SMC Scottish Medicines Consortium
Advising on new medicines for Scotland
www.scottishmedicines.org.uk
NHS SCOTLAND
Delta House • 50 West Nile Street • Glasgow • G1 2NP • Tel 0141 225 6999 • Chairman: Dr Alan G MacDonald

nusinersen 12mg solution for injection (Spinraza®) SMC No 1318/18

Biogen Idec Ltd

6 April 2018

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in NHS Scotland. The advice is summarised as follows:

ADVICE: following a full submission considered under the ultra-orphan process

nusinersen (Spinraza®) is accepted for restricted use within NHS Scotland.

Indication under review: for the treatment of 5q spinal muscular atrophy (SMA).

SMC restriction: patients with symptomatic type 1 SMA (infantile onset)).

In randomised, controlled, phase III studies of children with SMA, nusinersen treatment was associated with significant improvements in motor function compared with a sham injection. In infants with type I SMA, nusinersen significantly prolonged the time to permanent assisted ventilation or death.

This SMC advice takes account of the benefits of a Patient Access Scheme (PAS) that improves the cost-effectiveness of nusinersen. This advice is contingent upon the continuing availability of the PAS in NHS Scotland or a list price that is equivalent or lower.

This advice takes account of the views from a Patient and Clinician Engagement (PACE) meeting.

The license holder has indicated their intention to resubmit.

Overleaf is the detailed advice on this product.

Chairman
Scottish Medicines Consortium

Indication

For the treatment of 5q spinal muscular atrophy (SMA).[1]

Dosing Information

The recommended dosage is 12mg administered by intrathecal injection over one to three minutes. New treatment should be initiated as early as possible after diagnosis with four loading doses on days 0, 14, 28, and 63, followed by maintenance doses administered every four months thereafter. It is recommended that the volume of cerebral spinal fluid, equivalent to the volume of nusinersen to be injected, is removed prior to administration.

Treatment with nusinersen should only be initiated by a physician with experience in the management of spinal muscular atrophy (SMA). Treatment should be administered by health care professionals experienced in performing lumbar punctures. Information on long term efficacy is not available. The need for continuation of therapy should be reviewed regularly and considered on an individual basis depending on the patient's clinical presentation and response to therapy.[1]

Product availability date

May 2017

Nusinersen meets SMC ultra-orphan criteria.

Background

Spinal muscular atrophy (SMA) is an inherited, autosomal recessive, neurodegenerative disorder resulting from deletions or mutation in the gene (*SMN1)* that codes for the survival of motor neuron (SMN) protein. This reduces levels of the SMN protein leading to a loss of spinal (and lower bulbar) motor neurons and progressive muscle weakness. A second SMN gene (*SMN2*) produces a shortened and less functional SMN protein. SMA is a clinical spectrum of disease with disease severity linked to fewer numbers of *SMN2* gene copies and a younger age of symptom onset. Five clinical subtypes (type 0, I, II, III and IV) have been classified according to age of onset and the patient's maximal functional status prior to degeneration. Prognosis worsens the earlier the age of onset of symptoms. Nusinersen is an antisense oligonucleotide drug that modifies pre-messenger ribonucleic acid (RNA) splicing of *SMN2* to promote retention of exon 7. Translation of the pre-messenger RNA produces functional, full-length SMN protein.[1-5]

The submitting company has requested that SMC considers nusinersen when positioned for use in patients with infantile-onset SMA (those who have or are most likely to develop type 1 SMA), and in patients with later-onset SMA (those who have or who are most likely to develop type II or III SMA). The economic analysis excluded use of nusinersen in pre-symptomatic SMA and therefore only relates to patients who have type I SMA (infantile onset) and who have type II and III SMA (later-onset).

Nusinersen for use in this indication has been considered by SMC using its decision-making framework for the assessment of ultra-orphan medicines.

Nature of condition

Five clinical subtypes of SMA have been classified according to age of onset and the patient's maximal functional status prior to degeneration. The submitting company has requested that SMC considers nusinersen when positioned for use in patients with type I, II or III SMA.

Patients with type I SMA, "non-sitters", present up to six months of age with symptoms such as hypotonia, weakness, poor feeding and then respiratory impairment. Without respiratory support, patients with type I SMA rarely survive beyond two years of age. Type I SMA is the most common type and accounts for approximately 50% of new diagnoses of SMA. Patients tend to have two or three copies of the *SMN2* gene.

Patients with type II SMA develop symptoms between six and 18 months of age and they achieve a maximal motor milestone of sitting independently. Rarely some can stand but patients are unable to walk unsupported. Life expectancy is reduced and this can range from two to over 40 years of age. Patients can develop proximal weakness, hypotonia and skeletal changes such as scoliosis. Respiratory impairment can occur but it tends to be milder than the impairment seen in type I SMA.

Patients with type III SMA develop symptoms between 18 months and adulthood and this is the least severe of the paediatric subtypes. Patients have an almost normal life expectancy and reach a motor milestone of being able to walk independently. Motor weakness develops slowly in patients with type III SMA. Approximately half of patients with type IIIa (onset between 18 and 36 months) lose ambulation in 10 years, whereas 90% of patients with type IIIb (onset >36 months) are still walking after 20 years.[3-6]

There are no specific treatments for SMA and supportive management includes respiratory, nutritional, orthopaedic / rehabilitation, and eventually palliative care.[4, 7, 8] Clinical experts consulted by SMC considered that there is unmet need for a disease modifying treatment for people living with SMA.

A patient and clinician engagement (PACE) meeting was held to consider the added value of nusinersen in the context of treatments currently available in NHS Scotland. At the PACE meeting, attention was drawn to the fact that SMA is a complex, progressive, neuromuscular condition. It is associated with multiple complications requiring complex medical and supportive care. Managing SMA is physically, emotionally and practically demanding for the person with SMA, their family and carers. Supportive care includes intensive physiotherapy routines to maintain / support health. People become increasingly reliant upon supportive aids such as non-invasive ventilation, wheelchairs, specialised beds, hoists, standing supports and adaptive aids to assist in activities of daily living. The physical debilitation associated with SMA ultimately reduces the person's ability to live independently and can affect their inclusion in, and contribution to, society via work.

Impact of new technology

Summary of evidence on comparative efficacy

The key evidence for the company's proposed positioning comprises the phase III studies ENDEAR (CS3B) and CHERISH (CS4). [2, 9]

ENDEAR was a multi-centre, double-blind, randomised, sham-controlled study which investigated the effects of nusinersen in patients with type I (infantile-onset) SMA. Eligible patients were aged up to seven months at screening with a diagnosis of 5q-linked SMA with symptom onset before six-months of age. Diagnosis was genetically-confirmed (either homozygous deletion, homozygous mutation or heterozygous deletion / mutation of *SMN1*) and patients were required to have two copies of the *SMN2* gene. Patients were at least in the third percentile for body weight, receiving adequate hydration and nutrition (with or without gastrostomy), and having medical care in accordance with the consensus statement for standard of care in SMA.[2]

Patients were randomised in a ratio of 2:1 to receive nusinersen by intrathecal injection (n=80) or sham injection (n=41). Randomisation was stratified by disease duration at screening (≤12 weeks or >12 weeks from symptom onset). The dose of nusinersen was based on the estimated volume of cerebrospinal fluid for the child's age that was equivalent to a dose of 12mg in a person ≥2 years of age (Table 1). Four loading doses (or sham skin prick) were given on days 1, 15, 29, and 64, followed by maintenance doses administered every four months thereafter. Dedicated study personnel, aware of study assignment, administered the injection; parents and investigators responsible for assessments were not present for the procedure, maintaining study blinding.[2]

Table 1: Dose of nusinersen administered to children ≤2 years of age in the ENDEAR study.[2]

Age at time of dose	Estimated CSF volume	Injection volume	Dose
0 to 3 months	120mL	4mL	9.6mg
3 to 6 months	130mL	4.3mL	10.3mg
6 to 12 months	135mL	4.5mL	10.8mg
12 to 24 months	140mL	4.7mL	11.3mg

CSF = cerebrospinal fluid

There were two co-primary endpoints: the proportion of patients achieving a motor-milestone response, and event-free survival (time to death or the use of permanent assisted ventilator support [tracheostomy or ventilator support for at least 16 hours per day for more than 21 consecutive days, in the absence of an acute reversible event]).[2]

Motor-milestone response was defined as an improvement in at least one category of section 2 of the Hammersmith Infant Neurological Examination (HINE-2), and more categories with improvement than categories with worsening function. HINE-2 was assessed at screening, and after two, six, 10 and 13 months of follow-up. HINE-2 categories were marked on a scale 0 up to 4, with each point representing an incremental step in achieving motor milestones in the category. Seven of the eight HINE-2 categories were assessed (kicking, head control, rolling, sitting,

crawling, standing and walking); voluntary grasp was excluded from the assessments. Improvement in each category was an increase in score of at least one point, with the exception of kicking in which a response was an increase of at least two points or achievement of full score.[2]

An interim analysis of the motor milestone co-primary outcome was pre-specified once approximately 80 patients had been enrolled in the study for at least six months. At this data cut-off (June 2016, n=78), a motor-milestone response was achieved in 41% (21/51) of nusinersen patients and in 0% of control patients. The difference was statistically significant (p<0.001) and resulted in early termination of the study upon the recommendation of an independent data and safety monitoring board.[2]

In the final analysis set (data cut-off November 2016, n=110), for patients who had been enrolled at least six months before the data cut-off, the motor-milestone response rate was 51% (37/73) in the nusinersen group. 22% of nusinersen patients achieved full head control, 10% achieved supine to prone rolling, 8% achieved independent sitting (5% stable sit and 3% able to pivot / rotate whilst seated) and 1% achieved standing with support. No patients in the control group (0/37) achieved a milestone response. Treatment effect at this cut-off was not formally statistically tested due to statistical significance at the interim analysis.[2]

Event-free survival was significantly prolonged with nusinersen treatment when compared with control;[2] results and secondary endpoints are presented in Table 2.

Table 2: Event-free survival and secondary outcomes at the final analysis data cut-off (November 2016) in the ENDEAR study[2, 4]

Outcome		nusinersen (n=80)	sham control (n=41)
Event-free survival	Event rate	39%	68%
	Median event-free survival	NR	22.6 weeks
	Hazard ratio (95% CI)	0.53 (0.32 to 0.89), p=0.005	
Secondary Outcomes			
CHOP-INTEND	Mean score at baseline	26.63	28.43
	Response rate*	71% (52/73) (p<0.001 vs. control)	2.8% (1/37)
Overall survival	Event rate	16%	39%
	Median survival	NR	NR
	Hazard ratio (95% CI)	0.37 (0.18 to 0.77), p=0.004	
Use of permanent assisted ventilation	Event rate, %	23%	32%
	Median time to event	NR	NR
	Hazard ratio (95% CI)	0.66 (0.32 to 1.37), p=0.13	

Proportions based on ITT population unless noted in table. CI = confidence interval, NR = not reached, CHOP-INTEND = Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (16-item, 64-point validated motor assessment; higher scores indicate greater motor skill), * response defined as ≥4-point improvement in score.

The CHERISH study investigated the effects of nusinersen in patients with type II or type III (later-onset) SMA. This was a multi-centre, randomised, sham-controlled, double-blind study. Eligible patients were aged between two to 12 years of age with a diagnosis of 5q SMA with symptom onset after six-months of age. Diagnosis was genetically-confirmed (either homozygous deletion, homozygous mutation or heterozygous deletion / mutation in *SMN1*). Patients could sit independently, but had never walked independently, they had an estimated life expectancy exceeding two years and scored between 10 and 54 in the Hammersmith Functional Motor Scale (expanded) (HFMSE) test on screening.[9, 10]

Patients were randomised in a ratio of 2:1 to receive nusinersen 12mg by intrathecal injection (n=84) or sham injection (n=42). Randomisation was stratified by age at screening (<6 or ≥6 years). Three loading doses (or sham skin prick) were given on days 1, 29, and 85, followed by a maintenance dose administered six months later (at nine months).[4, 9]

The primary endpoint of the study was the change from baseline in HFMSE score at 15 months. The HFMSE is a validated measure of motor function for ambulatory patients with SMA. It comprises 33 items grouped into seven domains (sitting, rolling, transitions / crawling, standing / stepping, transitions / kneeling, squat / jump, and stairs). Each item is scored on a scale of 0 to 2, and the HFMSE total score ranges from 0 to 66; higher scores indicate better motor function. Clinically meaningful improvements in HFMSE total score were defined as an increase in at least three points.[4, 9]

At baseline, mean HFMSE total scores were 22.4 and 19.9 in the nusinersen and control groups respectively. An interim analysis of the primary outcome was conducted once all patients had been in the study for at least six months and at least 39 patients had undergone assessment at 15 months.[9] At the data cut-off (August 2016), 35 nusinersen patients and 19 control patients had a 15-month assessment; imputation was required for 72 patients. At the interim analysis, the least squares mean (LSM) change in HFMSE total score from baseline at 15 months was 4.0 in the nusinersen group and -1.9 in the control group; treatment difference was 5.9 points (95% CI: 3.7 to 8.1), p<0.0001. At the final analysis (data cut-off March 2017), imputation of 15-month assessments were required for 18 (21%) nusinersen patients and for 8 (19%) control patients. The LSM change in HFMSE total score from baseline at 15 months was 3.9 points in the nusinersen group and -1.0 in the control group; treatment difference 4.9 (95% CI: 3.1 to 6.7). This was not formally statistically tested as statistical significance was demonstrated at interim analysis.[11]

Secondary outcomes, listed as per the hierarchical testing procedure, are presented in Table 3.

Table 3: Secondary outcomes in CHERISH, assessed at 15 months[1, 11]

Outcome		nusinersen (n=84)	sham control (n=42)
Achievement of clinically significant improvement in HFMSE total score from baseline (≥3 points)	Proportion	57%	26%
	Odds ratio (95% CI), p-value	5.59 (2.09 to 14.91) p=0.0006	
Achievement of any new WHO motor milestone	Proportion	20% (30/66)	5.9% (2/34)
	Treatment difference (95% CI), p-value	14% (-6.6 to 34.2) p=0.08	
Number of new WHO motor milestones achieved per child*	LSM	0.2	-0.2
Change from baseline in Revised Upper Limb Module test score*	LSM	4.2	0.5
Achievement of the motor milestone of standing alone*	Proportion	1.5%	2.9%
Achievement of the motor milestone of walking with assistance*	Proportion	1.5%	nil

Proportions based on ITT population, unless noted in table. HFMSE = Hammersmith Functional Motor Scale (expanded), CI = confidence interval, WHO = World Health Organisation, LSM = least squares mean *outcomes not formally statistically tested due to failure of previous endpoint to demonstrate statistical significance (as per hierarchical testing procedure)

Clinical Global Impression of change was assessed by investigators and carers. At each visit, greater proportions of patients in the nusinersen group compared with the control group were judged to be either much improved or to have had any improvement.[4, 12]

Interim analysis of the NURTURE study (n=20) provides data for using nusinersen in infants with genetically confirmed 5q SMA with no signs or symptoms of disease. All patients were aged ≤6 weeks at enrolment and had either two or three copies of the *SMN2* gene and a CMAP ≥1 millivolt. At a median follow-up of 317.5 days (range 2 to 524) no patients had died or required respiratory intervention (tracheostomy, or invasive / non-invasive ventilation for ≥6 hours/day for ≥7 days continuously). Motor-function tests (including CHOP-INTEND, HINE milestones and WHO milestones) were considered to be consistent with normal development rather than the expected natural history of type I SMA.[4, 13]

Summary of evidence on comparative safety

In ENDEAR, adverse events (AEs) were reported in almost all patients; 96% (77/80) of nusinersen patients and 98% (40/41) of control patients. AEs which led to discontinuation from the study occurred in 16% and 39% of patients respectively; they all subsequently led to death. The AEs that led to death were predominantly respiratory in nature (9% and 29% of nusinersen and control patients) and this included respiratory failure. The AEs that led to death were judged to be consistent with those observed in SMA type I.[2]

No AEs in either group were determined to be treatment-related; events possibly related to study treatment were reported in 11% of nusinersen patients and 15% of control patients. AEs possibly related to treatment in nusinersen patients were pyrexia (n=2), decrease in body temperature, increase in body temperature, tachycardia, naevus anaemicus, cellulitis, post-procedural swelling, nystagmus and suspected vasculitis (all n=1).[2]

In the CHERISH study, almost all patients experienced an AE; 93% (78/84) of nusinersen patients and 100% of control patients. No patients in either group discontinued treatment due to an AE.[11]

AEs possibly related to study treatment was reported in 29% (24/84) of nusinersen patients and in 9.5% (4/42) of control patients. This was thought to be related to an imbalance in lumbar-puncture related AEs. One patient in the nusinersen group was judged to have an AE related to their treatment (post-sedation nausea [procedural nausea]).[11, 12] Most common serious AEs were: pneumonia (2.4% of nusinersen patients versus 14% of control patients), respiratory distress (2.4% versus 4.8% respectively), influenza (nil versus 4.8%), faecaloma (nil versus 4.8%), and dehydration (nil versus 4.8%).[11]

Summary of clinical effectiveness issues

In the ENDEAR study, clinically important improvements in motor function were observed with nusinersen treatment when compared with control.[2] Motor milestones achieved by children treated with nusinersen were considered by the European Medicines Agency (EMA) to be beyond those seen in patients receiving standard of care, who have a steady deterioration in motor function.[4] The ENDEAR study also demonstrated an approximate 50% reduction in the risk of death or requirement of permanent ventilation. At a median time on study of 280 days for nusinersen patients, 39% of patients had died or required permanent ventilation; median time to event had not been reached.[2]

Motor function improvements were also achieved with nusinersen compared with control in children with type II or type III SMA in the CHERISH study; significantly greater proportions of children had clinically important improvements in motor function (assessed by HMFSE).[9]

Participants from both phase III studies were offered to enrol in an open-label extension study, SHINE, which is expected to finish in 2022.[4]

Clinical outcomes were achieved despite imbalances in baseline characteristics that suggest children in the nusinersen groups in both studies had a greater burden of symptoms associated with the disease.[2, 9]

Subgroup analysis of the ENDEAR study suggests the treatment effect (event-free survival) of nusinersen is better in patients commenced on treatment soon after symptom onset.[2, 4] Subgroup analysis of CHERISH also suggested a greater treatment effect (motor outcomes) in those treated with a shorter disease duration.[4]

Nusinersen was well tolerated; there were no treatment discontinuations related to AEs in the phase III studies. AEs reported in ENDEAR and CHERISH were consistent with SMA. The EMA noted that there may be difficulties, and consequently a risk of AE, associated with intrathecal administration of nusinersen, particularly in very young children and in those with scoliosis. The EMA warned that other antisense oligonucleotides have been associated with renal toxicity, thrombocytopenia and coagulation abnormalities. These toxicities have not been observed with nusinersen during its clinical development, but a class-effect cannot be excluded yet.[4]

There are limitations of the evidence. The dosage regimen in CHERISH was different to the licensed dosing schedule limiting the generalisability of the results. However based on dose-response relationships demonstrated in early phase studies,[4] a greater treatment effect may be expected with use of the licensed dose.

Both studies were stopped early following interim analyses. Event-free survival data from ENDEAR are relatively immature; at the final analysis data cut-off, 49% (59/121) of patients had an event.[2] Since the study was stopped early and patients were transitioned to the open-label extension study SHINE, future analyses of this endpoint are likely to be confounded by treatment switching.

There is also an absence of data to determine if nusinersen delays respiratory deterioration in children with type II or III SMA. Neither study investigated the effect of nusinersen on feeding complications of SMA.

Phase I and II studies provide supporting data for use of nusinersen over two to three years. The SHINE study will provide longer-term outcome data and is expected to finish in 2022.

Children living with type II or III SMA can survive to adulthood; phase I and II studies provide supporting data for nusinersen initiation in adolescents.

Clinical experts consulted by SMC have advised that nusinersen represents a major therapeutic advancement in the management of SMA given the milestones achieved by infants with type I SMA and the prolonged time to death or need for permanent ventilation. They considered the place in therapy was in the treatment of infants with type I SMA.

Clinical experts advised that the introduction of nusinersen may impact on the patient and / or service delivery since the treatment would require admission, allocation of theatre time and the availability of trained specialists to administer the intrathecal dose. Patients with less severe SMA sub-types, who have stable disease may require more frequent review and attendance for administration of nusinersen, compared with current arrangements.

At the PACE meeting, it was noted that clinical study and experience of use in the real-world setting suggests that nusinersen can change the prognosis of all types of SMA and is considered a step change in the management of the condition. Improvement of muscular strength and the arrest of progressive weakness has the potential to improve the quality and dignity of life for patients by allowing them to self-care and prolong their independence. Nusinersen reduces the burden of hospitalisation to manage the complications of SMA, and it is expected that patients treated may have reduced requirement for respiratory support and scoliosis surgery. Risks and discomfort associated with intrathecal injection were considered to be outweighed by the benefits of treatment. Nusinersen would be used in addition to current supportive therapies, and it may prevent the need for many such therapies.

*Other data were also assessed but remain commercially confidential.**

Patient and clinician engagement

A PACE meeting with patient group representatives and clinical specialists was held to consider the added value of nusinersen, as an ultra-orphan medicine, in the context of treatments currently available in NHS Scotland.

The key points expressed by the group were:

- SMA is a devastating, progressive condition characterised by neuromuscular deterioration which can be life-shortening, and is associated with multiple major complications requiring complex medical and supportive care.
- Nusinersen addresses the unmet need for a treatment which alters the progression of SMA. Current management is merely supportive in nature and involves postural / mobility equipment; nutritional and respiratory care; and spinal surgery in addition to traditional therapies such as physiotherapy.
- Nusinersen may increase life expectancy (most notably in type I SMA) and slow the decline of neuromuscular function. This has the potential to improve the quality and dignity of life for patients by allowing them to self-care and prolong their independence.
- Nusinersen may reduce the burden of hospitalisation for complications of SMA, and it is expected that patients treated may have a reduced requirement for respiratory support and scoliosis surgery.
- The condition has a large impact on families and carers who experience physical, emotional and financial stress. Effective, disease-modifying treatment with nusinersen may improve the quality of life of families and carers by easing such pressures.
- The addition of nusinersen may prevent the need for many of the supportive therapies currently provided. Initiation of treatment early following diagnosis / symptom onset would potentially lead to greatest clinical benefit for the individual.
- PACE participants felt that the clinician and patient / parents would be likely to agree a treatment plan at the initiation of treatment including the timeframe for stopping treatment upon failure to stabilise motor deterioration.
- There is established peer support, through the Scottish Muscle Network and UK-wide North Star network, to assist in clinical decision-making and management of this patient group.

Additional Patient and Carer Involvement

We received patient group submissions from the SMA Trust, SMA Support UK and Muscular Dystrophy UK, all three are registered charities. The SMA Trust has not received any funding from pharmaceutical companies in the past two years. SMA Support UK has received 7.9% pharmaceutical company funding in the past two years, including from the submitting company. Muscular Dystrophy UK has received 0.1% pharmaceutical company funding in the past two years, including from the submitting company. Representatives from all three charities participated in the PACE meeting. The key points of their submissions have been included in the full PACE statement.

Value for money

The submitting company presented two cost-utility analyses to evaluate nusinersen in combination with supportive care for (i) infantile-onset (type I SMA) and (ii) later-onset (those who have or who are most likely to develop type II or III SMA). It is worth noting that the economic analyses submitted by the company excludes patients with pre-symptomatic SMA. In both analyses nusinersen with supportive care is compared against supportive care alone, which is termed as 'real world care' (RWC) in the economic models. RWC is reflective of standard of care received by sham-procedure control patients in the ENDEAR and CHERISH studies.

Clinical evidence for the company's infantile model was based on the phase III ENDEAR study, with long term extrapolation for mortality employing other published studies.[2, 14, 15] Clinical evidence for the later-onset model was based on the phase III CHERISH study with long term extrapolation for mortality based upon other published studies. [11, 16]

The infantile model included patients with mean age of 5.6 months, 55% of whom are female, based on ENDEAR. The base case analysis adopted a 40-year time horizon. The later-onset model included patients with a mean age of 43.7 months, 53% of whom are female, based on CHERISH, and adopted an 80-year lifetime horizon.

De novo Markov models were developed for the infantile and later-onset analyses. The models capture life years gained (LYG), quality adjusted life years (QALYs) and costs for each arm. A NHS Scotland and social work perspective is used in the base case analysis. Supplementary analyses also present results from the carer perspective, including utility impacts and costs for carers in the cost per QALY incremental cost-effectiveness ratio (ICER).

The infantile model adopted a 10-state Markov model, following patients from baseline to alternative health states: worsen, stabilise, improve (response based states), and death. From the stable or improved states patients may also transition to milestone based functioning states such as 'sits without support', and 'stands without assistance'. The later-onset model structure is similar to infant-onset, with 10 Markov states, but with modifications to reflect response based and functioning states appropriate for type II and III SMA.

In the short term (the period of follow up in the clinical studies), model transitions are dictated by observed response and milestones in the studies. In the longer term transitions are calculated based on mean scores among small numbers of patients in each 'state', using rate of change within the study period. Rate of change in score observed in nusinersen and control arms in ENDEAR (CHOP INTEND scores) and CHERISH (HFMSE scores) is assumed to continue beyond study follow-up. In the nusinersen arm these are applied to predict further improvements (so that in the nusinersen arm improvements are maintained indefinitely, whereas in the RWC arm a progressive natural history course is assumed; i.e. patients may either remain stable or deteriorate). After improvement there appears to be no progression to poorer states possible in the nusinersen arm, based on this approach.

Life expectancy was calculated by estimation of relative hazards compared to the age-matched general population at the end of follow up in two previously published studies for type I SMA and type I SMA with later-onset milestones and later-onset patients.[14, 15] In the infantile case, achievement of milestones associated with later onset resulted in long term survival being based

on the published study,[14, 15] with an adjustment factor (base case 0.9). In the later-onset model, achievement of milestones associated with type III SMA resulted in long term survival being based on general population mortality, again with an adjustment factor (base case 0.5). Adverse events were not included in either model.

The analysis included medicine acquisition and administration costs for nusinersen (administered via lumbar puncture) as well as SMA management and end of life costs.

Utilities for health states in the later-onset model were derived from mapping PedsQL (measured as part of the CHERISH study among later onset patients) on to the EQ-5D using a published algorithm. Values for the infantile model were based on the later-onset utilities with some adaptation as they were regarded as being sufficiently similarity to infants.

A Patient Access Scheme (PAS) was proposed by the submitting company and was assessed by the Patient Access Scheme Assessment Group (PASAG) as acceptable for implementation in NHS Scotland. SMC would wish to present the with-PAS cost-effectiveness estimates that informed the SMC decision. However, owing to the commercial in confidence concerns regarding the PAS, SMC is unable to publish these results. As such, only the without-PAS figures can be presented.

The base case analysis for infantile-onset estimated an ICER without PAS for nusinersen of £428,964 per QALY compared to RWC. Incremental life years and QALY gains were 5.55 and 5.02 QALYs respectively with nusinersen, with an incremental cost of £2,151,509.

Base case results for the infantile model and a number of scenario analyses, including an analysis which captured carer perspectives (carer costs and utilities), are presented in Table 4.

Table 4: Infantile model results (without PAS for nusinersen)

Analysis	**ICER (£)**	
Base case	428,964	
Including carer perspective	424,502	
ITT population	412,931	
Age at symptom onset <=12 weeks	410,227	
Age at symptom onset >12 weeks	509,907	
Disease duration <=12 weeks	409,213	
Disease duration >12 weeks	414,978	
	Lower ICER	Upper ICER
Discounting Outcomes: 0%, 6%	301,001	534,612
Discounting Costs: 0%, 6%	549,328	371,290
Factor to adjust later-onset mortality risk: 0.72, 1	526,618	350,421
Nusinersen vial price: 5mL 2.4 mg/mL: £60,000, £90,000	344,599	513,328
Alternative Time horizon: 10 years, 30 years	568,564	429,473
Mortality risk factor: 0.5, 1 (base case 0.9)	649,134	350,421
25% who reach treatment plateau progress like RWC	£481,053	
50% who reach treatment plateau progress like RWC	£509,268	
75% who reach treatment plateau progress like RWC	£535,684	

The base case analysis for later-onset estimated an ICER without PAS for nusinersen of £1,624,951 per QALY compared to RWC. Incremental life years and QALY gains were 1.38 and 2.29 QALYs respectively with nusinersen, at an incremental cost of £3,728,246. Base case results for the later-onset model and a number of scenario analyses are presented in Table 5.

Table 5: Later-onset model results (without PAS for nusinersen)

	ICER (£)	
Base case	1,624,951	
Including carer perspective	1,151,867	
	Lower ICER	Upper ICER
Discounting Outcomes: 0%, 6%	520,450	3,040,275
Patient Utility: *Walks unaided:* 0.7, 1	537,609	376,151
Alternative Time horizon: 20 years, 60 years	3,646,210	1,660,229
Mortality risk factor: 0.75, 1	1,228,407	894,932
25% who reach treatment plateau progress like RWC	£2,171,662	
50% who reach treatment plateau progress like RWC	£2,270,128	
75% who reach treatment plateau progress like RWC	£2,371,426	

Key weaknesses with the modelled cost-effectiveness analysis include:

- The company's base case results are based upon assumptions which maintain favourable outcomes for nusinersen. For example improvements seen in the ENDEAR and CHERSH trials for nusinersen are assumed to be maintained indefinitely over the longer term of the analyses. Transition probabilities observed in the study periods (13.5months and 15 months for ENDEAR and CHERISH respectively) for nusinersen are maintained indefinitely rather than applying a natural history rate to the nusinersen data at the end of the trial. Therefore progression of disease on nusinersen is impossible in the long term.
- The analysis restricts the comparator supportive care alone to worsening disease over time. Whilst this may be a reasonable assumption it is not clear that the model should prevent future worsening of disease in treated patients. This appears to be a favourable assumption for nusinersen and potentially overestimates survival and QALY gains in the nusinersen arm base case model.
- There is a lack of long term survival data from ENDEAR and CHERISH studies. In the analyses long term survival modelling is based on previously published studies, along with assumptions on mortality risk which are uncertain and substantially increase the ICER under sensitivity analyses.
- For type I SMA (infantile) a stopping rule applies to 20% of the 1% who have scoliosis surgery, and in type II and III SMA (later-onset) 43% of patients undergo scoliosis surgery and 20% of those discontinue after surgery. The second stopping rule for both infantile and later-onset models is when patients deteriorate to the worsened state (≥4-point worsening from baseline). Beyond study follow-up for the infantile and later-onset models (13 and 15 months respectively) there is no deterioration and patients will remain on therapy for life. The company also referenced that because no patients receiving nusinersen in any of the phase II or phase III trials discontinued treatment, there was no clear stopping rule.
- The ICERs presented for both the infantile (type I SMA) and later-onset (type II and III SMA) models were above conventional levels of cost-effectiveness, and there were additional weaknesses with the economic evaluation as also outlined above.

*Other data were also assessed but remain commercially confidential.**

Impact beyond direct health benefits and on specialist services

An effective treatment may ameliorate the physical and emotional stresses, that families and carers experience, from witnessing the gradual progression of the condition, hospitalisations for complications, and the fear for the future consequences of SMA (such as major scoliosis surgery). In addition, less time required for caring would release more time to spend with other family members and friends. Improvements in the health of the person with SMA can reduce financial pressures by increasing the opportunity for carers to return to, or increase working hours, and reducing the expenditure for equipment and adaptations.

There is established peer support, through the Scottish Muscle Network and UK-wide North Star network, to assist in decision-making and management of this patient group. Policies for safe administration of intrathecal medicines are in place across NHS Scotland. PACE participants reported that, from local experience of use to date, in children with type I SMA, local anaesthetic with or without sedation has facilitated dose administration and a general anaesthetic has not been required.

Standardised assessments (eg CHOP-INTEND and HFMSE) would be used to monitor response. PACE participants felt that an agreement to stop treatment if motor deterioration was not stabilised, would be facilitated by open discussions between the clinician and patient / parents from the outset.

The company provided an analysis which used a wider perspective as noted above.

Costs to NHS and Personal Social Services

Infantile-onset
The submitting company estimated there would be 5 patients eligible for treatment with nusinersen in year 1 rising to 6 patients in year 5 to which confidential uptake rates were applied.

Later-onset
The submitting company estimated there would be 43 patients eligible for treatment with nusinersen in year 1 rising to 48 patients in year 5 to which confidential uptake rates were applied.

SMC is unable to publish the with PAS budget impact due to commercial in confidence issues. A budget impact template is provided in confidence to NHS health boards to enable them to estimate the predicted budget with the PAS.

*Other data were also assessed but remain commercially confidential.**

Conclusion

The Committee also considered the benefits of nusinersen in the context of the SMC decision modifiers that can be applied when encountering high cost-effectiveness ratios and agreed that a number of the criteria were satisfied: the absence of other treatments of proven benefit and a substantial improvement in life expectancy in the type 1 SMA population. In addition, as nusinersen is an ultra-orphan medicine, SMC can accept greater uncertainty in the economic case.

After considering all the available evidence and the output from the PACE process, and after application of the appropriate SMC modifiers, the Committee accepted nusinersen for restricted use in the type 1 SMA population in NHS Scotland.

Additional information: guidelines and protocols

An international consensus statement for the standard of care in SMA was published in 2007.[8] Recommendations cover supportive respiratory care, gastrointestinal / nutritional care, orthopaedic care / rehabilitation, and palliative care. Management decisions require consideration of the individual's / family's goals, balancing quality of life, long-term survival, availability of resources and wishes to prolong care at home rather than in healthcare facilities. It is recommended that treatment options and goals are discussed early in the disease course and regularly reviewed.

Additional information: comparators

There are no relevant comparators.

Cost of relevant comparators

Medicine	Dose Regimen	Cost per year (£)
nusinersen	**12mg administered by intrathecal injection Four loading doses on days 0, 14, 28, and 63 Maintenance doses every four months**	**Year 1 450,000 Subsequent years 225,000**

Doses are for general comparison and do not imply therapeutic equivalence. Costs from BNF online on 20 December 2017. Costs calculated using the full cost of vials / ampoules assuming wastage. Costs do not take any patient access schemes into consideration.

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This assessment is based on data submitted by the applicant company up to and including 16 February 2018.

**Agreement between the Association of the British Pharmaceutical Industry (ABPI) and the SMC on guidelines for the release of company data into the public domain during a health technology appraisal:*
http://www.scottishmedicines.org.uk/About_SMC/Policy_statements/Policy_Statements

Medicine prices are those available at the time the papers were issued to SMC for consideration. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and NHS Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

Patient access schemes: A patient access scheme is a scheme proposed by a pharmaceutical company in order to improve the cost-effectiveness of a medicine and enable patients to receive access to cost-effective innovative medicines. A Patient Access Scheme Assessment Group (PASAG), established under the auspices of NHS National Services Scotland reviews and advises NHS Scotland on the feasibility of proposed schemes for implementation. The PASAG operates separately from SMC in order to maintain the integrity and independence of the assessment process of the SMC. When SMC accepts a medicine for use in NHS Scotland on the basis of a patient access scheme that has been considered feasible by PASAG, a set of guidance notes on the operation of the scheme will be circulated to Area Drug and Therapeutics Committees and NHS Boards prior to publication of SMC advice.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.