National Institute for Health and Care Excellence

Single Technology Appraisal (STA)

Masitinib for treating amyotrophic lateral sclerosis

Response to consultee and commentator comments on the draft remit and draft scope (pre-referral)

Please note: Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees.

Comment 1: the draft remit

Section	Consultee/ Commentator	Comments [sic]	Action
Appropriateness	Motor Neurone Disease Association	We believe that it would be appropriate to refer this topic to NICE for appraisal. Motor neurone disease (MND) is a profoundly debilitating illness that remains lacking in treatment options, with only one disease-modifying treatment currently available. Any credible new treatment should be appraised by NICE	Comment noted.
	UK Clinical Pharmacy Association	Yes	Comment noted.
Wording	Motor Neurone Disease Association	*Does the wording of the remit reflect the issue(s) of clinical and cost effectiveness about this technology or technologies that NICE should consider? If not, please suggest alternative wording.* Yes	Comment noted.

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	UK Clinical Pharmacy Association	*Does the wording of the remit reflect the issue(s) of clinical and cost effectiveness about this technology or technologies that NICE should consider? If not, please suggest alternative wording.* Yes	Comment noted.
Timing Issues	Motor Neurone Disease Association	Survival times for MND are short: a third of people die within a year of diagnosis, and half within two years. Any delay to the appraisal of the treatment will therefore mean that a substantial portion of the MND population at that time will be unable to access it (if the appraisal is positive). Appraisal of any treatment for MND must therefore be undertaken with urgency, to maximise the number of people who can benefit from any positively appraised treatment.	Comment noted.

Comment 2: the draft scope

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Background information	AB Science	**Introduction** Riluzole is the only currently approved, mildly efficacious treatment for ALS (Amyotrophic Lateral Sclerosis, also known as Lou Gehrig's disease) in the US and in Europe. Riluzole received marketing authorization in 1995 in the USA, and in 1996 in Europe. In the years that followed, over 60 molecules have been investigated as a possible treatment for ALS. However, all of the pharmaceuticals that reached the clinical trials stage since riluzole's approval have failed to demonstrate clinical efficacy. **Objective**	Comment noted.

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		Identification and endpoint analysis of large-scale clinical trials conducted globally in ALS patients. **Methods** In May-June 2016, a systematic search for randomized, placebo-controlled clinical trials (RCTs) in ALS patients was performed across the MEDLINE and Clinicaltrials.gov databases (published in English language). In addition, ARISLA (*Fondazione Italiana della Ricerca per la Sclerosi Laterale*) list of global ALS trials was used as a supportive information source. Search criteria: Advanced phase (Phases II, II-III, and III) RCTs that have recruited ≥100 ALS patients and with the results published between 1995 and June 2016 were included. For the compounds identified in this manner, the search was further expanded to include all the early-stage trials that served as a justification for large-scale studies, regardless of the number of patients recruited. **Results** Clinical trials with 22 compounds are presented in this analysis. A total of 48 studies, with a cumulative recruitment of 12,885 ALS patients, are described. **Conclusions** Of the 48 RCTs analyzed in this report, no study that recruited ≥100 patients was successful on the primary efficacy endpoint(s). Only 3 studies recruiting ≥100 patients have reached statistical significance in any of the secondary efficacy endpoints. **Interpretation**	

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		This review of past RCTs reveals that the development of effective pharmacological therapies in ALS is a major challenge. A near comprehensive lack of success from over 20 years of drug development is a reflection on the complexity of this neurodegenerative disease, which involves both cortical and spinal components of motor neuron circuitry and non-neuronal cells that support the motor neurons. The success of masitinib to achieve its primary and secondary endpoints in the clinical setting of a phase 3 RCT, as well as relevant post-paralysis preclinical models of ALS, is therefore a significant progress;	
	Motor Neurone Disease Association	We feel the background information is accurate, bar one small point that could usefully be clarified. It states that ALS affects 80% of patients, which allows for some ambiguity: does this mean 80% of people living with MND at any one time, or 80% of diagnoses? Differing survival times for different forms of MND mean that the two figures are not the same. The reference for the statement is our own guide for GPs and primary care teams, which cites Talbot, K et al. Motor Neuron Disease: a practical manual, Oxford Care Manuals, 2010, P41. This states that ALS 'represents at least 80% of all MND cases' – meaning diagnoses, rather than people living with MND at any one time. We recommend that this is made clearer in the final scope; the next edition of our guide will be revised to remove any ambiguity on this point.	Comment noted. During the workshop, attendees advised that the international definition of amyotrophic lateral sclerosis is broader than the UK definition. Some of the epidemiology information has been removed from the scope because it is not clear which definition will be used in the marketing authorisation.
The technology/ intervention	AB Science	Masitinib (AB1010) is a non-cytotoxic New Chemical Entity with anti-cancer and anti-inflammatory properties. Within this application, masitinib is intended for the treatment of adult patients with amyotrophic lateral sclerosis (ALS). Masitinib belongs to the pharmacological class of drug known as tyrosine kinase inhibitors (TKI). In terms of selectivity, masitinib has been shown to be	Comment noted.

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		one of the most selective kinase inhibitors relative to all those currently approved or under clinical development [Anastassiadis, 2011; Davis, 2011]. The exact molecular pathway causing motor neuron degeneration in ALS is unknown, but as with other neurodegenerative diseases, it is likely to involve a complex interplay between multiple pathogenic cellular mechanisms that may not be mutually exclusive. These include: genetic factors, excitotoxicity, oxidative stress, mitochondrial dysfunction, impaired axonal transport, neurofilament aggregation, protein aggregation, inflammatory dysfunction and contribution of non-neuronal cells. The scientific rationale for the use of masitinib in the treatment of ALS is based on the following features: • As a primary mechanism of action, masitinib acts on neuroglia through the inhibition of a receptor found on glial cells called CSF1R (colony-stimulating factor 1 receptor). There exists robust evidence in the scientific literature to link neuronal damage in ALS with microgliosis, in particular the emergence of aberrant glial cells; a process regulated by the CSF1/CSF1R signaling pathway. Through targeting this pathway, masitinib is able to inhibit glial cell proliferation, including aberrant microglial cells that are strongly associated with motor neuron degeneration, and also retard microglia cell migration. • As a secondary mechanism of action, masitinib acts on mast cells through inhibition of the c-Kit/SCF and LYN/FYN signaling pathways. Consequently, masitinib is capable of regulating mast cell activity including mast cell–microglia cross-talk, leading to a reduction in the release of inflammatory mediators. There is putative evidence in the literature to suggest that inhibition of mast cell activity, and thus a reduction in the release of proinflammatory and vasoactive mediators, is likely to contribute to masitinib's overall therapeutic effect in ALS by regulating the neuroinflammatory network and modulating blood-brain barrier (BBB) and blood-spinal cord barrier permeability.	

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		The development of masitinib in ALS is therefore primarily based on its pharmacological action in microglia cells and secondarily on mast cells. This dual therapeutic approach in potently targeting both microglia and mast cell activity, thereby modulating neuroinflammation and slowing microglial-related disease progression, provides a strong medical plausibility for the use of masitinib in ALS. It is through this multifaceted mechanism of action that masitinib appears capable of generating the beneficial treatment effects observed in humans (as evidenced from interim analysis of a randomized, placebo-controlled, phase 3 study AB10015) and also from relevant preclinical animal studies ($SOD1^{G93A}$ rats 7 days after paralysis onset, i.e. in the therapeutic setting).	
	Motor Neurone Disease Association	Targeting CNS inflammation is a viable therapeutic strategy for MND. We cannot comment on the pharmacological specificity of the intervention.	Comment noted.
	UK Clinical Pharmacy Association	*Is the description of the technology or technologies accurate?* Yes	Comment noted.
Population	Motor Neurone Disease Association	We note that the population covered is exclusively people with ALS, and accept that the nature of the evidence about the efficacy of Masitinib requires that it be framed in this way. However, the same limitation applied to riluzole at the time of its technology appraisal; in a letter accompanying the TA, however, NICE advised clinicians to use their professional judgement in deciding whether to prescribe it for other variants of MND. Subsequent papers have suggested that riluzole is appropriate for other forms. We recommend that any technology appraisal for Masitinib proceed on a similar basis if at all possible	Comment noted. The appraisal committee is only able to make recommendations within the marketing authorisation, which is anticipated to be people with amyotrophic lateral sclerosis. During the appraisal, the committee will discuss how this disease was

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			defined in the trials of masitinib and the summary of product characteristics.
Comparators	AB Science	Comparator of study AB10015 is riluzole	Comment noted.
	Motor Neurone Disease Association	'Best alternative care' can best be defined as the co-ordinated, multidisciplinary care outlined in chapters 9 to 21 of the full version of NICE guideline NG42, on the assessment and management of MND. This includes day-to-day care and therapy, respiratory support including non-invasive ventilation, management of muscle problems and saliva, and nutritional support include gastrostomy. It does not include riluzole, which is covered by its own separate technology appraisal.	Comment noted.
	UK Clinical Pharmacy Association	*Are these the standard treatments currently used in the NHS with which the technology should be compared?* Yes	Comment noted.
Outcomes	AB Science	Efficacy outcomes were the following: • ALSFRS-R (primary) • Forced Vital Capacity • CAFS (Combined Assessment of Function and Survival) • Quality of Life • Survival	Comment noted. It was agreed at the workshop that CAFS and ALSFRS are important scales and widely used but NICE scopes do not usually state which specific measures are used. These scales fall under the outcome of

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			'disease progression', which is in the scope.
	Motor Neurone Disease Association	We note that 'time to first tracheotomy' was also an outcome for the riluzole technology appraisal, and has presumably been included here on that basis. While it may be a helpful proxy for survival, tracheotomy is not a routine aspect of MND care, and is not included in NG42. We wonder whether a different or additional outcome that reflects mainstream practice in MND care could be identified. The other indicators seem appropriate.	Comment noted. Attendees at the workshop disagreed with this statement. The clinical expert at the workshop stated that tracheotomy is common in clinical practice, it is measured in trials, and it should be included in the scope.
	UK Clinical Pharmacy Association	*Will these outcome measures capture the most important health related benefits (and harms) of the technology?* Yes	Comment noted.
Economic analysis	AB Science	<u>Quality of Life</u> The most commonly used QOL scales in ALS clinical trials is the Amyotrophic Lateral Sclerosis Assessment Questionnaire (ALSAQ-40), which was retained in study AB10015. Quality of life was significantly improved in study AB10015. <u>Functional Benefit</u> According to the survey conducted by Castrillo-Viguera (Amyotroph Lateral Scler. 2010), the majority of clinicians and clinical researchers surveyed believe that a therapy that resulted in a change of 20% or greater in the slope of the ALSFRS-R would be clinically meaningful. All participants endorsed a	Comment noted.

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		25% or higher change in the ALSFRS-R score as at least somewhat clinically meaningful (score of 4 or higher). <u>Survival benefit</u> Survival is not the most appropriate endpoint to assess clinical benefit in the context of a clinical trial, and ALSFRS-R is more appropriate The main issue limiting use of survival is the fact that most ALS trials are not of sufficient duration for many patients to reach this endpoint, severely reducing power. The only two options to resolve this problem are to increase study duration or sample size, both of which contribute to cost, and reduce trial efficiency. The current draft guidance from ALS community [Guidance for Industry Drug Development for Amyotrophic Lateral Sclerosis] recommends that ALS trials need outcomes more sensitive to change than survival. Such a choice requires the assumption that the treatment would not negatively impact survival if it improved the alternative outcome. Guidance EMA/531686/2015, Corr.1 states that "*As primary efficacy variable in ALS trials can use either time to death […] or function (ALSFRS-R), or both. For proof of efficacy a clear and significant effect on one domain and a trend on the other may be sufficient*" The guidance also states that "*All trials of ALS should include testing of respiratory function.*" Study AB10015 strictly complied with this requirement, as there was a significant benefit on the primary criterion ALSFRS-R, supported by a significant benefit in the FVC as a secondary endpoint, and a trend of benefit on overall survival as a secondary endpoint.	

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	Motor Neurone Disease Association	The short survival times in MND mean that a time horizon of up to three years might be appropriate; the majority of people with MND will die within this period, and so it should give a sufficient indicator of efficacy.	Comment noted.
Equality and Diversity	Motor Neurone Disease Association	As MND can impair swallow, this may be a form of physical disability that is excluded from the scope. For those who cannot take a drug orally, as Masitinib is to be administered (we infer in tablet form), its benefits may not be realised. It would be helpful if any future appraisal could consider, or seek information from the developers about, the efficacy of taking Masitinib in a crushed form, for instance to be swallowed with a thick fluid such as yoghurt, or in a suspension form, to be taken orally; and the possibility of it being administered via a gastrostomy tube.	Comment noted. At the scoping workshop, the company advised that the other ways of administering masitinib are outside the licence. Usually, NICE appraisal committees only make recommendations for use within the marketing authorisation.
Innovation	Motor Neurone Disease Association	Any new disease-modifying treatment could be said to be a step change for MND: subject to the findings of the appraisal, Masitinib can be expected to lead to an extension of survival times and, therefore, an increase in the size of the MND population. For a rare and rapidly progressive disease, even a modest effect can significantly increase these totals, proportionally speaking. Regarding benefits that may not be captured in the QALY calculation, Appendix M of the NICE guideline considers evidence around quality of life in MND at length. It finds that the quality of life achieved by people with MND is not fully captured in QALY assessments; accordingly, there is a danger that a treatment that prolongs life without substantially improving quality of life may achieve a lower QALY score than is truly merited, because of inadequacies in the QALY scales used. The guideline development group was able to take these shortcomings into account and reach conclusions about the cost	Comment noted. The appraisal committee will discuss any benefits that are not included adequately in the QALY calculation.

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		effectiveness of MND care, albeit with some effort. NICE must take similar care with Masitinib to ensure that the QALY calculation truly reflects the extent to which people with MND value their quality of life.	
	UK Clinical Pharmacy Association	Masitinib has a unique mechanism of action. It promises a new treatment option for a life threatening disease with a high unmet medical need	Comment noted.
Questions for consultation	Motor Neurone Disease Association	*Are there any people who cannot have riluzole and therefore have best supportive care only (if so, what are the reasons for not having riluzole)?* Some people with MND do not take riluzole because they cannot tolerate its side effects, which can include liver damage. Others choose not to take it, feeling that a modest extension of life, in the face of a drastic deterioration in quality of life, is not desirable. We do not have figures for the proportion of people with MND who do not take riluzole, but from our extensive contact with people living with MND, we believe that those who do not take it are in a clear minority. *Where do you consider masitinib will fit into the existing NICE pathway, 'Motor Neurone Disease' (2016)?* We would expect Masitinib to sit under 'Assessment and Management', in a similar position to riluzole (we say this provisionally, subject to the publication of further information by the company). *NICE intends to appraise this technology through its Single Technology Appraisal (STA) Process. We welcome comments on the appropriateness of appraising this topic through this process. (Information on the Institute's*	Comment noted.

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		Technology Appraisal processes is available at http://www.nice.org.uk/article/pmg19/chapter/1-Introduction) We are satisfied that the use of this process is appropriate.	
	UK Clinical Pharmacy Association	Is there a place for masitinib monotherapy in patients have history of severe hypersensitivity to Riluzole? Is there a place for masitinib monotherapy in patients who cannot take riluzole because of liver disease?	Comment noted. During the scoping workshop, the company advised that masitinib will be licensed for use in combination with riluzole. Thus, masitinib monotherapy is not included in the scope.

The following consultees/commentators indicated that they had no comments on the draft remit and/or the draft scope

Department of Health