NICE National Institute for Health and Care Excellence

Highly Specialised Technologies (HST) criteria checklist

Tofersen for treating amyotrophic lateral sclerosis caused by SOD1 gene mutations

Introduction

The NICE HST criteria checklist is to highlight where a technology meets/partially meets or does not meet the criteria for routing to the HST programme. Its purpose is to show the details of why a technology may not be appropriate for HST evaluation, but also where it has been identified as suitable. For more information, please see section 7 of NICE health technology evaluation topic selection: the manual

Key – does the technology meet the criteria? Please use the colour key to advise if the technology meets the criteria

Met	There is clear and strong evidence that this criterion is met
Not met	There is no evidence or limited evidence that the criterion is met. There is some evidence, or the evidence available is unclear.

MA wording: [redacted] (expected MA wording only)

Number	Criterion	Description of how the technology meets the criteria	Does the technology meet the criteria?
1.	The disease is very rare defined by 1:50,000 in England	Amyotrophic lateral sclerosis (ALS) is the most common type of motor neurone disease (MND). Superoxide dismutase (SOD1) variants have been identified to cause around 15% of familial and 1% of sporadic ALS[1].	Met

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		Prevalence estimates of ALS vary in the literature depending on how you define ALS (range 3-13:100,000) and there are geographical variations but prevalence is likely to be larger than 1:50,000 • Prevalence data reported in NG42 (Motor neurone disease: assessment and management, 2016) states that ~4000 people have MND of which 90% have ALS in England and Wales. This translates to 3:50,000. • Company highlighted that NG42 is not up to date: recent meta analyses at consultation reported 2,700 patients in the UK with ALS, based on a median prevalence estimate of 4.03:100,000 (2:50,000) people Over 180 variants have been identified associated with SOD1 and the variants are distributed throughout the gene and protein. This differs to other genetic causes of ALS, where variants arise in specific functional domains of proteins. Some variants in SOD1 may also be coincidentally found in people with ALS but not cause their disease.[2] The Prioritisation Board (PB) understood that SOD1-ALS may present with certain symptoms more commonly than in other ALS forms, such as lower motor neurone symptoms. Unlike most forms of ALS, SOD1-ALS is rarely associated with frontal temporal dementia and people with SOD1-ALS are less likely to have significant cognitive impairment than other forms of ALS. SOD1-ALS is also associated with a younger age of onset. PB was aware that mutations in SOD1 are causative of ALS in SOD1-ALS due to the aggregation of SOD1 protein in cells. This contrasts with the vast majority of ALS, which is associated with aggregation of TDP-43 protein. Therefore,	

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		treatments for ALS based on targeting the TDP-43 protein would not be expected to provide therapeutic benefit to people with SOD1-ALS. SOD1-ALS, in general, has been shown to have a shorter expected life expectancy compared to other forms of ALS. Genetic testing is required to identify SOD1-ALS from other ALS forms, but this test is not complex and testing for SOD1-ALS is increasingly used as routine practice. PB was aware that symptoms of SOD1-ALS are not entirely specific to ALS caused by SOD1 mutations alone as there is significant heterogeneity in clinical presentation and these symptoms are found in other causes of ALS too. Based on advice from ALS experts, and a growing clinical consensus, PB considered the disease prevalence in this case to be related to SOD1-ALS, given the differences in aetiology, clinical symptoms and prognosis. [2 - 4] PB were aware that estimates of SOD1-ALS (see criterion 2 below) show that there are around 59 prevalent cases of SOD1-ALS in England, with the highest estimates around 120 cases. This means that the prevalence of SOD1-ALS is significantly less than 1 in 50,000. For the reasons stated PB considered that this criterion was met.	
2.	Normally no more than 300 people in England are eligible for the technology in its licensed indication and no more than 500 across all its indications	Tofersen would only be used in people with SOD1 mutations. The company provided prevalence figures from Brown et al: • Around 2,700 people have ALS, at any time in the UK • Around 2,278 people have ALS in England (based on a population of population of 56,536,400) • Of these, 5-10% (114 – 228 people) have the familial type and 90-95% (2050 – 2164 people) have the sporadic type[5, 6]	Met

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		• SOD1 gene mutations cause 14.8% of familial and 1.2% of sporadic ALS.[7] • Total = 59 prevalent cases in England (0.1:50,000) • Highest estimates include 120 people with SOD1-ALS. At the scoping workshop the stakeholders explained that there is not currently equitable access to genetic screening. Only people meeting R58 “Adult Onset Neurodegenerative disorder” criteria are currently tested (people who are symptomatic and a) aged under 50 or b) with family history of ALS). Post workshop, the testing criteria has been updated to capture a broader population within the criteria for ALS with or without frontotemporal dementia: a) Evidence of lower motor neuron (LMN) degeneration by clinical, electrophysiologic or neuropathologic examination, AND b) Evidence of upper motor neuron (UMN) degeneration by clinical examination, AND c) Progressive course, AND e) No evidence of other aetiology It is unclear if the previous restrictions impacted the number of people eligible for treatment but clinicians at the scoping workshop did not expect a large increase in diagnoses following the expansion of testing. Genetic testing for SOD1 mutations can take up to a year to receive, once diagnosed with an SOD1 mutation, tofersen would be used in combination with standard of care treatments. For the reasons stated above, PB considered that this criterion was met.	

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3.	The very rare condition significantly shortens life or severely impairs its quality	SOD1-ALS affects the brain and spinal cord and is associated with progressive degeneration of motor skills.[8] Progression of the disease leads to increased muscle weakness and problems with communicating and breathing. Most people typically do not survive beyond 2-3 years of developing symptoms, and shorter survival times are assocatied with SOD1-ALS, compared to other forms of ALS.[9,10] • (https://www.mndassociation.org/app/uploads/mnd-association-key-messages-infographic.pdf) For the reasons stated above, PB considered that this criterion was met.	Met
4.	There are no other satisfactory treatment options, or the technology is likely to offer significant additional benefit over existing treatment options.	• **Additional benefit of tofersen:** Tofersen does not present itself as curative treatment option. Initial results from pivotal trial (VALOR and OLE, primary outcome: change from baseline to week 28 in the Revised Amyotrophic Lateral Sclerosis Functional Rating Scale (ALSFRS-R)) showed tofersen did not statistically improve clinical end points and was associated with adverse events. However, the benefits of tofersen are being further evaluated in the extension phase[11] • **Current treatment options:** There is an available treatment (Riluzole) recommended in NICE TA20 for people with ALS. Riluzole is not curative and extends median survival by 2-3 months only (TA20 review papers). Feedback from stakeholders during the scoping workshop noted that riluzole is offered to all patients at diagnosis of ALS. However, it is not considered a very effective treatment option by clinicians. The PB considered that conditions with a NICE recommended treatment option would not normally meet	Met

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		this HST criterion. But, it agreed that, for the eligible population (ALS caused by SOD1 mutations) the poor survival benefit associated with riluzole meant that it could not be classed as a satisfactory treatment option. For the reasons stated above, PB considered that this criterion was met.	

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2. Opie-Martin, S., Iacoangeli, A., Topp, S.D. et al. (2022) The SOD1-mediated ALS phenotype shows a decoupling between age of symptom onset and disease duration. Nat Commun 13, 6901. https://doi.org/10.1038/s41467-022-34620-y

3. Millecamps, S., Salachas, F., Cazeneuve, C et al. (2010) SOD1, ANG, VAPB, TARDBP, and FUS mutations in familial amyotrophic lateral sclerosis: genotype-phenotype correlations. J. Med. Genet, 47 (8).

4. Wicks, P,. Abrahams, S,. Papps, B. et al (2009) SOD1 and cognitive dysfunction in familial amyotrophic lateral sclerosis. J Neurol, 256 (2) :234-41.

5. Gowland A et al. (2019) Predicting the future of ALS: the impact of demographic change and potential new treatments on the prevalence of ALS in the United Kingdom, 2020-2116

6. Sheffield MND Care and Research Centre (2015) What is the difference between MND and ALS? Accessed September 2021.

7. Zou et al. (2017) Genetic Epidemiology of Amyotrophic Lateral Sclerosis: A Systematic Review and Meta-Analysis. J Neurol Neurosurg Psychiatry. 88(7):540-549.

8. Amyotrophic Lateral Sclerosis Frontotemporal Degeneration. 20(3-4):264-274.

9. Talbot K (2009). Motor neuron disease. Practical Neurology. 9(5):303.

10. Simon NG et al. (2014) Quantifying disease progression in amyotrophic lateral sclerosis. Ann Neurol. 76(5):643-657.

11. Timothy M. Miller et al. (2022) Trial of Antisense Oligonucleotide Tofersen for SOD1 ALS. N Engl J Med; 387:1099-1110