NICE National Institute for Health and Care Excellence

NICE guidance

Mexiletine for treating the symptoms of myotonia in non-dystrophic myotonic disorders

Technology appraisal guidance

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Your responsibility

The recommendations in this guidance represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, health professionals are expected to take this guidance fully into account, alongside the individual needs, preferences and values of their patients. The application of the recommendations in this guidance are at the discretion of health professionals and their individual patients and do not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian.

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Commissioners and providers have a responsibility to promote an environmentally sustainable health and care system and should assess and reduce the environmental impact of implementing NICE recommendations wherever possible.

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1 Recommendations

1.1 Mexiletine (Namuscla) is recommended, within its marketing authorisation, as an option for treating the symptoms of myotonia in adults with non-dystrophic myotonic disorders. It is recommended only if the company provides mexiletine (Namuscla) according to the commercial arrangement.

Why the committee made these recommendations

Treatments for the symptoms of myotonia in adults with non-dystrophic myotonic disorders already include imported mexiletine (which is not licensed in the UK). Other sodium channel blockers are used if mexiletine is not suitable. NICE's remit for this appraisal is to appraise Namuscla, the only brand of mexiletine with a UK marketing authorisation.

Clinical trial evidence suggests that mexiletine is better than placebo at reducing the symptoms of myotonia. But the trial did not compare mexiletine with other sodium channel blockers. Also, a higher dose of mexiletine was used in the clinical trial than people would normally have in the NHS.

The economic model does not compare mexiletine with other sodium channel blockers that are used in the NHS. Because of this, mexiletine's clinical benefit compared with these medicines is uncertain. However, the cost-effectiveness estimates for mexiletine compared with best supportive care are within the range that NICE considers a cost-effective use of NHS resources. It is uncertain if they would exceed this range when compared with other sodium channel blockers. Therefore, mexiletine (Namuscla) is recommended.

2 Information about mexiletine

Marketing authorisation indication

2.1 Mexiletine (Namuscla, Lupin) is indicated 'for the symptomatic treatment of myotonia in adult patients with non-dystrophic myotonic disorders'.

Dosage in the marketing authorisation

2.2 The dosage schedule is available in the summary of product characteristics.

Price

2.3 The list price is £5,000 per 100×167 mg capsules (excluding VAT; BNF online, accessed September 2021). The company has a commercial arrangement. This makes mexiletine (Namuscla) available to the NHS with a discount. The size of the discount is commercial in confidence. It is the company's responsibility to let relevant NHS organisations know details of the discount.

3 Committee discussion

The appraisal committee considered evidence submitted by Lupin, a review of this submission by the evidence review group (ERG), NICE's technical report, responses from stakeholders, and consultation comments from stakeholders, experts and members of the public. See the committee papers for full details of the evidence.

Disease background and current clinical management

Non-dystrophic myotonia can affect the quality of life of patients and carers

3.1 Non-dystrophic myotonia (NDM) refers to a group of rare genetic disorders affecting skeletal muscle chloride or sodium ion channels. The most common symptom is myotonia, which is a delay in muscle relaxation and can lead to muscle locking and stiffness. The patient expert explained the constant effect of myotonia on quality of life for people with the condition and their carers. It can cause general muscular discomfort and pain, lack of sleep and major falls because muscle locking can cause falls and also limit the ability to break a fall. The patient expert highlighted that this leads to avoiding stairs where possible. It can also cause embarrassment for people with NDM because slurring speech and facial locking after sneezing can be misunderstood by other people. The patient organisation emphasised the invisible nature of the disease because of its rarity. The patient expert also noted constant worry about triggers (such as cold weather) that could affect myotonic episodes. The clinical experts explained that symptom severity varies between people, and can also vary over time for each individual (for example, it can affect different parts of the body). Some people need constant treatment and others choose episodic management, for instance, during cold weather. If the disease is not managed, the patient expert explained that care is sometimes needed for tasks such as climbing stairs, lifting or bathing.

Current clinical management involves using mexiletine and other sodium channel blockers

3.2 Current clinical management of NDM includes muscle warming routines, specialist physiotherapy and avoidance of triggers. However, the clinical experts

stated that pharmacological management should be offered to any person with NDM who is seeking treatment because it is affecting their daily lives. Sodium channel blockers (such as mexiletine, carbamazepine, acetazolamide, flecainide and phenytoin) have been used off label for many years to treat NDM. Off-label imported mexiletine was used most because benefits can be seen very quickly. The clinical experts explained that a recent randomised controlled trial showed evidence of efficacy of another sodium channel blocker, lamotrigine, which is also sometimes used if mexiletine is contraindicated, not effective or not tolerated. The patient expert explained that using mexiletine addressed most of the symptoms of NDM with near-normal muscle function and manageable side effects. The committee concluded that mexiletine is currently the preferred, established treatment for NDM and other options are available when mexiletine is not suitable.

The company should compare mexiletine with other sodium channel blockers

3.3 The committee was aware that the remit for this appraisal was to appraise mexiletine (Namuscla) within its licensed indication for NDM. It understood that it would make recommendations within the terms of the marketing authorisation, as published in the manufacturer's summary of product characteristics. It noted that the comparator in the scope for this appraisal was established clinical management without mexiletine, including but not limited to lamotrigine and best supportive care. The company considered that mexiletine (Namuscla) is now the only licensed treatment for NDM and therefore compared mexiletine with placebo to represent best supportive care. The company also indicated that lamotrigine is not established in clinical practice because few people take it. The company explained that lamotrigine has a longer titration period than mexiletine, with intensive monitoring to reach higher doses if needed. It also believed that pain and fatigue are influenced by the placebo effect, and other sodium channel blockers would have no additional benefit to placebo as implemented in their comparison with best supportive care. The committee recalled comments from the evidence submissions that clinicians in England had used lamotrigine with success in people whose disease did not respond to mexiletine or who could not have mexiletine because of cardiac arrythmias. At consultation, the Association of British Neurologists (ABN) believed it was not reasonable to consider other sodium channel blockers as comparators. The ABN commented that lamotrigine is rarely used because

they suggested it was not as effective as mexiletine and has a high discontinuation rate. But it noted that there is a direct comparator trial being set up. The committee considered that established clinical management without mexiletine cannot currently be observed in the NHS because mexiletine is already established in clinical practice with off-label use and, more recently, an interim access agreement for the licensed treatment (Namuscla). Therefore, the committee deemed the most appropriate comparison to be with what people currently taking mexiletine would have if mexiletine was not available. The clinical experts stated that if mexiletine was not available, patients would have another sodium channel blocker. The patient organisation representative and patient expert at the first committee meeting agreed with this. The committee concluded that comparing mexiletine with best supportive care was not appropriate because people would be offered other active treatments such as lamotrigine or other sodium channel blockers if mexiletine was not available, and that other active treatments would likely be more effective than best supportive care.

Clinical evidence

The main clinical-effectiveness evidence comes from the MYOMEX trial, with supporting evidence from other studies

3.4 The main clinical evidence for mexiletine comes from MYOMEX, a randomised crossover trial of 26 patients with NDM comparing mexiletine with placebo. The primary outcome was muscle stiffness as measured by visual analogue scale, but the efficacy evidence used in the economic model was a secondary outcome measure, the Individualised Neuromuscular Quality of Life (INQoL) questionnaire (see section 3.10). Supporting evidence came from 3 other studies:

- Suetterlin et al. (2015) – a retrospective review of 63 UK patients with NDM taking mexiletine for 6 months or more
- Statland et al. (2012) – a randomised crossover trial of 59 patients comparing mexiletine with placebo

- Stunnenberg et al. (2015) – an aggregated study of patients individually randomised to mexiletine or placebo in a crossover design for 30 patients with NDM in the Dutch neuromuscular database.

These trials were used as supporting clinical evidence and used to inform some economic model parameters and scenario analyses. The committee concluded that all the evidence, combined with the statements that mexiletine has been standard practice for over 15 years, suggest mexiletine is effective for relieving myotonia symptoms. However, the committee also noted that there were no comparisons of mexiletine with an active comparator.

MYOMEX is broadly generalisable to NHS clinical practice

3.5 MYOMEX included people aged between 18 and 65 with genetically confirmed NDM and with myotonic symptoms severe enough to justify treatment. The severity of symptoms was evaluated by whether it affected more than 1 segment of the body and if it impacted on 3 or more daily activities. The clinical experts explained that there are no formal methods of assessing severity of NDM because of the large amount of heterogeneity between patient symptoms and needs (see section 3.1). However, they considered that the severity inclusion criteria would be broadly generalisable to NHS clinical practice. The company noted that the small number of people aged over 65 who have treatment for NDM would not have different treatment to those under 65, therefore it does not consider the age criteria to be a limitation. The committee concluded that MYOMEX was broadly generalisable but noted the limitations of the inclusion criteria.

There are significant limitations with the design of the MYOMEX trial

3.6 A large proportion of patients in MYOMEX had previously had mexiletine. The clinical expert stated that this would be expected because there are few people with NDM who have not had mexiletine because it is a rare condition and mexiletine is routinely offered as a first treatment option. The ERG noted, and the clinical expert agreed, that the recognisable side effects of mexiletine could have effectively unblinded patients to which treatment they had. This is supported by the Statland et al. study in which around 80% of patients correctly guessed which treatment they had. The ERG considered that unblinding could potentially bias results because most of the outcomes are patient reported.

Additionally, the ERG noted that there was potential for a carry-over effect between the 2 phases of the crossover trial if there was not enough time between the phases (the washout period). People in the MYOMEX trial had a 4- to 8-day washout period and the company presented analysis that there was no statistical evidence of a carry-over effect and the ERG noted that data from the first phase only also showed similar changes in muscle stiffness to both phases combined. However, the ERG noted the Statland et al. trial had at least a 7-day washout period and there was a statistically significant carry-over effect. The committee noted that MYOMEX included few patients and it was uncertain if the trial was powered to detect a carry-over effect. It also noted that MYOMEX had a short duration of only 18 days in each phase, so there is uncertainty in how effectiveness is maintained over a lifetime of treatment. At consultation, the company said that no risk of bias was found in the MYOMEX trial but did not provide evidence on this. The committee concluded that potential for unblinding and carry-over effects, short trial duration and few patients contribute substantial uncertainty to the MYOMEX results.

The dose and dosing schedule of mexiletine in MYOMEX does not match how it is used in clinical practice

3.7 Namuscla is a new formulation of mexiletine that uses different dose measurements to previous off-label use (a 167 mg capsule of Namuscla formulation is equivalent to 200 mg of imported mexiletine). However, all the clinical evidence uses the imported formulation of mexiletine. The daily dose in the MYOMEX trial started at 200 mg for 3 days, at which point all patients had a dose titration up to 400 mg for a further 3 days and then a final titration to 600 mg for 12 days, at which point efficacy was assessed. The summary of product characteristics for Namuscla states that the dosing schedule is based on clinical response and can be increased after at least 1 week of treatment in 167 mg (200 mg imported mexiletine dose equivalent) increments to a maximum dose of 500 mg (600 mg equivalent). The clinical experts stated that the rapid forced dose titration to 600 mg in MYOMEX does not represent current clinical management and is not in line with the summary of product characteristics. Currently, some people have dose titration in smaller off-label 100 mg dose increments at a more cautious rate of titration to avoid gastric side effects of mexiletine. Some people who are experienced with mexiletine use could have a faster rate of titration, but the clinical experts considered that this would not be as fast as in MYOMEX. The committee considered that because of

the short duration of the MYOMEX trial, some adverse events might not have been reported. In clinical practice, such adverse events could take much longer than the MYOMEX trial duration to emerge. The clinical experts stated that most patients currently have between 300 mg and 400 mg of imported mexiletine but patients with more severe symptoms, or patients with specific subgroups of myotonia that need greater doses, can have 600 mg doses or greater. The company considered the average daily dose of 417 mg in the Suetterlin et al. retrospective review to be the most accurate dose for modelling, and therefore included 15 capsules a week (equivalent to a daily dose of 429 mg) in its base case. The committee noted the difference between this dose and the 600 mg dose that was used at the point of assessment of efficacy in MYOMEX. It considered that it is not usually appropriate to separate the costs and benefits of treatments. The company stated that people in MYOMEX had the opportunity to immediately continue treatment with mexiletine at a dosage adapted to their clinical response and tolerance to the drug, after the initial titration to 600 mg. The company explained that the average dose used in clinical practice at the largest treating centre in the UK was 300 mg to 400 mg, with 600 mg not usually needed to reach maximum quality-of-life improvements. The company stated that the experts it consulted with had estimated that 400 mg was the average dose in clinical practice. The committee decided it was appropriate to consider the costs of the 429 mg dose (informed by Suetterlin et al. and clinical expert opinion on current practice). However, it also considered a scenario with the costs of the 600 mg dose (as was seen in MYOMEX), because it was mindful that efficacy estimates in the trial were taken once treatment had been titrated up to the 600 mg daily dose, so there would be uncertainty around the clinical-effectiveness results. The committee concluded that the dose and dosing schedule in MYOMEX does not reflect how mexiletine is currently used or would be used in clinical practice, so the cost of mexiletine is uncertain.

The company's economic model

The company's economic model does not represent clinical practice

3.8 The company's economic model has a simple structure with 3 states: 'alive on treatment', 'alive with no treatment' and 'death'. The transition between alive on treatment and alive with no treatment is based on the discontinuation rate of

the Suetterlin et al. study, and the transitions to death are based on general population mortality. The ERG considered that the model was simplistic and did not represent conventional health states such as disease severity or disease progression. However, in the absence of more data on the natural history of the disease, it was adequate for a comparison with best supportive care. The ERG also provided an indicative comparison with lamotrigine. It considered an indirect treatment comparison was not possible so provided analysis that varied the expected utility value of lamotrigine between best supportive care and mexiletine. The committee considered that 'alive with no treatment' would not happen in clinical practice because other treatments are available and would be used (see section 3.3). This would affect both how the comparator arm is created in the model and the subsequent treatments after stopping mexiletine. The committee also noted that not everyone's disease in clinical practice would be expected to respond to treatment with mexiletine; MYOMEX and the Suetterlin et al. study selected patients whose disease would be more likely to respond (see section 3.6). The committee concluded that the economic model does not reflect what would happen in clinical practice.

The natural history of the disease is not well characterised

3.9 The company considered that the disease progresses over time based on testimony that symptoms worsen after diagnosis. Therefore, it included a 15% reduction in quality of life after a modelled 'progression' event in the model. This event was modelled to happen at a faster rate for people who had not had treatment; the rate was estimated based on clinical opinion elicited through a Delphi panel. The clinical experts stated that there is no long-term evidence on the natural history of the disease and that treatment is only aimed at relieving symptoms. It is not disease modifying. However, some patients may experience muscle weakening later in life, which may be affected by treatment status. The ERG considered that the implementation of any disease progression in the model and its impact on quality of life was very uncertain. A single decrease in quality of life is not likely to reflect the natural history of the condition and the appropriateness of a 15% reduction in addition to differences seen in the trial was not justified by the evidence. The ERG removed this assumption in its base case with minimal effect on the incremental cost-effectiveness ratio (ICER). The committee considered that the natural history of the disease is uncertain and likely to be dependent on each patient's needs and preferences. It also considered that if an effect existed, the evidence for a differential rate of

progression was not robust and the size of the effect on quality of life was not supported by any evidence. The committee concluded that there was no evidence of a worsening of disease for people having best supportive care and because mexiletine only treats the symptoms of the disease, it agreed with the ERG's removal of this assumption. At consultation, the company removed any disease progression assumptions from its analyses.

Health-related quality of life

Generic quality-of-life instruments can measure health-related quality of life in people with NDM

3.10 MYOMEX measured only the condition-specific INQoL tool as a quality-of-life measurement. The company considered that the suitability of generic quality-of-life measurement tools such as EuroQoL 5 dimensions (EQ-5D-3L) to effectively capture the quality-of-life implications of muscle locking in NDM is unknown. Therefore, the company used INQoL data conceptually mapped to EQ-5D-3L utility values using company valuation studies in its base case. The ERG considered that the company did not show that generic measures of quality of life are unable to measure health-related quality of life of people with NDM. It considers generic instruments can be advantageous for capturing broader aspects of health, including comorbidities and adverse events. At the request of the NICE technical team, the ERG provided SF-36 data from the Statland et al. trial mapped to EQ-5D-3L utilities as a scenario analysis. The committee noted that generic quality-of-life instruments are included in the NICE reference case to achieve consistency in decision making across different diseases. The committee considered that domains such as physical function and activity in the SF-36 matched issues described by the patient expert. It considered that generic quality-of-life instruments can measure health-related quality of life of people with NDM, particularly through domains such as mobility, usual activities and pain. However, it recognised that some elements of muscle locking may be more difficult to capture. It concluded that the generic SF-36 data from the Statland et al. trial could be included in its considerations.

The utility values derived from the company's discrete choice valuation experiment are implausible

3.11 The company required a valuation study to map INQoL measurements from

MYOMEX to EQ-5D-3L utility values (see section 3.10). The company commissioned a discrete choice experiment (DCE), which compared 2 hypothetical health states drawn from the INQoL questionnaire. The ERG noted several problems with the DCE valuation studies:

- A lack of clear ordering preference in the language used to describe health states (monotonicity), for example the difference between 'some' and 'moderate' problems may not be clear to people taking part.
- Many logical inconsistencies, some of which could not be explained by lack of clear ordering. This suggests lack of understanding or attention to the task.
- Lack of adequate quality-control checks (other than whether the task was completed).
- Eight attributes of the INQoL were varied at the same time, which may have been too complex for people taking part.

Conceptual mapping to EQ-5D-3L introduces several problems including issues with anchoring the valuation model to the appropriate top and bottom EQ-5D-3L health state. The company chose a scenario that assumed the worst health state in the INQoL was equivalent or 'anchored' to the worst state in the EQ-5D-3L but also provided a scenario with different anchoring assumptions. The ERG considered that the utility values derived from each of the scenarios were substantially different, which showed considerable uncertainty with the conceptual mapping method. The committee saw the individual patient utility values for MYOMEX patients derived from the DCE study and considered the range of utility values to be implausible and some patients to have implausibly low utility. The clinical experts agreed that some of the utility values were implausibly low and did not represent the patient population seen in clinical practice. The committee concluded that the utility values and modelled treatment effect derived from the DCE were implausible and considered other valuation methods.

The utility values derived from the company's vignette valuation study and from the Statland et al. study are uncertain

3.12 The company also provided a vignette time trade-off study that asked people taking part to compare living in a hypothetical health state drawn from the INQoL for 10 years compared with 10 minus a given number of years in perfect health. The ERG considered that the vignette study had many of the same problems as the DCE study (see section 3.11) but also had potential issues with the study design, such as lack of warm up exercises for the complex task and lack

of explanation for some of the health states. The ERG preferred the vignette study because it avoided issues with conceptual mapping and produced a more plausible treatment effect. The committee agreed that the utility values derived from the vignette study were more plausible. The ERG also presented utility values derived from SF-36 data in the Statland et al. trial (see section 3.10), which produced a treatment effect much lower than any of the company valuation studies. The ERG considered this to be validation that the vignette study should be considered but cautioned that the algorithm to map SF-36 to EQ-5D-3L utilities can underestimate severe health states. The ERG also considered the data from Statland et al. publication to be limited because only the reported mean values could be used and some data was missing for the crossover periods. The committee noted that section 5.3.9 of NICE's guide to the methods of technology appraisal 2013 states that when mapping to EQ-5D, the mapping function chosen should be based on data sets containing both health-related quality-of-life measures. The committee considered this was only available for the SF-36 data and it had not been justified that SF-36 instrument could not measure quality of life of people with NDM (see section 3.10). The committee noted that all utility values presented were not compared with other sodium channel blockers and were therefore not the comparison of interest (see section 3.3). However, for the comparison with best supportive care, it considered that both sets of utility data presented were highly uncertain. The committee concluded that both sets of utility values could be considered with caution.

The company's hybrid model cannot overcome the problems with the discrete choice experiment

3.13 At consultation, the company provided analyses using a new hybrid model approach, combining data from the DCE and the vignette study. The ERG considered that the hybrid modelling had been well conducted, and that linking data from the 2 studies resolved the anchoring issues for the DCE. But it explained that reanalysis of data taken from the DCE would not be able to resolve the DCE's design issues. The ERG still preferred the vignette approach for utility valuation. Many of the treatment effect utility values are considered confidential so cannot be shown here. The Statland et al. mapping gave a treatment effect of 0.1, whereas the vignette approach gave a value greater than this. The company's preferred hybrid model resulted in an even larger treatment effect than both the Statland et al. mapping and the vignette

approach. The committee considered that the treatment effect from the Statland et al. mapping would be an underestimate (because the algorithm used reduces extreme values), giving an unrealistic difference in the utilities on and off treatment. In the absence of a burden of disease study, the committee considered both the vignette approach and the Statland et al. mapping in their decision making, and agreed that the utility increase from mexiletine would be somewhere between the values generated by these 2 approaches. The committee considered there was a high level of uncertainty associated with these 2 utility valuation approaches.

The reduction in quality of life for carers of people with NDM should be removed as an assumption

3.14 At technical engagement, the company considered there to be a case for including carer disutility in the appraisal because carers would also expect to have a reduction in quality of life without treatment. The company included a carer disutility as published in NICE's highly specialised technologies guidance on ataluren for treating Duchenne muscular dystrophy with a nonsense mutation in the dystrophin gene of 0.11 for an estimated 20% of patients with severe NDM. The ERG considered it could be appropriate to apply a carer disutility for patients who had no treatment, but it was uncertain how many people have severe enough symptoms to need care. It also noted that the disutility from NICE's guidance on ataluren for treating Duchenne muscular dystrophy is for non-ambulatory patients with progressive loss of motor function in the upper body, but no patients in MYOMEX needed to use wheelchairs or walking aids to complete a walking test of 3 to 5 metres. The clinical expert stated that non-ambulatory patients with NDM are very rare, having only ever seen 1 patient who needed to use a wheelchair. The committee considered that patients not having mexiletine would have another treatment (see section 3.3), and therefore the carer disutility would have been overestimated. The committee noted comments from the consultation that people with the condition and their carers had a better quality of life because of mexiletine, and carers would face a lifetime of caring without it. The company had planned to present results from a carer study, but this had ethical approval delays. Instead, it provided a scenario using carer disutility for carers of people with multiple sclerosis as a proxy. The ERG thought the resulting disutility could be an overestimate and noted that this scenario also includes carers of non-ambulatory people, with substantial uncertainties unresolved. The committee

acknowledged the impact of caring for someone with NDM has, but that there was no appropriate data available to do a relevant scenario analysis. It concluded that it had not seen enough evidence to justify including consideration of carer quality of life, and that inclusion of this assumption is highly uncertain and should be removed.

Resource use

The costs of resource use for people with NDM who are not having treatment is likely to be overestimated

3.15 The company considered that people who do not have treatment would use 3 times the number of resources as somebody having mexiletine. This includes increased costs for admissions for falls, physiotherapy and other therapies. The company validated this multiplier using estimation from an advisory board. The ERG considered the justification behind the advisory board findings to be incorrect because it used both the estimated frequency of resource use and the estimated number of people using the resource when only the frequency of resource use is needed for use in the model. The ERG therefore used only the frequency of resource use multiplier in its base case. The committee considered that this change had minimal effect on the ICER. It also noted that any comparison with best supportive care would overestimate the difference in resource use because many people would have other active treatments such as lamotrigine or other sodium channel blockers (see section 3.3). The committee concluded that the ERG amendments were likely to be appropriate for any comparison with best supportive care but would not reflect what would happen in clinical practice.

Cost-effectiveness estimate

Because of the uncertainty an acceptable ICER is £20,000 per QALY gained

3.16 NICE's guide to the methods of technology appraisal notes that above a most plausible ICER of £20,000 per quality-adjusted life year (QALY) gained, judgements about the acceptability of a technology as an effective use of NHS resources will take into account the degree of certainty around the ICER. The committee will be more cautious about recommending a technology if it is less

certain about the ICERs presented. The committee noted the high level of uncertainty, specifically:

- Impact from differing cost and potential difference in effectiveness of mexiletine because of the different options for the average dose (429 mg, 600 mg) preferred by the company and the ERG.
- Problems with the MYOMEX clinical trial, including potential carry-over effects and unintentional blinding, short trial duration and a small number of patients.
- Unknown true treatment effect in terms of utility from mexiletine treatment.

Therefore, it agreed that an acceptable ICER would be around £20,000 per QALY gained.

Mexiletine is cost effective for people with NDM

3.17 Both the company's and ERG's base case after consultation included removing the disease progression assumptions (see section 3.9). But the ERG base case used the vignette valuation study (see section 3.12), 600 mg mexiletine dose for the costs and benefits of treatment (see section 3.7), reduction of the resource use multiplier (see section 3.15) and removed carer disutility because of the uncertainty around symptom severity and need for care (see section 3.14). The committee-preferred assumptions differed from the revised ERG base-case assumptions for the comparison with best supportive care. It considered that:

- It is appropriate to consider the costs of the 429 mg dose in line with clinical practice. However, this is associated with uncertainty because the mexiletine efficacy data has been derived from the 600 mg equivalent dose (see section 3.7).

- It is appropriate to explore scenarios using utilities derived from SF-36 data in the Statland et al. trial because it has the advantage of being a generic health-related quality-of-life measurement, as well as to consider those produced by the ERG-preferred vignette approach. However, the committee noted that there is substantial uncertainty in the utility values. (see section 3.12 and section 3.13).

  Using the vignette approach and the scenario with the 429 mg dose, the ICER was £19,039 per QALY gained for mexiletine (Namuscla) compared with best supportive care. When the 600 mg dose was used, the ICER exceeded £30,000 per QALY. The committee considered that comparison with best supportive care was not appropriate (see section 3.3) and the indicative ERG analysis comparison with lamotrigine (see section 3.8) suggests this would increase the ICER if lamotrigine's treatment effect was greater than placebo. It accepted that if the utility gain associated with an active comparator was very modest, the ICER would remain below £20,000 per QALY gained. The committee recognised the serious limitations in the cost-effectiveness modelling. However, it also acknowledged that the evidence base is necessarily weaker for some technologies, such as those used to treat rare diseases. On balance, and taking into consideration the likelihood of decision error and its consequences, the committee concluded that mexiletine (Namuscla) was a cost-effective use of NHS resources and recommended it for routine commissioning.

Equalities considerations

There are no equality issues that can be addressed by the committee

3.18 The committee noted that disability is a protected characteristic and that people with NDM have a disability that could make travel to regional neurology centres for treatment more difficult. The committee noted that any equalities issue relating to geographical access to treatment with NDM would already be realised because mexiletine is current standard practice. However, the committee concluded that this potential equality issue could not be addressed in the guidance recommendations.

3.19 At consultation, it was noted that there are possible sex-based differences in alternative treatment suitability. For example, an increased risk of major birth defects in pregnancy have been seen with phenytoin, and changes in the body during pregnancy may affect lamotrigine levels or therapeutic effect. However,

the committee noted that mexiletine should be avoided during pregnancy. It concluded that this potential equality issue could not be addressed in the guidance recommendations.

4 Implementation

4.1 Section 7 of the National Institute for Health and Care Excellence (Constitution and Functions) and the Health and Social Care Information Centre (Functions) Regulations 2013 requires clinical commissioning groups, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in this appraisal within 3 months of its date of publication.

4.2 The Welsh ministers have issued directions to the NHS in Wales on implementing NICE technology appraisal guidance. When a NICE technology appraisal recommends the use of a drug or treatment, or other technology, the NHS in Wales must usually provide funding and resources for it within 2 months of the first publication of the final appraisal document.

4.3 When NICE recommends a treatment 'as an option', the NHS must make sure it is available within the period set out in the paragraphs above. This means that, if a patient has symptoms of myotonia in non-dystrophic myotonic disorders and the doctor responsible for their care thinks that mexiletine (Namuscla) is the right treatment, it should be available for use, in line with NICE's recommendations.

5 Appraisal committee members and NICE project team

Appraisal committee members

The 4 technology appraisal committees are standing advisory committees of NICE. This topic was considered by committee D.

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

The minutes of each appraisal committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

NICE project team

Each technology appraisal is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the appraisal), a technical adviser and a project manager.

Adam Brooke and Amy Crossley
Technical leads

Christian Griffiths
Technical adviser

Kate Moore
Project manager

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Accreditation