Recommendations from the Managed Access Oversight Committee

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

Clinical eligibility criteria evidence review

Opening remarks

1. This document summarises points raised by members of the Managed Access Oversight Committee (MAOC) on 8 March 2021 in response to the evidence report provided by the External Assessment Centre (EAC) CEDAR dated 22 February 2021.

2. This document should be read along with the evidence report provided by the External Assessment Centre (EAC) CEDAR.

3. The EAC recommended that, due to the small amount of evidence the low quality of the evidence and apparent low efficacy of nusinersen in non-ambulant type III SMA patients, the current Managed Access Agreement (MAA) is not extended to include the administration of nusinersen to non-ambulant type III Spinal Muscular Atrophy (SMA) patients. For further detail please refer to the EAC evidence report.

Recommendation of the Managed Access Oversight Committee

4. The MAOC do not support the recommendation of the EAC and instead recommend that the nusinersen managed access clinical criteria should be revised to enable access to all non-ambulant type III SMA patients who meet the starting criteria within the MAA.

Why the Managed Access Oversight Committee made this recommendation

5. The MAOC considered whether there is sufficient new evidence in relation to non-ambulant type III SMA patients that would allow them to be included within the ongoing Managed Access Agreement.

6. The MAOC heard that the EAC considered that the evidence submitted was not of sufficient quality for decision-making and furthermore did not demonstrate that that there would be a similar clinical benefit for those who had lost the ability to walk independently compared to those who had never gained the ability to walk independently.

7. On reviewing the evidence, the MAOC considered that the objectives of the interim review did not allow for the evidence to be considered fairly. They highlighted:

- The criteria applied in assessing the quality of the evidence for decision-making was not considered in the context of SMA being a rare disease.
- The current SMA classification systems was never intended to distinguish between groups of patients for commissioning purposes as the biology of the disease is the same for all patients – the distinction being made in the evidence between groups of patients is not meaningful from a patient perspective.
- The thresholds for clinically meaningful benefit in the research, which has been relied upon by the EAC, do not account for the benefits of treatment that patients report.
- Additionally, the framing of the question does not reflect that stabilisation (as opposed to an improvement) for type III SMA patients who had lost independent ambulation is the aim of treatment for patients whose disease state has progressed.
- The patient voice was not considered with the clinical evidence.

8. The MAOC unanimously considered that the evidence presented:

- Demonstrated that there was clinical benefit of nusinersen treatment for type III SMA patients who had lost independent ambulation.
- Is sufficient for the eligibility criteria of the MAA to be extended to include type III SMA patients who had lost independent ambulation.

Managed Access Oversight Committee discussion

9. The key themes discussed by the MAOC are summarised below.

The SMA clinical classification system was never intended to be used as clinical criteria for treatment access

10. The MAOC considered that the current SMA classification system was intended to aid our understanding of disease states, not act as a barrier to access treatment.

11. The boundaries between the different SMA clinical classifications are not clear cut and the application of a type can be a subjective decision.

12. The type III subgroup is the most heterogenous part of the prevalent patient population. it is not reasonable to expect patients who may be different ages, have progressed to different stages or at different paces to achieve the same outcomes from treatment. However, trying to identify smaller subgroups within SMA types would create challenges to the future re-appraisal of nusinersen by reducing the size of the patient groups studied in the evidence.

13. The MAOC noted that the assessment of ambulation is very subjective and can be measured in different ways by the multidisciplinary care team and the patient and/or their carer.

14. Furthermore, the MAA applies the WHO definition for independent which we heard is not commonly used in clinical classification and so has created inconsistencies with regards to nusinersen access.

15. Therefore, restricting access to patients based on SMA type and ambulation status is not supported by the MAOC.

For type III SMA patients who had lost independent ambulation stabilisation (as opposed to improvement) is the aim of treatment

16. The MAOC:

- Noted that the mode of action of nusinersen preserves motor neurones, rather than creating new ones.

- Agreed that preserving function is a valuable and meaningful outcome for patients.

17. Therefore, the MAOC feel that the context of this review which is aiming to confirm whether type III SMA patients who had lost independent ambulation receive a 'comparable clinical benefit' to type II SMA patients is flawed. Instead, the benchmark for these patients should be stabilisation of disease.

18. The MAOC noted that the evidence presented for one of the studies cited by the EAC demonstrates stabilisation of Hammersmith Functional Motor Scale Expanded and (Revised) Upper Limb Module in non-ambulant type III SMA patients treated with nusinersen.

19. The MAOC noted that rather than focusing on whether treatment can provide functional gains for patients it may be best to consider the deterioration that will be prevented by treatment.

The disease assessment scales presented in the evidence have limitations and may not capture everything that is important to patients

20. The MAOC agreed that maintaining upper limb and fine motor skills are in some ways more important to patients, as they are able to maintain a higher degree of independence if they maintain these functional abilities, even if they have lost the ability to walk. The assessment tools used in clinical studies to assess these functions have limitations.

21. The MAOC considered that the current MAA clinical criteria and the objectives of the review (themselves based on the original appraisal decision-problem) place too much emphasis on gaining improvements in walking ability rather than maintaining other elements of independence that the MAOC agreed were of value to patients such as:

- Improved hand function which maintains the ability to write or type
- The ability to manage the hand control on a powerchair
- The ability to lift a cup.

22. The MAOC noted other benefits of treatment which are important to patients but are not captured in the scales presented in the evidence review. For example,

    - Increased energy levels allowing patients to perform better at work or school
    - Being able to transfer independently to a wheelchair
    - Maintaining voice strength and the ability to talk.

23. The clinical members of the MAOC noted that they have observed benefits of treatment in their type III patients that are not always captured by the current assessment scales.

24. The patient group members of the MAOC noted that it is important to remember that we treat patients not scales, and the value of the patient voice and experience.

The patient voice was not considered with the clinical evidence

25. The MAOC were disappointed that the patient reported evidence was not presented in detail by the EAC and agreed that the patient voice and experience should be considered along with the clinical evidence to determine what is a clinically meaningful outcome of treatment from a patient perspective.

26. The MAOC highlighted the impact that being unable to access treatment has on a patient's mental health. This is exacerbated as there are currently no alternative disease modifying treatments and patients may see their friends and siblings being able to access nusinersen treatment leading to conflicting emotions and distress.

27. The MAOC considered that if patients were not receiving a benefit from nusinersen, which requires an invasive procedure to administer, they would choose to discontinue treatment.

The evidence was not fairly considered in the context of a rare disease

28. The MAOC considered that the agreed outline of objectives made the assessment challenging as the evidence base is limited on account of the population of interest being a subgroup of a subgroup with a rare disease.

29. The MAOC highlighted that their expectation of this review was to consider real world evidence as opposed to randomised studies (which they considered unethical in this patient group, as there are available treatments that provide clinical benefits).

30. It was noted that the patient numbers included in the studies represented in the submission are what might be expected for a rare disease. Sample sizes and duration of follow-up in all the real-world studies of nusinersen were impacted by the brief timeframe between licensing of nusinersen in 2017 (when patients could start treatment) and the data-cut required to provide evidence for the review submission (August 2020).

31. The analysis of registry data is based on real world evidence collected from clinical practice across multiple countries and should be considered generalisable to patients in the UK.

32. The MAOC noted that information presented on the natural history of disease was lacking from the evidence base considered in the review and that this information would be important to understanding the clinical benefits of treatment for type III SMA patients who had lost independent ambulation. Clinical representatives noted that outcomes in this patient group are expected to deteriorate over time if untreated.

33. The MAOC highlighted that several publications they considered relevant to this evidence review had not been included in the EAC's report or presentation and requested further detail on reasons why this evidence was omitted.

Additional recommendations from the Managed Access Oversight Committee for consideration

34. The MAOC further recommends that:

- Expectations concerning the quality and quantity of evidence should be reconsidered in the context of a rare disease.
- Real world data provided by Biogen and patient reported evidence should be considered along with the other clinical data.
- Further information on how the EAC selected the publications for assessment in the final EAC report and the reasons for exclusion of any publications.

Next steps

35. The recommendations from the EAC and the MAOC do not align. To facilitate publication of a final decision by NICE, the evidence and the recommendations from the EAC and the MAOC will be referred to Technology Appraisal Committee C for adjudication.

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