Healthcare Improvement Scotland | SMC Advice on new medicines

SMC2307

mexiletine 167mg hard capsules (Namuscla®)

Lupin Healthcare (UK) Ltd

06 November 2020

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in NHSScotland. The advice is summarised as follows:

ADVICE: following a resubmission assessed under the orphan process

mexiletine (Namuscla®) is accepted for use within NHSScotland.

Indication under review: for the symptomatic treatment of myotonia in adult patients with non-dystrophic myotonic disorders.

In a short-term, phase III, crossover study, mexiletine significantly improved muscle stiffness compared with placebo when measured on a visual analogue scale.

This advice applies only in the context of an approved NHSScotland Patient Access Scheme (PAS) arrangement delivering the cost-effectiveness results upon which the decision was based, or a PAS/ list price that is equivalent or lower.

This advice takes account of views from a Patient and Clinician Engagement (PACE) meeting.

Chairman
Scottish Medicines Consortium

Indication

For the symptomatic treatment of myotonia in adult patients with non-dystrophic myotonic disorders.

Dosing Information

The recommended starting dose of mexiletine is 167mg daily (one capsule per day). After at least 1 week of treatment, based on the clinical response, the daily dose can be increased to 333mg daily (two capsules per day). After at least 1 further week of treatment, based on clinical response, dose can be further increased to 500mg daily (three capsules per day). Maintenance treatment is between 167mg to 500mg daily (one to three capsules per day), according to the intensity of symptoms and the clinical response, taken regularly throughout the day.

The dose should not exceed 500mg/day. Regular reassessment should be implemented, not to continue long-term treatment in a patient not responding or not experiencing benefit of the treatment.

Before starting mexiletine treatment, detailed and careful cardiac evaluation should be carried out; throughout treatment with mexiletine, cardiac monitoring needs to be continued and adapted as a function of the heart condition of the patient.

The capsules should be swallowed with water, avoiding the supine position. In case of digestive intolerance, capsules should be taken during a meal.

Refer to the Summary of product characteristics (SPC) for further detail.[1]

Product availability date

January 2019

Mexiletine meets SMC orphan criteria.

Summary of evidence on comparative efficacy

Myotonic disorders are rare, hereditary diseases caused by a malfunction of muscle ion channels. They comprise dystrophic myotonias and non-dystrophic myotonias, the latter affecting skeletal muscle. Patients with non-dystrophic myotonias mainly experience stiffness in skeletal muscles but patients can also experience muscle weakness, pain and impairment in physical activity. Mexiletine is a class Ib antiarrhythmic medicine which acts by blocking sodium channels and is mainly active on muscle fibres subject to repeated discharges (such as skeletal muscle). It improves myotonic symptoms by decreasing muscle stiffness through reduction in the delay of muscle relaxation.[1, 2]

The key evidence comes from a randomised, double-blind, phase III, crossover study (MYOMEX) in patients with non-dystrophic myotonia conducted in France. Eligible patients were aged 18 to 65 years with genetically defined myotonia congenita (a chloride channelopathy) or paramyotonia congenita (a sodium channelopathy). They had myotonia symptoms severe enough to justify treatment with mexiletine based on clinical criteria (involving at least two segments [upper limb,

lower limb or face]) and disabling criteria (impacting on at least three of seven daily activities: talking, writing, feeding, hygiene, getting dressed, walking and climbing stairs). Patients had normal cardiac examination performed by a cardiologist including an electrocardiogram and cardiac ultrasound. Study patients could have previously received mexiletine provided treatment had stopped at least 3 days earlier. The study compared mexiletine with placebo using a crossover design of two 18-day treatment periods separated by a 4 day wash-out period. Eligible patients were randomised equally to receive mexiletine or placebo during period 1 (18 days) followed by a 4-day washout before crossing over to placebo or mexiletine during period 2 (18 days). The mexiletine dose was started at 167mg daily and titrated by increments of 167mg every 3 days to reach a maximum daily dose of 500mg in 1 week. Randomisation was stratified by diagnoses (myotonia congenita or paramyotonia congenita).[2]

The primary outcome was the score of stiffness severity which was self-reported by the patient using a visual analogue scale (VAS) ranging from 0 (no stiffness) to 100 (worst possible stiffness). The statistical plan tested for potential carry-over effect between period 1 and period 2 by comparing the difference between the two treatments using a linear mixed model on ranks. Since this indicated no significant effect of treatment sequence, the results from the two treatment periods were combined. There was a significant reduction (improvement) from baseline to the end of treatment in the primary outcome of stiffness score following treatment with mexiletine compared with placebo ($p<0.001$). Details are presented in Table 1.

Table 1: Results for the primary outcome (stiffness VAS score) in the modified intention to treat population of MYOMEX study[1, 2]

	Mexiletine (n=25)	**Placebo (n=25)**
Median (range) stiffness VAS score at baseline	71.0 (11, 100)	81.0 (27, 98)
Median stiffness VAS score at end of treatment	16.0	78.0
Absolute change in median (range) stiffness VAS score from baseline	-42.0 (-93, 35)	+2.0 (-94, 35)
Percentage change in stiffness VAS score from baseline	-78%	+2%
Percentage of patients with an absolute change in stiffness VAS from baseline ≥50mm at end of treatment	57% (12/21)	14% (3/22)

VAS: visual analogue scale, mm: millimetres; the modified intention to treat population included all randomised patients with at least one available evaluation related to the primary outcome or a VAS measurement at the end of either treatment period.

Results for stiffness VAS scores in the per protocol population (n=22) were reported to be similar to the modified intention to treat population.[2]

The secondary outcomes of the MYOMEX study included the chair test (defined as the time needed to stand up from a chair, walk around the chair and sit down again), individualised neuromuscular quality of life (INQoL) - overall quality of life (100-point scale with higher scores indicating poorer quality of life), Clinical Global Impression (CGI) efficacy index, assessed by the patient and the investigator (where efficient was reported as good or fair in the case report form), preference between the two treatment periods, the Clinical Myotonia Scale (CMS)-Severity Global Score (range 0 to 104, where 0=normal) and the CMS-Disability Global Score (range 0 to 27, where

0=normal). Results for these secondary outcomes favoured mexiletine over placebo; details are presented in Table 2 below. The statistical plan did not control for type I error in analysing secondary outcomes and therefore the results reported for these outcomes are descriptive only and not inferential (no p-values reported).

Table 2: Results for the secondary outcomes in the modified intention to treat population of MYOMEX study[1, 2]

Secondary outcome	Mexiletine (n=25)	Placebo (n=25)
Chair test: mean (SD) value at baseline (seconds)	7.3 (3.5)	
Absolute mean (SD) change in chair test from baseline (seconds)	-2.1 (2.9)	0.2 (1.6)
Mean (SD) INQoL - overall quality of life at baseline	47.8 (20.4)	
Absolute mean (SD) change in INQoL from baseline	-20.7 (24.6)	2.6 (15.0)
Preferred treatment	80% (20/25)	20% (5/25)
CGI Efficacy Index: judged as efficient by investigator at day 18	92% (22/24)	20% (5/25)
CGI Efficacy Index: judged as efficient by patient at day 18	92% (23/25)	24% (6/25)
Mean (SD) CMS-Severity Global Score at baseline	53.8 (10.0)	
Absolute mean (SD) change in CMS-Severity Global Score from baseline	-29.8 (16.0)	-6.2 (19.0)
Mean (SD) CMS-Disability Global Score at baseline	7.8 (2.8)	
Absolute mean (SD) change in CMS-Disability Global Score from baseline	-5.1 (3.1)	-0.8 (3.4)

SD: standard deviation; INQoL: individualised neuromuscular quality of life; CGI: Clinical Global Impression; CMS: Clinical Myotonia Scale; the modified intention to treat population included all randomised patients with at least one available evaluation related to the primary outcome or a VAS measurement at the end of either treatment period.

The INQoL comprised individual symptom domains (weakness, locking, pain, fatigue) and daily living domains (activities, independence, social relationship, emotions, body image) and results indicated that there were greater improvements in each domain after treatment with mexiletine compared with treatment with placebo.[2]

Supportive evidence comes from a randomised, double-blind, phase II, crossover study in 59 patients with non-dystrophic myotonia. Eligible patients were aged ≥16 years with clinical symptoms and signs of non-dystrophic myotonia and myotonic potentials on electromyography. They were randomised to receive mexiletine hydrochloride 200mg (equivalent to 167mg of mexiletine) or placebo orally three times daily for 4 weeks. After a washout period of 7 days, they received the alternative treatment for a further 4 weeks. The primary outcome was a stiffness severity score recorded by patients during the third and fourth week of each treatment period using an interactive voice response (IVR) diary on a 9-point scale (1=minimal and 9=worst ever; 0=no symptoms for analysis). Analysis of the primary outcome was performed in 57 patients who

completed IVR diary assessments in weeks 3 to 4 for both periods 1 and 2 and was analysed separately for each treatment period, since tests indicated a carryover effect.[2, 3]

The stiffness score was significantly lower (better) after treatment with mexiletine compared with placebo in both treatment periods. In period 1, the mean stiffness score was 2.53 in the mexiletine group and 4.21 in the placebo group; difference −1.68 (95% CI: −2.66 to −0.71), p<0.001 and in period 2, 1.60 versus 5.27 respectively; difference -3.68 (95% CI: -3.85 to -0.14), p=0.04. The treatment effect was higher in period 2 than period 1, possibly due to unintentional unblinding of study patients who may have overestimated the effect of mexiletine in period 2. Secondary outcomes, including pain score, weakness score and tiredness score, analysed in the overall population without taking account of the treatment periods, favoured mexiletine over placebo.[2, 3]

Summary of evidence on comparative safety

There are limited controlled data and follow-up to establish the clinical safety of mexiletine for the indication under review however the safety profile as an antiarrhythmic is well-established. This is further supported by long term data from a retrospective chart review, post marketing surveillance data and data from a Periodic Safety Update Report since marketing authorisation.[5]

The key safety issue with mexiletine is the risk of inducing an arrhythmia or accentuating a pre-existing arrhythmia, either diagnosed or undiagnosed. This risk is minimised by the recommended cardiac monitoring.[1]

During the key MYOMEX study, an adverse event was reported by 60% (15/25) of patients during treatment with mexiletine and 36% (9/25) of patients during treatment with placebo and these were considered to be related to study treatment in 44% and 12% of patients respectively. No serious adverse events were reported with either treatment. One patient treated with mexiletine discontinued treatment due to an adverse event.[2]

The following adverse events were considered treatment-related in the mexiletine and placebo groups respectively: nausea (two patients and one patient), upper abdominal pain (two patients and no patients) and insomnia (three patients and no patients). One patient discontinued study treatment due to tachycardia in a context of anxiety which was considered as severe and related to mexiletine.[2]

Summary of clinical effectiveness issues

Non-dystrophic myotonias mainly affect skeletal muscles and although these conditions are generally not life-threatening or fatal, they can cause major disability and have a substantial effect on quality of life. Mexiletine was originally developed and licensed as a treatment for ventricular arrhythmias but the company submission notes that this was discontinued in 2008 for commercial reasons. This new formulation of mexiletine has received marketing authorisation for the symptomatic treatment of myotonia in adult patients with non-dystrophic myotonic disorders.

There are no other licensed treatments for myotonia in patients with non-dystrophic myotonia. It has been approved in France for the symptomatic treatment of myotonic syndromes and has been used as an unlicensed medicine for the treatment of non-dystrophic myotonia in the UK for decades. Several medicines are also used off-label, including flecainide, phenytoin, procainamide, and tocainide. The EMA notes that these medicines cannot be recommended as treatment for myotonia, because of associated severe side effects.[1, 2]

The key study (MYOMEX) in patients with myotonia congenita and paramyotonia congenita used a randomised, double-blind, short, crossover design and reported statistically significant improvements in muscle stiffness following treatment with mexiletine compared with placebo. There is no defined minimum clinically important difference for stiffness VAS score and the clinical relevance is uncertain but this was considered sufficient by the EMA to support clinical efficacy in NDM patients. This was supported by results for secondary outcomes of pain, weakness, tiredness and quality of life as well as results of the phase II crossover study [1-3]

There are a number of limitations with the MYOMEX study including the small number of patients (n=25) but this is an orphan medicine. However the European Medicines Agency (EMA) noted the importance of the choice of primary and secondary outcomes given the small sample size and that other outcomes (for example direct muscle strength assessment) could have been included. Most of the study outcomes were subjective.[2]

The duration of each treatment period in the MYOMEX study was limited to approximately 18 days which is short for the treatment of a chronic condition. Myotonia can be highly variable between and within patients and the stiffness VAS score was assessed by patients to reflect symptoms over the last 3 days. This may not represent chronic treatment.

The EMA noted that there was some uncertainty in the treatment effect observed with mexiletine in the MYOMEX study related to the crossover design. Statistical analysis of the phase II crossover study indicated a carry-over effect and the two treatment periods were analysed separately. It was therefore considered that there was a substantial risk of a carry-over effect although statistical testing did not find this. In addition, the potential overestimation of treatment effect observed in the phase II crossover study, was also considered a potential risk in phase III MYOMEX study in which approximately half of enrolled patients had received previous mexiletine.[2]

The MYOMEX study population includes patients with myotonia congenita (n=13) and paramyotonia congenita (n=12). There is no controlled evidence in patients with other subtypes of non-dystrophic myotonia. Study patients were required to have symptoms severe enough to justify treatment according to clinical and disability criteria. The study criteria included symptoms affecting at least 2 segments and that had an impact on at least 3 daily activities.[1, 2]

During the study, all patients underwent a forced titration of mexiletine to 500mg. This is the maximum recommended dose and may differ from dosing in clinical practice which is likely to be titrated according to symptoms.[1, 2]

The safety profile of mexiletine as an antiarrhythmic is well-established. The most important safety issue is that it can trigger arrhythmias or aggravate an existing arrhythmia, whether or not it has been diagnosed. The SPC provides recommendations for monitoring. To minimise the risk of cardiac arrhythmias, patient alert cards and an educational guide for healthcare professionals are

to be issued. The EPAR notes that there is a planned registry study to determine the long-term safety and tolerability of mexiletine for this indication.[1, 2]

There are no data comparing mexiletine with other medicines that may be used off-label for these patients in clinical practice.

The introduction of mexiletine would offer a licensed treatment option for the symptomatic treatment of myotonia in adult patients with non-dystrophic myotonic disorders. This licensed formulation of mexiletine (Namuscla®) is available only as a 167mg capsule (equivalent to mexiletine hydrochloride 200mg).[1]

Patient and clinician engagement (PACE)

A patient and clinician engagement (PACE) meeting with patient group representatives and clinical specialists was held to consider the added value of mexiletine, as an orphan medicine, in the context of treatments currently available in NHSScotland.

The key points expressed by the group were:

- Non-dystrophic myotonic disorders are a spectrum of rare, life-long conditions. The symptoms include muscle stiffness, pain, weakness and fatigue and can vary from mild to severe.
- There are limited treatment options available, including unlicensed lamotrigine, carbamazepine and mexiletine. This formulation of mexiletine (Namuscla®) is the only medicine licensed for this indication.
- Mexiletine may relieve myotonic symptoms resulting in improved mobility and ability to perform daily activities. It may also reduce the incidence of falls and associated complications. This may relieve the physical and emotional impact of the condition and improve quality of life.
- Mexiletine may produce gastrointestinal side effects but these are generally considered manageable and outweighed by the improvements in myotonic symptoms. Cardiac monitoring is required for treated patients but there are not expected to be any service implications.

Additional Patient and Carer Involvement

We received a patient group submission from Muscular Dystrophy UK, which is a registered charity. Muscular Dystrophy UK has received 0.1% pharmaceutical company funding in the past two years, including from the submitting company. A representative from Muscular Dystrophy UK participated in the PACE meeting. The key points of their submission have been included in the full PACE statement considered by SMC.

Summary of comparative health economic evidence

The submitting company presented a cost-utility analysis (CUA) comparing mexiletine against a no treatment comparator for the treatment of myotonia symptoms in adult patients with non-dystrophic myotonic disorders. Clinical experts advised that current treatments in Scotland for the

indication under review include unlicensed (generic) mexiletine or off-label phenytoin, lamotrigine, acetazolamide, and benzodiazepines. Therefore the 'no treatment' comparator in the economic analysis does not reflect current practice.

The cost-utility analysis is based on individual patient level data from the modified intention-to-treat (mITT) sample (n=25) of genetically identified non-dystrophic myotonic adults aged 18–65 years recruited to the MYOMEX study. The no treatment arm is represented by the placebo arm from the MYOMEX study. An NHSScotland perspective is taken and the model is run over a one year time horizon. The company suggests there is insufficient evidence on the natural history of the disease to enable a lifetime evaluation. However, they also note that evidence indicates patients perceive increasing severity over a lifetime, and they also state that the beneficial outcomes from the MYOMEX study (mean treatment duration 19 days) can be expected to persist over a lifetime resulting in substantial impacts on quality of life. Given these statements, longer time horizons were requested to formally reflect the full costs and benefit impacts associated with continued use of mexiletine.

The company explained that there are no distinct health states in non-dystrophic myotonia, and therefore their analysis was based on costs and quality of life changes for each individual patient in the MYOMEX study based on the treatment (i.e. mexiletine) and non-treatment (i.e. placebo) arms. In effect this is an individual patient level data analysis, based on the mITT sample assuming the treatment duration and effect last for a one year, as opposed to the mean treatment duration of 19 days in the MYOMEX study.

Key evidence from the MYOMEX study came from (i) the Individualised Neuromuscular Quality of Life (INQoL) measure which was a secondary outcome in MYOMEX but used as a primary outcome in the CUA to inform utility values, and (ii) the Clinical Myotonia disability Scale (CMS) score, which was used to derive disease severity levels and support dimensions upon which resource use estimates were assumed by clinical experts. This evidence from MYOMEX was further supported by evidence from three other sources, which was used to inform alternative estimates in sensitivity analyses.[3-5]

As previously discussed, non-dystrophic myotonia does not have an impact on survival. However, myotonia symptoms can cause significant lifetime morbidity which affects health related quality of life. Therefore no survival impacts were measured in the MYOMEX study and the primary outcome for the economic analysis is health related quality of life, presented in the form of quality adjusted life years (QALYs).

Quality of life was measured by the INQoL scale. Key results from the MYOMEX study showed improvement in all of the INQoL domains after treatment with mexiletine with the greatest impact observed in patient activity. However, the study was not powered for this secondary outcome. The company highlighted that this is not unusual in the context of a rare condition. In order to derive utility values from the INQoL questionnaire a discrete choice experiment (DCE) and mapping exercise was undertaken. The process involved six key steps: (i) simplification of the INQoL – reducing the 45 questions down to 8 questions which related to the 5 dimensions of the EQ-5D, (ii) a response reduction stage where the 6-7 response levels from INQoL were reduced to 4 levels relating the EQ-5D-5L levels (iii) combining 8 questions (linked to the 5 EQ-5D questions) with the reduced response levels using a published orthogonal design to generate 32 choice questions for

the DCE scenarios (iv) conducting the DCE (online with a sample of 508 participants representative of UK population), (v) statistical analysis of the dataset and derivation of utility values (vi) adjustment for inconsistencies. The utility values used in the economic analysis were calculated based on utility decrements applied to each of the 8 pre-selected categories: muscle weakness, muscle locking, pain, tiredness, ability to wash, ability to undertake leisure activities, anxiety and depression.

The costs included in the CUA are those related to the medicines cost of mexiletine, cardiac evaluation prior to and up to 48 hours after medicine initiation, adverse events and health care utilisation costs related to non-dystrophic myotonic support (such as physiotherapy, occupational health and wheel chairs). Medicines costs were dependent on compliance (94.8%) and discontinuation (8%). Three weeks of treatment costs were incurred prior to discontinuation of mexiletine, as per MYOMEX study. Adverse events were included in the analysis as a cost for gastrointestinal disturbance and probability of dyspepsia for those with gastrointestinal disturbance.

No resource data was collected during the MYOMEX study, therefore assumptions were made by the company and clinical experts. They specified relevant resource items and the specific quantities of these according to specific health dimensions of non-dystrophic myotonic disease and severity of that disease. A proxy was developed whereby the seven dimensions of the CMS disability rating scale (speech, handwriting, eating, hygiene, dressing, walking, and ascending/descending stairs) were used to assign 8 key resource use elements: physiotherapy sessions, occupational health sessions, speech therapy, day case attendance at hospital, use of a wheel chair, use of a walking stick, and walking frame and no mobility aid. The amount and frequency of these resources was dependent on disease severity (mild, moderate or severe) from the CM disability score data in the trial.

This resubmission has been assessed under the fast track resubmission process. A Patient Access Scheme (PAS) was submitted by the company and assessed by the Patient Access Scheme Assessment Group (PASAG) as acceptable for implementation in NHSScotland. Under the PAS, a discount was offered on the list price of the medicine. The base case 'with PAS' analysis estimated an incremental cost-effectiveness ratio (ICER) of £36,523 per QALY over a one year time horizon, with the QALY gains solely driven by difference in quality of life due to treatment with mexiletine. The base case and key sensitivity analyses results are shown in table 3 below.

Upon request the company provided a Markov model based lifetime analysis, with the same key inputs and some amendments to assumption based on UK clinical audit data from a large, long term skeletal muscle channelopathy cohort[5]. The lifetime analysis was run over 56 years (until all patients were dead), assuming that the treatment and treatment effect evidenced in MYOMEX continued throughout the patients' lifetimes. In the lifetime base case analysis the discontinuation rates, probability of adverse events and dosing schedules were changed from the one year time horizon base case to alternative values derived from the cohort study[5], e.g. the daily dosing schedule was reduced from 600mg daily to 429mg. The New Drugs Committee (NDC) agreed that the base case lifetime analysis with more realistic dosing schedule of 429mg daily would be the most appropriate base case analysis and this resulted in with PAS ICER of £30,000. This is

presented in Table 3 as the base case, followed by the one year time horizon and other key sensitivity analysis results.

Table 3: Base case and selected sensitivity analysis results with PAS, mexiletine versus no treatment

	Base case / Scenario analysis	Incremental cost-effectiveness ratio (ICER) With PAS
	NDC preferred Base case: lifetime analysis (dosing 429mg)	£30,000
	Initial Base case: one year time horizon (dosing 600mg)	£36,523
1	Lifetime analysis (dosing 600mg)	£42,039
2	10% multiplier on quality of life waning for no treatment arm (dosing 429mg)	£26,544
3	Requested lifetime: assume 22233 EQ5D=Worst HS INQoL and a 30% upper bound for utility decrements applied simultaneously (dosing 429mg)	£25,717
4	Requested lifetime: assume 22233 EQ5D=Worst HS INQoL and the 20% lower bound for utility decrements applied simultaneously (dosing 429mg)	£41,790

A wide range of one way sensitivity analysis were undertaken on key parameters, applying an arbitrary 20% for an upper and lower bound around the mean values used in the analysis. The parameters with the greatest impact were due to utility decrements that describe extreme impact of non-dystrophic myotonic on leisure activities and daily activities as well as extreme and moderate impact on mental health. All sensitivity analyses on cost and resource use parameters had a negligible impact on the ICER.

Scenario analyses explored alternative data sources to inform compliance estimates, dosing schedules and alternative worst case assumptions for relating the worst INQoL rating to the worst EQ-5D score possible. The model results were relatively robust to all one way sensitivity analyses undertaken and the few scenario analyses explored, with the exception of 600mg daily dosing (from MYOMEX) which substantially increases the ICER. Including a quality of life waning effect in the no treatment arm only (to reflect worsening disease overtime for untreated patients) improved the base case ICER. Applying the 20% or 30% upper bounds (in effect assigning bigger disutility to the condition - which favours mexiletine treatment) for all utility decrements reduces the ICER, while applying the lower bounds increases the ICER.

There were a number of weaknesses associated with the analysis:

- In general, the process undertaken to estimate utility values is appropriate. The DCE itself had a large sample size, representative of UK general population, with robust statistical analyses undertaken on the final dataset. However, there were some key methodological

inconsistencies and assumptions used throughout the process which has introduced bias and subjectivity to the analysis, undermining the validity of the final results. The simplification and reduction steps at the outset of the process were undertaken on assumptions made by the company and clinical experts, as opposed to using qualitative or quantitative methodology to elicit relevant attributes and statistical analysis of these, resulting in subjectivity and the possibility for selection bias at the outset. The company explained that a qualitative or quantitative methodology to elicit relevant attributes and statistical analysis of these was not possible due to the size of the datasets available. In the final utility calculation, the decision to use 8 INQoL questions to apply utility decrements to (some of which are highly correlated), as opposed to 5, introduced the possibility of double counting, potentially further biasing the results. The company however asserted that double counting of utility decrements had not been introduced. The company's submission explains the process was validated by 3 clinical experts and one health economic expert in preference elicitation who was "*broadly supportive of the overall approach".* However, despite a robust analysis of the final dataset, the process undertaken at the early stages have resulted in uncertainty and it is unclear if and how this impacts on the validity of the results. It is not that the utility values derived are necessarily wrong, but there are numerous underlying inconsistencies and uncertainties used to generate them at the early stage which undermines their validity. The utility values likely bias the analysis towards mexiletine.

- The expert and company 'elicitation' exercise to determine which resource items and the specific quantity that would be used according to what dimension of the CMS is highly subjective. There is no reference to a specific qualitative methodology that was followed to determine/elicit these values, e.g. a Delphi panel, which would have made this process more robust and less subjective and open to bias. However, given lack of other information, this approach enabled determination of resource use which was considered appropriate to the three clinical experts involved. It is noted that differences in resource use costs are not a significant driver of the findings.
- There are weaknesses in the evidence base underpinning the model; the economic analysis is based on the MYOMEX study which had a small sample size (n=25), and a short treatment duration (mean 19 days). Additionally, the key data source is the INQoL – which was a secondary outcome from MYOMEX for which the study was not powered to detect a significant difference.
- The treatment effect of mexiletine was assumed to be constant throughout the analyses. No sensitivity analysis was undertaken to explore the possibility of dissipating treatment effects over time or the use of stopping rules.

The Committee also considered the benefits of mexiletine in the context of the SMC decision modifiers that can be applied when encountering high cost-effectiveness ratios and agreed that a number of the criteria were satisfied: a substantial improvement in quality of life; and the emergence of a licensed medicine as an alternative to an unlicensed product that is established in clinical practice in NHS Scotland. In addition, as mexiletine is an orphan medicine, SMC can accept greater uncertainty in the economic case.

After considering all the available evidence and the output from the PACE process, and after application of the appropriate SMC modifiers, the Committee accepted mexiletine for use in NHSScotland.

*Other data were also assessed but remain confidential.**

Additional information: guidelines and protocols

There is a paucity of available guidance on the treatment of non-dystrophic myotonic disorders. The Scottish Muscle Network published an updated version of the "Scottish guideline for the management of myotonic dystrophy in adults" in January 2017.[6] This guidance outlines specific considerations for different specialties involved in the management of patients with mainly dystrophic myotonic dystrophy. The guidance states that "mexiletine is an effective short term treatment for grip myotonia. There are no studies on long term therapy. Myotonia in DM1 [Type 1 myotonic dystrophy] rarely requires therapy. It is recommended that mexiletine should only be prescribed by a neurologist and after cardiology review."[6]

Additional information: comparators

There are no other licensed comparators. Other medicines are used off-label, including phenytoin, lamotrigine, acetazolamide, benzodiazepines and quinidine.

Cost of relevant comparators

Medicine	Dose Regimen	Cost per year (£)
Mexiletine	**167 to 500mg daily**	**18,200 to 54,600**

Costs from BNF online on 5 November 2019. Costs do not take any patient access schemes into consideration.

Additional information: budget impact

The submitting company estimated the population eligible for treatment to be 14 patients per annum to which confidential estimates of treatment uptake were applied**.** The budget impact estimate was undertaken assuming many patients currently receive 'no treatment' (as per the economic analysis) and some received unlicensed mexiletine.

SMC is unable to publish the with PAS budget impact due to commercial in confidence issues. A budget impact template is provided in confidence to NHS health boards to enable them to estimate the predicted budget with the PAS.

*Other data were also assessed but remain confidential.**

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This assessment is based on data submitted by the applicant company up to and including 29 October 2020.

**Agreement between the Association of the British Pharmaceutical Industry (ABPI) and the SMC on guidelines for the release of company data into the public domain during a health technology appraisal: http://www.scottishmedicines.org.uk/About_SMC/Policy*

Medicine prices are those available at the time the papers were issued to SMC for consideration. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and NHS Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

Patient access schemes: A patient access scheme is a scheme proposed by a pharmaceutical company in order to improve the cost-effectiveness of a medicine and enable patients to receive access to cost-effective innovative medicines. A Patient Access Scheme Assessment Group (PASAG), established under the auspices of NHS National Services Scotland reviews and advises NHSScotland on the feasibility of proposed schemes for implementation. The PASAG operates separately from SMC in order to maintain the integrity and independence of the assessment process of the SMC. When SMC accepts a medicine for use in NHSScotland on the basis of a patient access scheme that has been considered feasible by PASAG, a set of guidance notes on the operation of the scheme will be circulated to Area Drug and Therapeutics Committees and NHS Boards prior to publication of SMC advice.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.