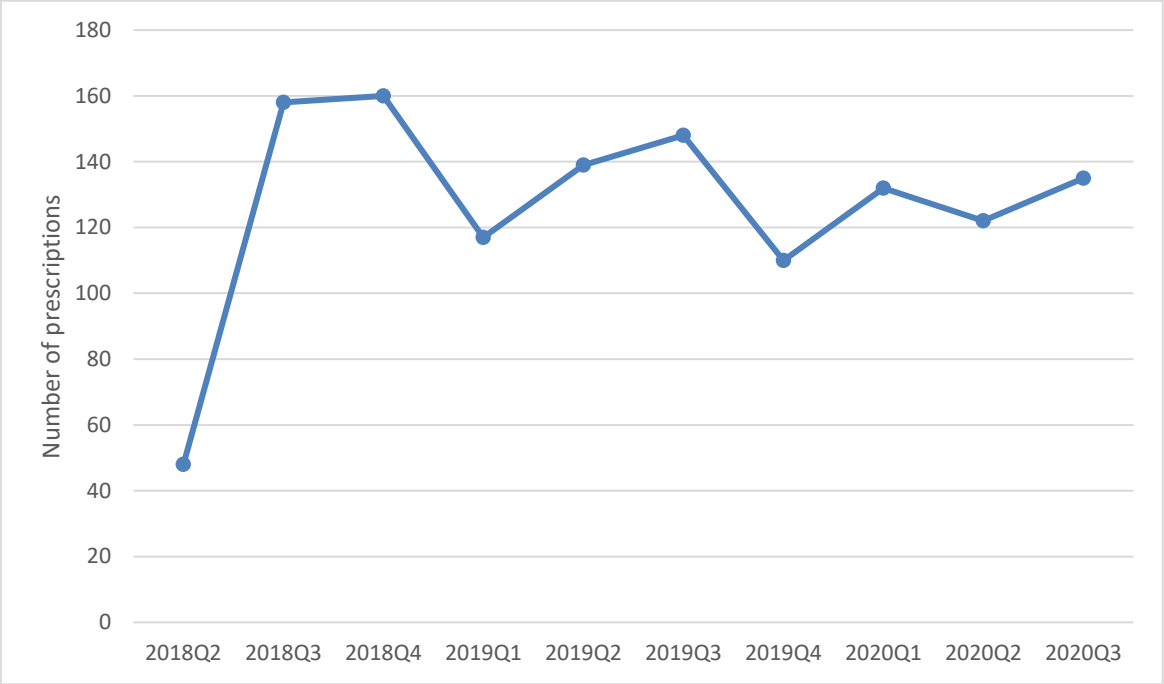


Figure 1: Number of nusinersen prescriptions supplied according to supply quarter
Note: Quarter 2 of 2018 only includes the month of June.

In Figure 1, the number of prescriptions dispensed averaged between 110 to 160 prescriptions per supply quarter. From when nusinersen was PBS listed in quarter 2 of 2018 to quarter 4 of 2019, the number of prescriptions appeared to fluctuate. However, from the first quarter of 2020 onwards the number of prescriptions dispensed appear to have stabilised with an average of 130 prescriptions each quarter.

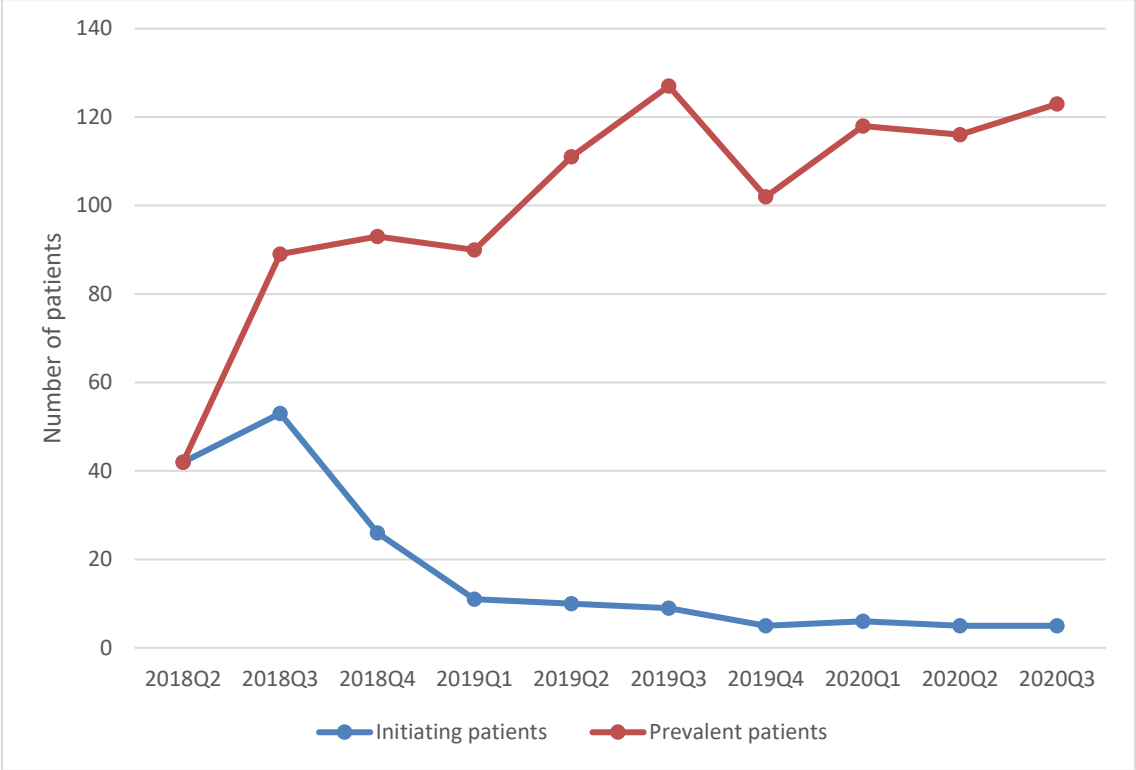


Figure 2: Number of incident and prevalent nusinersen patients according to supply quarter

Note: Quarter 2 of 2018 only includes the month of June. Where the patient count is between 1 and 4 (inclusive), a figure data point is set to 5 to protect patient confidentiality.

Overall, in Figure 2 the number of initiating patients appeared to stabilise from quarter 1 of 2019 onwards with an average of approximately 5 to 10 patients initiating treatment each supply quarter. The highest number of initiating patients occurred in quarter 3 of 2018. In contrast, the number of prevalent patients appears to fluctuate with a peak observed in quarter 3 of 2019 with 127 prevalent patients.

Utilisation by relevant sub-populations/regions or patient level analysis

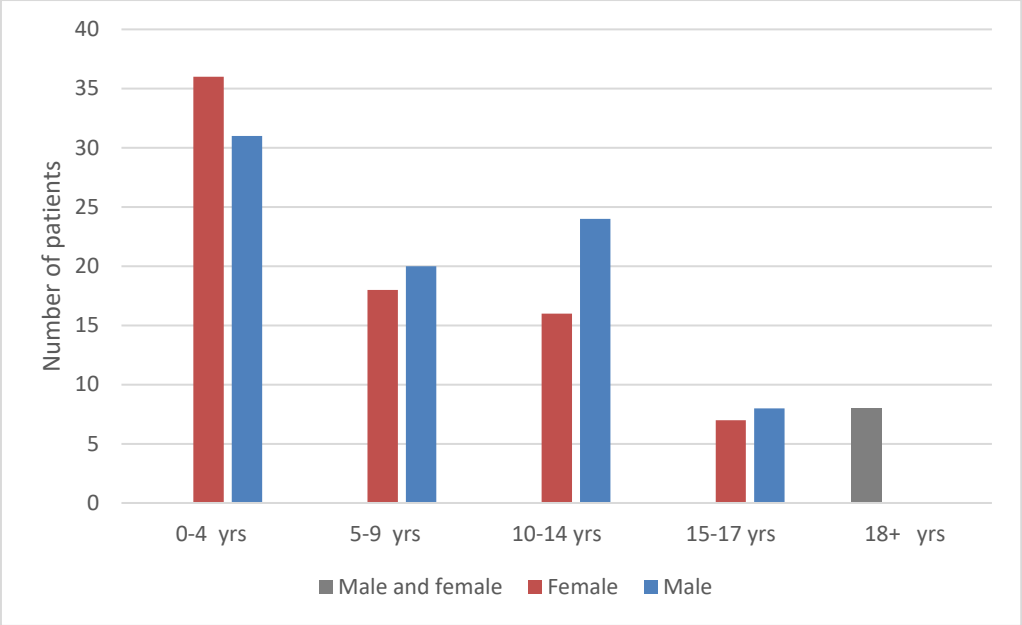


Figure 3: Age and gender distribution of initiating nusinersen patients

Note: The gender counts of initiating patients who are 18 years and over have been grouped due to low patient numbers to mitigate the risk of re-identification.

In Figure 3, the age distribution of initiating nusinersen patients is positively skewed, with the majority of patients (95.2%) initiating nusinersen treatment aged less than 18 years. The most common age group that initiate on nusinersen are those aged between 0 and 4 years old (39.9% of patients).

Overall, there was a similar ratio of male and female initiating patients. The mean age of initiating patients was 7.5 years and a median of 7 years. The age of patients ranged from 0 to 43 years.

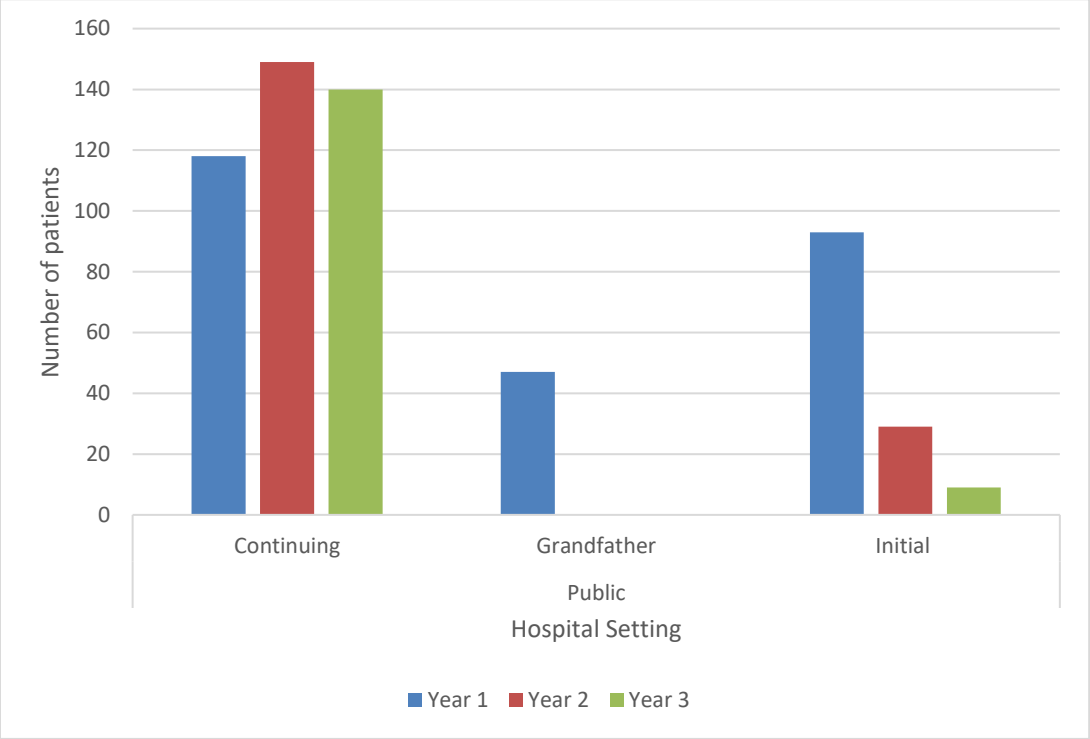


Figure 4: Number of patients according to treatment phase by listing year

Note: Year 3 only includes four months of data from June 2020 to September 2020 inclusive.
Note: The analysis includes the following listings: Section 100 (Highly Specialised Drugs) Public hospital item codes: 11363C (initial), 11378W (continuing), 11370K (grandfather); and Section 100 (Highly Specialised Drugs) Private hospital item codes: 11472T (initial), 11476B (continuing), 11470Q (grandfather).

In Figure 4, the number of initial, continuing and grandfathered patients are shown based on item codes according to the listing year. In the first year of nusinersen listing, 47 patients were grandfathered, 93 initiated nusinersen treatment and 118 continued nusinersen treatment. In its second year of listing, the number of initiating patients decreased with only 29 initiating treatment with nusinersen. However, the number of patients who continued nusinersen treatment increased to 149 in Year 2. In its third year of listing, with only four months of data from June 2020 to September 2020 inclusive, nine patients initiated and 140 patients continued nusinersen treatment.

It is noted that based on the recorded item codes, all patients received nusinersen treatment under Section 100 Highly Specialised Drugs Program for Public Hospitals, with no patients receiving nusinersen treatment under the Section 100 Highly Specialised Drugs Program for Private Hospitals.

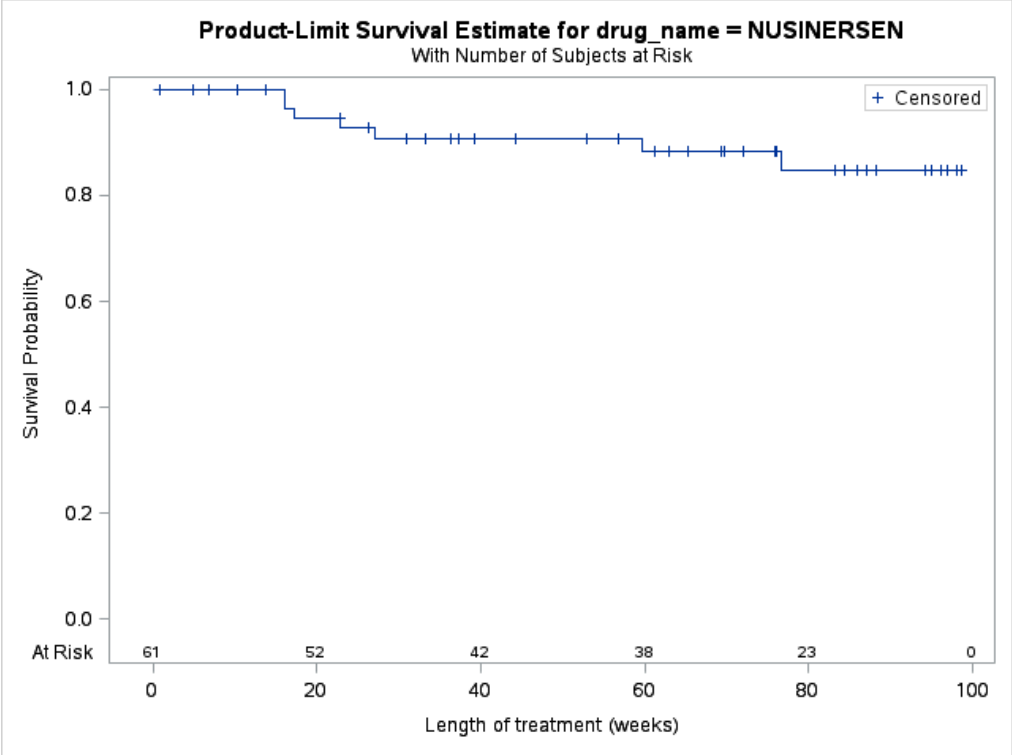


Figure 5: Nusinersen treatment duration (weeks) for patients initiating between 1 November 2018 and 30 September 2020

The data was too immature to fully analyse the time on nusinersen, with a median time on therapy not being reached within 28 months from first listing. Of the 61 patients initiating on nusinersen after 1 November 2018 who were followed up to 30 September 2020, 88.52% of patients were censored. The median survival probability was not reached.

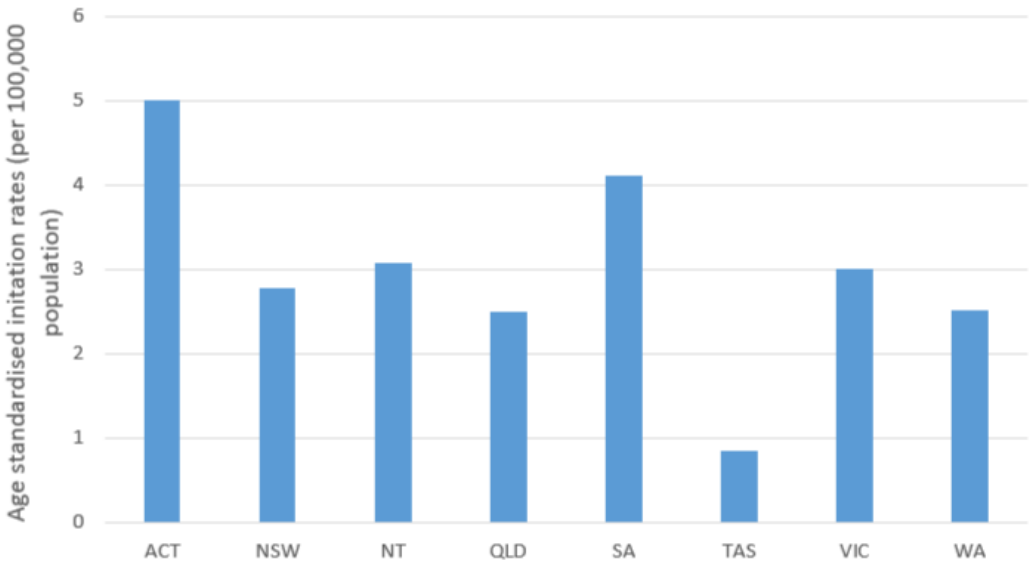


Figure 6: Age standardised nusinersen initiation rates according to state or territory, patients aged 0-18 years

Figure 6 shows the nusinersen initiation rates for each state and territory. The initiation rates are standardised by the age distribution and population size for each jurisdiction, and include patients aged up to 18 years. After standardisation, the ACT has the highest number of initiating patients relative to its population aged 0 to 18 years. SA has the second highest number of patients, with NSW, NT, QLD, VIC and WA having similar numbers of initiating patients relative to their population size. TAS has the lowest number of standardised initiating patients.

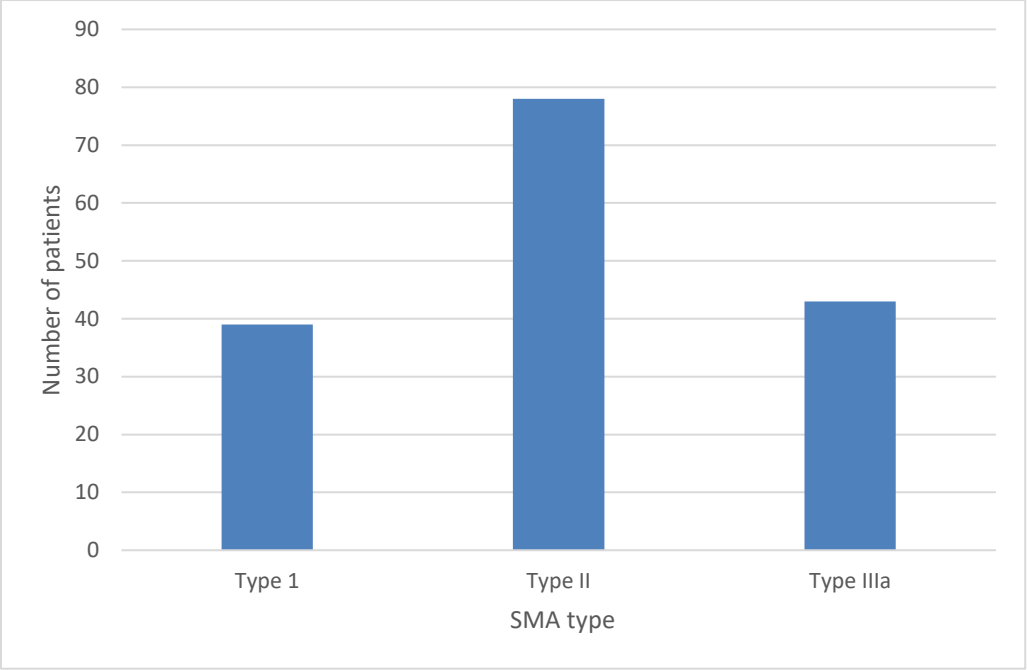


Figure 7: Number of initiating patients classified according to SMA type based on written Authorities applications

Note:
Type I SMA defined by onset before 6 months of age.
Type II SMA defined by onset between 6 and 19 months of age.
Type IIIa SMA defined by onset between 19 months and 3 years of age.

Since first listing to 30 September 2020, there have been 160 Authority applications approved for the supply of initial treatment with nusinersen. Overall, Figure 7 shows that Type II SMA patients account for the majority for patients supplied nusinersen treatment. There are a similar number of Type I and Type IIIa SMA patients supplied nusinersen.

Analysis of actual versus predicted utilisation

Committee-in-confidence

Table 6: Nusinersen actual versus predicted utilisation

Nusinersen listing years		Year 1	Year 2	Year 3
		June 2018 – May 2019	June 2019- May 2020	June 2020- May 2021
Patients	Predicted	[redacted]	[redacted]	[redacted]
	Actual	140	160	148
	Difference	[redacted]	[redacted]	[redacted]
Prescriptions	Predicted	[redacted]	[redacted]	[redacted]
	Actual	591	514	164
	Difference	[redacted]	[redacted]	[redacted]

Note: Year 3 predicted numbers are for the full year, actual numbers are four months of data (June 2020 to September 2020 inclusive).

From Table 6, actual patient and prescription figures were higher than estimated in listing Years 1 and 2. The number of patients in the first and second year of nusinersen listing was [redacted]. The actual patient numbers for Year 3 were [redacted] than predicted. However, the actual patient numbers for Year 3 only comprise of four months of data.

The actual number of nusinersen prescriptions dispensed were [redacted] than estimated in the first year. In its second year, the actual number of nusinersen prescriptions dispensed were [redacted] than estimated. With four months of data in Year 3, the number of actual prescriptions dispensed was [redacted] than estimated for the full year of listing.

Overall, there was a [redacted] in the number of patients and prescriptions observed in Year 1 than estimated compared to subsequent years.

It was estimated that [redacted] patients would be grandfathered from the sponsor's expanded access program. Based on the grandfathered treatment item codes (11370K and 11470Q) that were listed on the PBS until 29 February 2020, 47 patients were grandfathered from the sponsor's expanded access program which was [redacted] than estimated. [redacted]

End committee-in-confidence

Discussion

In the first year of listing, the number of patients supplied nusinersen was [redacted] higher than estimated and the number of prescriptions were [redacted] higher than estimated. There was a greater increase in the number of prescriptions supplied compared to the number of patients supplied nusinersen treatment, indicating patients are being dispensed more scripts than estimated. In the second year of listing, the number of treated patients were [redacted] higher than estimated and the number of prescriptions were [redacted] higher than estimated. At the time of analysis, there was only four months of data available for the third year of listing. Patient numbers are currently [redacted] lower and prescriptions [redacted] lower than was estimated for the full year.

At its March 2018 meeting, the PBAC considered uptake rates may not reach 100% and the estimated uptake rates provided in the November 2017 submission (Type I , II and III patients to be 80%, 100% and 80% respectively) to be reasonable (paragraph 5.59 nusinersen Public Summary Document March 2018) . Higher than estimated uptake rates may have contributed to the greater number of patients receiving nusinersen treatment in practice.

The incidence of SMA in Australia is estimated to be one in 10,000 live births.[2] In 2019, there were 305,832 registered births.[11] Therefore, the estimated incidence in 2019 would be 31 (1/10,000 × 305,832 registered births). In 2019, 34 patients initiated treatment with nusinersen, which was slightly higher than the calculated incidence.

The mean age of patients initiating nusinersen treatment in practice was 7.5 years, ranging from 0 to 43 years. In the ENDEAR trial referred to in the submission for infantile-onset SMA, patients initiating nusinersen treatment were younger.[12] The mean age of initiating patients in the trial was 163 days (approximately 0.45 years), ranging from 52 to 242 days (approximately 0.14 to 0.66 years). Additionally, the submission had referred to the CHERISH trial for childhood-onset SMA, where 83% of patients were less than 6 years old.[13] As such, the PBS population is older than the trial populations previously considered by the PBAC.

The listing of nusinersen on the PBS was extended to include Section 100 Highly Specialised Drugs Program Private Hospitals in November 2018. Based on the item codes relevant to the Private Hospitals program, no patients have been prescribed nusinersen under this program. This may be because specialist neuromuscular clinics and clinicians with expertise in treating patients with SMA are located in public hospitals (paragraph 2.2 nusinersen Public Summary Document July 2018). However, it may have been possible for patients to be processed under a different item code.

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[11] Australian Bureau of Statistics. Births, Australia, 2019 https://www.abs.gov.au/statistics/people/population/births-australia/latest-release. Accessed 9 December 2020

[12] Finkel R.S, Mercuri E, Darras B.T, Connolly A.M, Kuntz N.L, Kirschner J. Nusinersen versus Sham Control in Infantile-Onset Spinal Muscular Atrophy. The New England Journal of Medicine. 2017; 377, 1723-32.

[13] Mercuri E, Darras BT, Chiriboga CA, et al. Nusinersen versus sham control in later-onset spinal muscular atrophy. The New England Journal of Medicine 2018;378:625-35. DOI: 10.1056/NEJMoa1710504

An analysis of the median time on nusinersen was attempted, however the data was too immature and a median time on treatment had not been reached. For those patients initiating on nusinersen from 1 November 2018, 88 percent were continuing on therapy at the analysis end date (30 September 2020).

There are eight hospitals responsible for the management of SMA in Australia: Lady Cilento Children's Hospital (Brisbane), Royal Children's Hospital Melbourne, Monash Children's Hospital (Melbourne), John Hunter Hospital (Newcastle), Sydney Children's Hospital Randwick, Children's Hospital at Westmead, Adelaide Women and Children's Hospital and Perth Children's Hospital. Based on age-standardised initiation rates, taking into account the age distribution and population size of jurisdictions, the ACT had the highest number of patients initiating treatment. Patients in NSW, NT, QLD, VIC and WA had similar age-standardised initiation rates while TAS had the lowest number of initiating patients relative to its population.

The number of patients categorised according to SMA type varied, with Type II SMA patients accounting for the majority of those supplied nusinersen treatment in Year 1 and 2. The proportion of initiating patients with Type I SMA increased as the listing years progressed. In the Year 1, 23% of patients had Type I SMA, 26% of patients in Year 2 and 50% of patients in Year 3. The median age of initiating patients had decreased as listing years progressed. The median (range) age of patients was 8 years (0 to 43), 1.5 years (0 to 15) and less than 1 year (0 to 25) in Year 1, 2 and 3 respectively. This may suggest older patients with Type II and Type IIIa SMA have already initiated onto nusinersen by Year 3, with initiating patients more likely to be younger with Type I SMA.

There were slight variances between patient numbers in the Authority database and the PBS scripts database, particularly when comparing yearly data. These differences may be due to the delay between an authority approval and the supply of a prescription. Additionally, from Year 2 onwards, more initiating patients were supplied nusinersen treatment compared to the number of patients who submitted an authority application. For example, 22 patients had an initial supply of nusinersen treatment in Year 2, however only 15 initial applications were approved.

DUSC consideration

DUSC noted in the first year of listing, 47 patients were grandfathered onto nusinersen, 93 initiated and 118 continued treatment. DUSC noted in the Pre-Sub-Committee Response (PSCR) (p3), [redacted] The analysis did not note that "21 patients transitioned from the existing expanded access program (EAP-Type I patients) and 26 patients transitioned from the 1-month programme (including SMA types II and IIIa) to PBS supply [redacted] DUSC sought consumer input from SMA Australia who commented families had moved from New Zealand to Australia under the Reciprocal Health Care Agreement to gain access to nusinersen treatment. This may partly explain the higher than anticipated utilisation of nusinersen.

DUSC noted in the second year of listing, 29 patients initiated and 149 patients continued treatment. DUSC commented reasons for discontinuation could include participation in other programs and studies, using nusinersen treatment in combination with other treatments or initiation onto other agents. DUSC considered a future review should include additional data on discontinuation, including accounting for patient deaths. DUSC noted that an Australian registry is now recruiting and could be a potential data source for capturing future trends in treatment approaches and outcomes over time and longer term data on disease progression across SMA types and treatments.

DUSC noted of 61 patients who initiated after 1 November 2018, approximately 89% maintained therapy and median time on therapy had not been reached. DUSC considered the importance of continuing to follow patients to observe the median time on therapy in future analysis.

DUSC noted there was a greater increase in the number of prescriptions supplied compared to the number of patients supplied nusinersen treatment. The PSCR (p3) stated "Utilisation of nusinersen follows an irregular pattern due to the dosage regimen of 4 loading doses (in the first 2 months), followed by maintenance doses every 4 months…the actual average number of prescriptions was higher than predicted… This is well within the upper limit of 6 prescriptions for a patient's first year of treatment with nusinersen (4 loading doses + 2 maintenance doses)."

DUSC noted the PSCR (p1) stated the predicted patient numbers was based on advice from clinicians at 5 paediatric neuromuscular treatment centres. However, the PBS listing includes 8 treatment centres resulting in a wider drawing area for SMA patients. The PSCR (p1) commented the observed utilisation is appropriate due to the strict criteria and the sponsor considered that this ensured that only eligible patients initiate nusinersen treatment.

DUSC noted that the ACT and SA had the highest number of initiating patients with age standardisation (0-18 years) relative to its population size. DUSC commented that the ACT and SA do not have centre sites to prescribe nusinersen. Prior to PBS listing, patients in these jurisdictions would have encountered barriers to accessing trials and early access

programs. Once nusinersen was available on the PBS, DUSC considered that these untreated patients may have accounted for the high initiation rates due to its accessibility.

DUSC noted that Type II SMA was the most common type of patients treated with nusinersen. DUSC commented the original DUSC view of expected uptake rates (underestimated at 80% Type I, 100% Type II and 80% Type III) appears correct. DUSC noted SMA Australia commented there were less Type I patients due to early death with more Type II patients surviving. Clinicians are continuing treatment due to improvements observed in these patients.

DUSC noted comments from SMA Australia on the need for continued monitoring of treatment utilisation, particularly with new treatments becoming available. SMA Australia commented patients have passed away whilst on treatment, and reasons for discontinuation should be included in future analyses. Additionally, continued monitoring will assist in determining how long Type I patients with poorer survival outcomes continue to live beyond two years. DUSC noted SMA Australia stated that nusinersen treatment is enabling children to have a longer lifespan as children with Type I SMA are now starting school.

DUSC actions

DUSC requested that the report be provided to the PBAC for consideration.

Context for analysis

The DUSC is a Sub Committee of the Pharmaceutical Benefits Advisory Committee (PBAC). The DUSC assesses estimates on projected usage and financial cost of medicines.

The DUSC also analyses data on actual use of medicines, including the utilisation of PBS listed medicines, and provides advice to the PBAC on these matters. This may include outlining how the current utilisation of PBS medicines compares with the use as recommended by the PBAC.

The DUSC operates in accordance with the quality use of medicines objective of the National Medicines Policy and considers that the DUSC utilisation analyses will assist consumers and health professionals to better understand the costs, benefits and risks of medicines.

The utilisation analysis report was provided to the pharmaceutical sponsors of each drug and comments on the report were provided to DUSC prior to its consideration of the analysis.

Sponsors' comment

Biogen Australia Pty Ltd: The sponsor has no comment.

Disclaimer

The information provided in this report does not constitute medical advice and is not intended to take the place of professional medical advice or care. It is not intended to define what constitutes reasonable, appropriate or best care for any individual for any given health issue. The information should not be used as a substitute for the judgement and skill of a medical practitioner.

The Department of Health (DoH) has made all reasonable efforts to ensure that information provided in this report is accurate. The information provided in this report was up-to-date when it was considered by the Drug Utilisation Sub-committee of the Pharmaceutical Benefits Advisory Committee. The context for that information may have changed since publication.

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Appendices

Appendix A: Nusinersen restriction as at December 2020

Treatment Phase: Initial treatment of pre-symptomatic spinal muscular atrophy (SMA) - Loading doses

Treatment criteria:

- Must be treated by a specialist medical practitioner experienced in the diagnosis and management of SMA associated with a neuromuscular clinic of a recognised hospital in the management of SMA; or in consultation with a specialist medical practitioner experienced in the diagnosis and management of SMA associated with a neuromuscular clinic of a recognised hospital in the management of SMA.

Clinical criteria:

- The condition must have genetic confirmation of 5q homozygous deletion of the survival motor neuron 1 (SMN1) gene; OR
- The condition must have genetic confirmation of deletion of one copy of the SMN1 gene in addition to a pathogenic/likely pathogenic variant in the remaining single copy of the SMN1 gene,

AND

- The condition must have genetic confirmation that there are 1 to 2 copies of the survival motor neuron 2 (SMN2) gene,

AND

- The condition must be pre-symptomatic,

AND

- The treatment must be given concomitantly with standard of care for this condition,

AND

- The treatment must not exceed four loading doses (at days 0, 14, 28 and 63) under this restriction.

Population criteria:

- Patient must be aged under 36 months prior to commencing treatment.

Application for authorisation of initial treatment must be in writing (lodged via postal service or electronic upload) and must include:

(a) a completed authority prescription form; and

(b) a completed Spinal muscular atrophy PBS Authority Application Form which includes the following:

(i) confirmation of genetic diagnosis of SMA; and

(ii) a copy of the results substantiating the number of SMN2 gene copies determined by quantitative polymerase chain reaction (qPCR) or multiple ligation dependent probe amplification (MLPA)

Recognised hospitals in the management of SMA are Queensland Children's Hospital (Brisbane), Royal Children's Hospital Melbourne, Monash Children's Hospital (Melbourne), John Hunter Hospital (Newcastle), Sydney Children's Hospital Randwick, Children's Hospital at Westmead, Adelaide Women and Children's Hospital and Perth Children's Hospital.

Treatment Phase: Initial treatment - Loading doses

Treatment criteria:

Must be treated by a specialist medical practitioner experienced in the diagnosis and management of SMA associated with a neuromuscular clinic of a recognised hospital in the management of SMA; or in consultation with a specialist medical practitioner experienced in the diagnosis and management of SMA associated with a neuromuscular clinic of a recognised hospital in the management of SMA.

Clinical criteria:

- The condition must 5q homozygous deletion, mutation of, or compound heterozygous mutation in the SMN1 gene of type I, II or IIIa,

AND

- Patient must have experienced at least two of the defined signs and symptoms of SMA type I, II or IIIa prior to 3 years of age,

AND

- The treatment must be given concomitantly with standard of care for this condition,

AND

- The treatment must not exceed four loading doses (at days 0, 14, 28 and 63) under this restriction.

Population criteria:

- Patient must be 18 years of age or under.

Defined signs and symptoms of type I SMA are:

i) Onset before 6 months of age; and

ii) Failure to meet or regression in ability to perform age-appropriate motor milestones; or

iii) Proximal weakness; or

iv) Hypotonia; or

v) Absence of deep tendon reflexes; or

vi) Failure to gain weight appropriate for age; or

vii) Any active chronic neurogenic changes; or

viii) A compound muscle action potential below normative values for an age-matched child.

Defined signs and symptoms of type II SMA are:

i) Onset between 6 and 18 months; and

ii) Failure to meet or regression in ability to perform age-appropriate motor milestones; or

iii) Proximal weakness; or

iv) Weakness in trunk righting/derotation; or

v) Hypotonia; or

vi) Absence of deep tendon reflexes; or

vii) Failure to gain weight appropriate for age; or

viii) Any active chronic neurogenic changes; or

ix) A compound muscle action potential below normative values for an age-matched child.

Defined signs and symptoms of type IIIa SMA are:

i) Onset between 18 months and 3 years of age; and

ii) Failure to meet or regression in ability to perform age-appropriate motor milestones; or

iii) Proximal weakness; or

iv) Hypotonia; or

v) Absence of deep tendon reflexes; or

vi) Failure to gain weight appropriate for age; or

vii) Any active chronic neurogenic changes; or

viii) A compound muscle action potential below normative values for an age-matched child.

Recognised hospitals in the management of SMA are Lady Cilento Children's Hospital (Brisbane), Royal Children's Hospital Melbourne, Monash Children's Hospital (Melbourne), John Hunter Hospital (Newcastle), Sydney Children's Hospital Randwick, Children's Hospital at Westmead, Adelaide Women and Children's Hospital and Perth Children's Hospital.

Application for authorisation of initial treatment must be in writing and must include:

(a) a completed authority prescription form; and

(b) a completed Spinal muscular atrophy PBS Authority Application - Supporting Information Form which includes the following:

i) specification of SMA type (I, II or IIIa); and

(ii) sign(s) and symptom(s) that the patient has experienced; and

(iii) patient's age at the onset of sign(s) and symptom(s).

Treatment Phase: Continuing treatment - Maintenance

Treatment criteria:

Must be treated by a specialist medical practitioner experienced in the diagnosis and management of SMA associated with a neuromuscular clinic of a recognised hospital in the management of SMA; or in consultation with a specialist medical practitioner experienced in the diagnosis and management of SMA associated with a neuromuscular clinic of a recognised hospital in the management of SMA; or initiated by a specialist medical practitioner experienced in the diagnosis and management of SMA associated with a neuromuscular clinic of a recognised hospital in the management of SMA.

Clinical criteria:

- Patient must have previously received PBS-subsidised treatment with this drug for this condition,

AND

- The treatment must be given concomitantly with standard of care for this condition,

AND

- The treatment must be ceased when invasive permanent assisted ventilation is required in the absence of a potentially reversible cause while being treated with this drug.

  Recognised hospitals in the management of SMA are Lady Cilento Children's Hospital (Brisbane), Royal Children's Hospital Melbourne, Monash Children's Hospital (Melbourne), John Hunter Hospital (Newcastle), Sydney Children's Hospital Randwick, Children's Hospital at Westmead, Adelaide Women and Children's Hospital and Perth Children's Hospital.

  Invasive permanent assisted ventilation means ventilation via tracheostomy tube for greater than or equal to 16 hours per day.