



Cost-effectiveness of Nusinersen (Spinraza) for the treatment of 5q spinal muscular atrophy (SMA).

The NCPE has issued a recommendation regarding the cost-effectiveness of nusinersen (Spinraza). Following NCPE assessment of the applicant's submission, nusinersen (Spinraza) is not considered cost-effective for the treatment of 5q spinal muscular atrophy at the submitted price.

The HSE asked the National Centre for Pharmacoeconomics (NCPE) to carry out an assessment of the applicant's (Biogen Idec Ireland Ltd.) economic dossier on the cost effectiveness of nusinersen (Spinraza). The NCPE uses a decision framework to systematically assess whether a technology is cost-effective. This includes clinical effectiveness and health related quality of life benefits, which the new treatment may provide and whether the cost requested by the pharmaceutical company is justified.

Following the recommendation from the NCPE, the HSE examines all the evidence which may be relevant for the decision; the final decision on reimbursement is made by the HSE. In the case of cancer drugs the NCPE recommendation is also considered by the National Cancer Control Programme (NCCP) Technology Review Group.

About the National Centre for Pharmacoeconomics

The NCPE are a team of clinicians, pharmacists, pharmacologists and statisticians who evaluate the benefit and costs of medical technologies and provide advice to the HSE. We also obtain valuable support from clinicians with expertise in the specific clinical area under consideration. Our aim is to provide impartial advice to help decision makers provide the most effective, safe and value for money treatments for patients. Our advice is for consideration by anyone who has a responsibility for commissioning or providing healthcare, public health or social care services.

Summary

In October 2017 Biogen Idec Ireland Ltd submitted an economic dossier on the cost-effectiveness of nusinersen (Spinraza) for the treatment of 5q spinal muscular atrophy (SMA). A marketing authorisation for nusinersen was obtained from the EMA on the 30th May 2017.

5q Spinal muscular atrophy (SMA) is an autosomal recessive neuromuscular disorder characterised by progressive muscle atrophy and weakness. SMA presents across a spectrum of subtypes and varying severities based on age of symptom onset with greater disease severity linked to younger age of onset. SMA is caused by a homozygous deletion or mutation in the survival motor neurone 1 (SMN 1) gene, which results in decreased expression of the survival motor neurone (SMN) protein and degeneration of motor neurones in the spinal cord and brain stem. The survival motor neurone 2 (SMN 2) gene also encodes the SMN protein however 90% to 95% of the translated protein is truncated and non-functional as a result of aberrant splicing.

Nusinersen is an antisense oligonucleotide drug that modifies pre-mRNA splicing of SMN 2 to promote increased production of full length SMN protein and is the first disease modifying therapy indicated for the treatment of all patients with 5q SMA. It is in the form of a solution for injection; 12mg per 5 ml (2.4 mg/ml) in a single vial. The recommended licensed dose is 12 mg (5ml) per administration which is an intrathecal bolus injection over 1 to 3 minutes following lumbar puncture.

1. Comparative effectiveness

The submitted clinical evidence for nusinersen consisted of 8 clinical trials including two phase III trials ENDEAR in infantile onset SMA and CHERISH in later onset SMA, two phase II studies including the NURTURE trial in pre-symptomatic infants and study CS3A in infants aged 3 weeks or older up to 7 months. CS2 is a phase I/II study in children aged 2 to 15 years with symptomatic SMA and three phase I studies CS1, CS10 and CS12 were also presented. All the submitted clinical evidence was considered by the NCPE review group in this pharmacoeconomic assessment. Three studies, ENDEAR, CHERISH and NURTURE were

selected for detailed descriptions as these summarise the main evidence for the patient populations considered by the CHMP at product registration

The ENDEAR study was a randomised, double-blind, sham-controlled, phase III efficacy and safety trial of nusinersen in infantile onset SMA [8]. The primary end points were a motor-milestone response (defined according to results on the Hammersmith Infant Neurological Examination Module 2 [HINE-2]) and event-free survival (time to death or the use of permanent assisted ventilation [defined as tracheostomy or ≥ 16 hours ventilator support per day for > 21 days]). Secondary end points included overall survival and subgroup analyses of event-free survival according to disease duration at screening.

A total of 149 infants were screened and 122 were randomised (81 to the nusinersen group and 41 to the control group). In the final analysis 37 of 73 infants (51%) in the nusinersen group had a motor-milestone response versus 0 of 37 infants (0%) in the control group. For event free survival, 39% of infants in the nusinersen group (31/80) and 68% in the control group (28/41) had died or received permanent assisted ventilation. Therefore the risk of death or use of permanent assisted ventilation was 47% lower in the nusinersen group; $p = 0.0005$. A significantly lower percentage of infants in the nusinersen group died as compared with the control group i.e. 16% versus 39%. There was no significant difference in the requirement for permanent assisted ventilation between the groups (23% in the nusinersen group versus 32% in the control group; $p = 0.13$). Event free survival was higher among infants who had shorter disease duration at screening.

In the CHERISH study 126 patients with later onset SMA were randomised in a 2:1 ratio to receive 12 mg nusinersen intrathecally ($n=84$) or a sham procedure (control group; $n=42$) to determine the clinical efficacy, safety, tolerability and pharmacokinetics of nusinersen. The primary endpoint of the CHERISH study was the change from baseline in HFMSE score at 15 months. There was a significant 5.9 point difference in the primary endpoint HFMSE score at the interim analysis favouring nusinersen treatment and the study was stopped shortly after this finding. The final analysis also demonstrated a significant difference in the HFMSE score at 4.9 points. In relation to secondary endpoints the proportion of HFMSE responders was

significantly greater in the nusinersen group at 56.8% compared to 26.3% in the control group.

The NURTURE trial is a phase II open-label, multicentre, multinational, single arm study of 20 infants with pre-symptomatic, genetically diagnosed SMA who are deemed most likely to develop infantile onset or later onset SMA. Patients were enrolled at 6 weeks of age or younger and received nusinersen intrathecally on days 1, 15, 29, 64 with maintenance dosing on days 183, 302, 421, 540, 659 and 778. The primary endpoint was event-free survival i.e. time to death or respiratory intervention (defined as invasive or non-invasive ventilation for > 6 hours per day continuously for ≥ 7 days or tracheostomy).

From baseline to last study visit, 16 of 18 subjects achieved and maintained improvements in the CHOP INTEND score, which was deemed inconsistent with the natural history of SMA. Most subjects (n=11/18) had an increase of ≥ 4 points in the CHOP INTEND score when compared to baseline and 7 of the 18 achieved the highest attainable CHOP INTEND score at the data cut-off date. Compared to baseline, improvements in HINE motor milestones were achieved in 16 out of 18 subjects. At data cut off, 12 subjects were sitting independently, 9 were standing with or without support and 6 were walking with or without support.

The SHINE trial is a phase II open-label, multicentre, multinational, extension study for up to 274 patients who previously participated in ENDEAR, CHERISH or CS12. The study started in November 2015 and final data collection for the primary outcome measure is expected to be August 2022. The primary objective is to evaluate the long term safety and tolerability of nusinersen administered intrathecally.

2. Safety

Nusinersen was well tolerated in all the study populations. An integrated safety analysis was conducted using unblinded data from the eight studies presented above. Across the eight studies 260 infants and children were treated with nusinersen for a total of 355 patient years. The dossier highlights that only one treatment related adverse event occurred in a patient with later onset SMA in the CHERISH trial (nausea post sedation).

Most adverse events reported in infants and children exposed to nusinersen were consistent with the nature and frequency of events occurring in the context of SMA. Overall, the fatality rate of the nusinersen treated subjects was less than half that of the sham controlled subjects (7% versus 19%). The most common adverse events were respiratory or infectious in nature and were consistent with events typically observed in SMA patients.

3. Cost effectiveness

The cost effectiveness of nusinersen in infantile and later onset SMA was assessed using two separate Markov models, produced in MS Excel with a lifetime horizon. Cycle length in the two models was governed by the timing of motor function/motor milestone assessments and of maintenance dose administration in the pivotal trials. For infantile onset SMA the health states aimed to capture important elements of patient functioning and in addition to the ENDEAR trial used current knowledge of the natural history of SMA. The Markov model structure for later onset SMA reflects the starting position of patients in the CHERISH trial as well as current knowledge of the natural history of SMA and the potential effect of nusinersen on the course of the disease. Results in the base case represent the perspective of the Health Service Executive (HSE) however the model incorporates an option to include a wider societal perspective as a secondary analysis.

The difficulty in obtaining quality of life data in the infantile onset patient population is acknowledged. Utilities were obtained using PedsQL data collected as part of the CHERISH trial among later onset SMA patients and formed the basis of utility estimates in the infantile SMA model. Utilities for later onset SMA were derived from the CHERISH trial as PedsQL data was collected as part of that study which enabled mapping on to the EQ5D scale using a published mapping algorithm

The model incorporates cost data in relation to drug acquisition, health care costs by type of care, physician visits, hospitalisations, health materials e.g. prosthesis, wheelchair and portable oxygen costs and costs of social services including day care costs, occupational

therapy and physiotherapy costs. Drug costs were presented as costs per patient per year. The price per dose of nusinersen to the wholesaler is €83,300 and 6 doses are administered in year one to patients with infantile SMA. The final reimbursement price per patient in year 1 for infantile SMA, excluding VAT is €516,516 having taken into account wholesaler margin, patient care fees and rebates. Year 1 reimbursement price including VAT was estimated at €641,466 per patient. The final reimbursement price for subsequent years (ex VAT) was €258,630 per patient per year. When VAT was included the reimbursement price for subsequent years was €321,105. Annual health care costs by type of care was subdivided according to milestones consistent with SMA e.g. annual respiratory care costs varied from €23,958 for milestones consistent with infantile SMA, €9,246 for milestones consistent with type II SMA and €3,165 for milestones consistent with type III SMA. Corresponding costs for gastrointestinal care were € 3,306 in infantile SMA, €2,977 for type II SMA and €666 for type III SMA.

For nutritional care the annual cost was €1,590 for infantile SMA, €2,084 for type II SMA and €451 for type III SMA. Annual costs for orthopaedic care were estimated at €2,614 for infantile SMA, €2,433 for type II SMA and €595 for type III SMA. Administration costs were also provided for lumbar puncture procedures carried out in the inpatient setting (range €1,155 to €2,128), outpatient setting (range €257 to €727) and as a day case (range €747 to €2,140). A discount rate of 5% was applied in line with current guidelines. In the sensitivity analysis, the discount rate on costs and outcomes was set to 0% and 10%.

The base case deterministic incremental analysis of costs and outcomes for nusinersen versus standard care in infantile SMA demonstrated an incremental cost effectiveness ratio (ICER) of €501,069/QALY or €453,079/LYG. Probabilistic sensitivity analysis for infantile SMA resulted in ICERs of €498,480/QALY and €450,580/LYG. Subgroup analysis indicated improved cost-effectiveness when treatment was started earlier i.e. disease duration less than 12 weeks (€476,596/QALY) and where age at symptom onset was less than 12 weeks. Sensitivity analysis indicated that the ICER was greatly impacted by the discount rate applied, mortality risk factor, nusinersen vial price and patient utility. Considering the patient and caregiver perspective resulted in an ICER of €247,682/QALY.

For later onset SMA the incremental cost-effectiveness ratio was estimated at €2,107,108/QALY or €3,906,818/LYG. Probabilistic analysis resulted in ICERs of €2,163,798/QALY and €3,982,548/LYG. When patients and carers perspective is considered the ICER falls to €1,037,003/QALY. Sensitivity analysis of later onset SMA indicates that the ICERs are most sensitive to discount rates, patient utility and the nusinersen vial price.

4. Budget impact

The 5 year gross budget impact for nusinersen in infantile SMA was estimated at € 19.57 million if VAT is included. For later onset SMA the 5 year gross budget impact was € 18.61 million inclusive of VAT. Therefore the total 5 year gross budget impact, inclusive of VAT, for nusinersen treatment is approximately € 38.18 million. The 5 year net budget impact associated with nusinersen treatment in infantile SMA is €19.89 million, inclusive of VAT. The cost components in the net calculation include drug administration and disease management costs. In later onset SMA the net 5 year budget impact, inclusive of VAT was €17.99 million. Therefore the total 5 year net budget impact associated with nusinersen treatment is estimated at € 37.88 million.

5. Conclusion

This economic evaluation indicates that nusinersen cannot be considered cost-effective for the treatment of infantile or later onset SMA. A 10 fold reduction in the price of nusinersen for the treatment of infantile SMA is required to produce an ICER approaching the € 45,000/QALY threshold. For later onset SMA nusinersen is less cost-effective and a 20 fold price reduction results in an ICER just under € 100,000/QALY. The 5 year net budget impact is estimated at €37.88 million. Therefore reimbursement of nusinersen is not recommended at the submitted price.