NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Nusinersen for treating spinal muscular atrophy [NICE Technology Appraisal 588]

Clinical criteria evidence review

Final outcome summary

Opening remarks

1. This summary should be read together with the following papers published on the NICE website:

   - Evidence review outline of objectives
   - Evidence submission from Biogen (the company)
   - External Assessment Centre (EAC) report
   - Managed Access Oversight Committee (MAOC) recommendation report
   - NICE evidence review summary slides.

Outcome

2. Following a review of significant new evidence concerning the clinical criteria for nusinersen it is recommended that the:

   a. Clinical eligibility criteria within the nusinersen managed access agreement be extended to all patients who are non-ambulant with type III Spinal Muscular Atrophy (SMA); and

   b. Existing stopping rule for patients who are non-ambulant with type III SMA who lose ambulation after 12 months of treatment should be removed.

Background of the review

NICE's recommendation for managed access

3. In July 2019, NICE recommended nusinersen as an option for treating 5q SMA only if people have pre-symptomatic SMA, or SMA types I, II or III and the conditions in the MAA are followed.

4. The committee did not recommend nusinersen as an option for treating SMA type 0 and SMA type IV as the company did not present clinical evidence for these subgroups.

5. The clinical evidence presented to NICE's committee specifically excluded those who had gained independent ambulation and no evidence was presented on those who had since lost independent ambulation.

6. For this reason the clinical criteria were developed with clinical expert involvement using the latest evidence available at the time the recommendation and where there was evidence of patient benefit. Therefore, the MAA included the following clinical criteria:

    - "If gained independent ambulation prior to initiation of therapy must still be independently ambulant, with the exception paediatric patients who have lost independent ambulation in the previous 12 months" (defined as prior to 28th July 2019)

    - "Independent ambulation is defined as per the WHO definition: patient takes at least five steps independently in upright position with the back straight. One leg moves forward while the other supports most of the body weight. There is no contact with a person or object"

7. Patients with type III SMA who had lost independent ambulation over 12 months prior to the MAA publication were not eligible to start treatment with nusinersen as part of the MAA.

8. Exceptionally for a MAA, an evidence review clause was included in the final MAA, agreed between NHS England and NHS Improvement and Biogen, to account for the lack of clinical evidence at the time of the NICE technology appraisal concerning Type III SMA patients who are no longer ambulant.

9. Clause 4.2 of the final published MAA is as follows:

    - "The MAA Oversight Committee will consider any significant new evidence made available by Biogen in relation to the non-ambulant Type III SMA patients that may impact the eligibility criteria of the MAA. This does not commit any stakeholder to making an amendment to the MAA unless justified"

10. The MAA review clause 4.2 is a commitment by NICE to ensure any significant new evidence that becomes available and that may affect the treatment eligibility criteria within the MAA is reviewed for patients with non-ambulant type III SMA.

Clinical eligibility criteria evidence review

11. The nusinersen clinical eligibility criteria evidence review is a bespoke process that has been developed as a onetime decision-making point arising out of the terms of the MAA.

12. The review process and outline of objectives were developed with input from patient groups, clinicians, the company and NHS England and NHS Improvement to:

    - Support the decision-making role of the MAOC
    - Enable new evidence to be considered during the period of the MAA
    - Align with NICE's core values of transparency, independence, quality and scientific rigour.

13. The outline of objectives for the evidence review was developed with input from the MAOC and agreed by all MAOC members in a written declaration.

14. An overview of the evidence review process steps and a timeline are available on the nusinersen topic webpage of the NICE website: https://www.nice.org.uk/guidance/ta588/evidence

Why are the clinical criteria expanding?

15. During the evidence review new evidence was presented that demonstrated that stabilisation of motor function (rather than improvement) was a meaningful clinical outcome for patients who are non-ambulant with type III SMA.

16. The results published in Maggi et al (2020)[1] demonstrate stabilisation of Hammersmith Functional Motor Scale Expanded and (Revised) Upper Limb Module in non-ambulant type III SMA patients treated with nusinersen.

17. The MAOC agreed that stabilisation of motor function is a valuable and realistic outcome for this patient group, and that regaining the ability to walk was too high a threshold.

18. Therefore, the current MAA stopping criteria that requires type III patients to stop treatment if they lose ambulation was found to be unreasonable and it was recommended that this clinical criterion be removed from the MAA.

[1] Maggi L, Bello L, Bonanno S, et alNusinersen safety and effects on motor function in adult spinal muscular atrophy type 2 and 3Journal of Neurology, Neurosurgery & Psychiatry 2020;91:1166-1174.

Further considerations for the NICE re-appraisal of nusinersen

19. Reviewing clinical evidence only as part of this review has highlighted further considerations for the NICE re-appraisal of nusinersen at the end of the period of managed access, including:

- Cost effectiveness was not in scope for this review and subsequently no analyses of cost effectiveness were presented. The NICE re-appraisal of nusinersen will evaluate both the clinical and cost effectiveness of nusinersen in the licenced population using NICE's process and methods for technology appraisal in place at the time of the invitation to participate. Therefore, the company (Biogen) will need to demonstrate that nusinersen is clinically and cost effective for the treatment to be recommended by NICE for routine use on the NHS.

- Clinical uncertainties that were identified by the NICE committee in the original nusinersen appraisal remain. Further efforts from all parties of the MAA must focus on:
  - Patient Report Outcomes data to ensure that the patient voice and experience can be considered along with the clinical evidence.
  - Evidence on the long-term benefits of treatment, and how this differs by SMA subtype.
  - More evidence on the natural history of the disease.

20. Further data collection during the remainder of the managed access period will need to address these uncertainties so that the NICE committee can make the most informed assessment on whether nusinersen will be available to access via the NHS following a further appraisal of its clinical and cost effectiveness.

Implementation

21. The clinical criteria used by NHS clinicians to assess the eligibility of patients for treatment with nusinersen have been updated to allow access for patients who are non-ambulant with type III SMA.

22. A variation to the MAA has been agreed with input from the NHS England Clinical Panel to reflect the changes recommended as part of this review.

23. NHS capacity to deliver nusinersen to the newly eligible group of patients will expand further as COVID restrictions on social distancing ease.

Authors

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