NICE National Institute for Health and Care Excellence

Mexiletine for treating myotonia in adults with non-dystrophic myotonic disorders [ID1488]

Lead team presentation

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Company: Lupin

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Disease background

- Non-dystrophic myotonias (NDM) are a group of genetic diseases caused by mutations in skeletal muscle chloride or sodium ion channels
- The main subgroups are myotonia congenita (chloride channelopathies) and paramyotonia congenita (sodium channelopathies) but all NDMs have the same common feature of myotonia
- Myotonia is a delay in muscle relaxation following muscle contraction
- Muscle locking or stiffness (myotonic episode) describes the inability to relax a muscle which can cause issues such as inability to stand or sit freely, and the potential to fall – these episodes can last from seconds to minutes
- Triggers for myotonic episodes include:
  - Cold weather
  - Stressful situations
  - Using stairs

Patient perspective

- There are around 405 people in England who are living with non-dystrophic myotonic disorders (NDM)

Impact of symptoms

- Along with muscle locking, NDM symptoms including muscle weakness, pain, fatigue and risk of injury due to falls which have a large impact on quality of life
- Patients with NDM often feel anxious and may experience shaming or bullying due to the symptoms of their condition
- Patients often feel that “life is grinding to a halt” due to difficulties with employment, public transport, school, social activities and problems completing daily tasks
- Potential for physical functioning burden on family and carers if the disease is not managed

Current experience of treatment

- Patients may be prescribed drugs off label including mexiletine or another sodium channel blocker
- Patients who have taken mexiletine have experienced significant reduction in the impact of symptom episodes
- Some people try muscle warming routines, specialist physiotherapy or speech or occupational therapy
- Mexiletine is contra-indicated for use in pregnant women or people with cardiac arrhythmias

Mexiletine (NaMuscla, Lupin)

Mechanism	• Blocks sodium channels in muscle cells that are involved in the contraction and relaxation of muscles
Marketing authorisation	• EMA granted authorisation December 2018: “symptomatic treatment of myotonia in adult patients with non-dystrophic myotonic disorders”
Administration and dose	• Daily oral administration. Starting dose of 167mg (1 capsule equivalent to 200mg imported mexiletine), after at least one week, based on clinical response, it can be increased to 333mg (2 capsules, 400mg equivalent) with a further increase to 500mg (3 capsules, 600mg equivalent) after at least one further week
List price	• £5,000 per pack of 100 capsules (~£60,000 annual cost) • Confidential patient access scheme available
History of off-label use	• For more than 10 years, pharmacological management of NDM has involved using mexiletine off-license • Since marketing authorisation, Lupin has provided mexiletine at a confidential interim price discount

Decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission
Population	Adults with non-dystrophic myotonic disorders requiring treatment of symptomatic myotonia	As per final scope
Intervention	Mexiletine	As per final scope
Comparator	Established clinical management without mexiletine, including but not limited to: • lamotrigine • best support care.	• Best supportive care only – see Issue 3
Outcomes	The outcome measures to be considered include: • Muscular symptoms (including stiffness and weakness) • Fatigue • Motor function • Pain • Adverse effects of treatment • Health-related quality of life.	• Reported all outcomes as per final scope • Health-related quality of life and adverse events are included in the economic model

Professional group comments

Aim of treatment

- To ameliorate symptoms of non-dystrophic myotonia (reduction in muscle pain, cramps and stiffness)

Current clinical practice

- No formal guidelines
- After diagnosis and genetic confirmation, choice of drug is determined by individual clinician based on personal preference and experience
- Patients would be treated in specialist neuromuscular clinics only

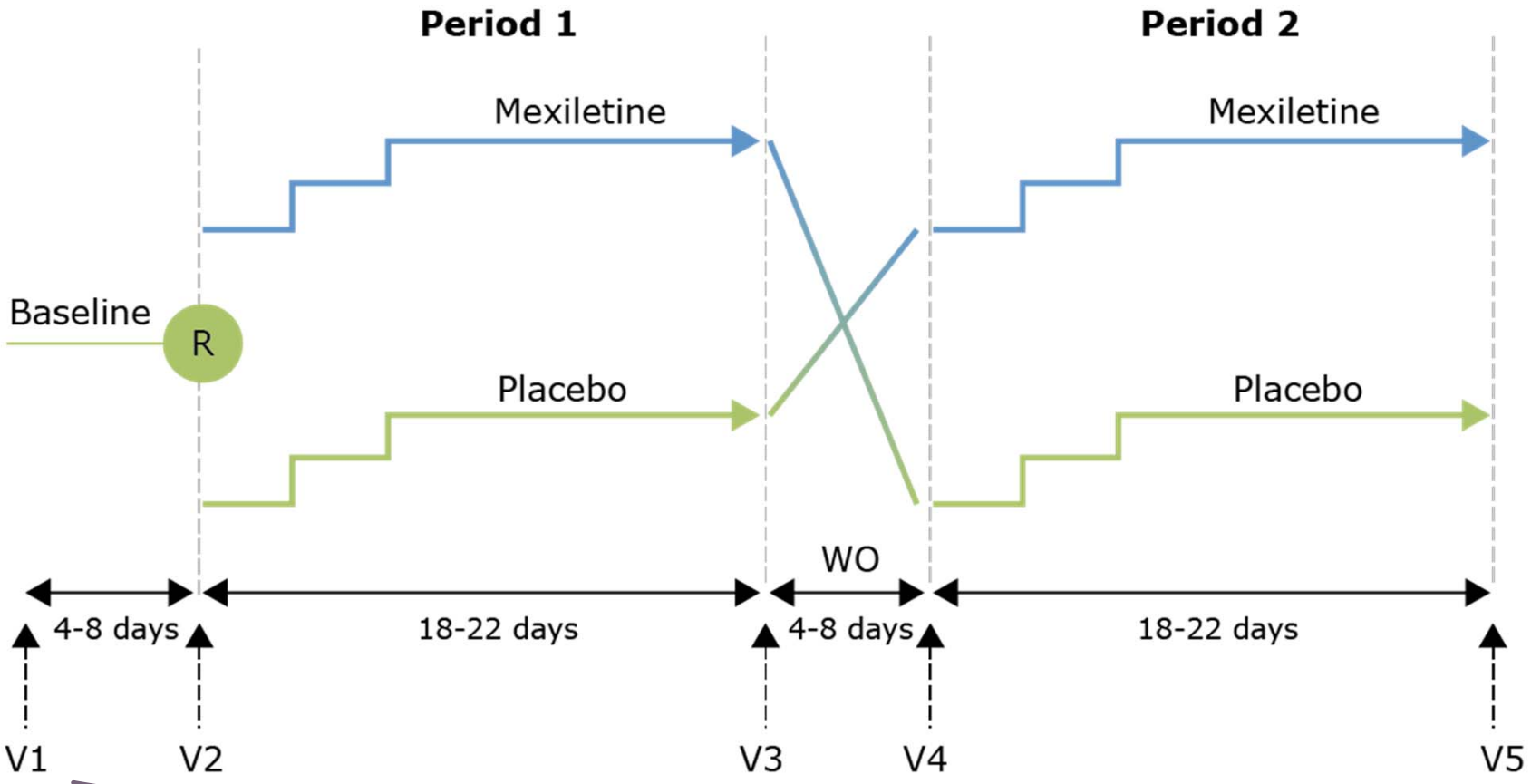
Current use of mexiletine

- Expect that mexiletine is more efficacious than other drugs – although slow titration with carbamazepine may be used until genetic diagnosis is established
- Requires ECG monitoring before starting treatment and at each dose increase
- NaMuscla could provide uniformity of supply as it is currently imported

Key clinical evidence - overview

Trial	N	Population	Design	Outcomes used in economic model
MYOMEX (pivotal)	26	Genetically confirmed NDM patients in France	Crossover RCT vs placebo, 18 days duration (see next slide)	Quality of life Adverse events Compliance
Suetterlin et al.	63	UK patients with NDM taking mexiletine	Retrospective review, minimum 6 months follow up	Average dose Discontinuation
Statland et al.	59	Patients with clinical symptoms or signs of non-dystrophic myotonia	Crossover RCT vs placebo, 4 weeks duration	Quality of life scenario
Stunnenberg et al.	30	Genetically confirmed NDM from the Dutch neuromuscular database	Aggregated N-of-1 trials vs placebo	Adverse event and compliance scenarios

Key clinical evidence – MYOMEX design



At screening, [redacted] patients ([redacted]) stopped mexiletine. [redacted] patients ([redacted]) had mexiletine prior to screening and [redacted] patients ([redacted]) were mexiletine naive

Key clinical evidence – MYOMEX results

Primary outcome – Stiffness measured by visual analogue scale

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Primary outcome – Stiffness measured by visual analogue scale

Issues discussed at technical engagement

- Issue 1: Generalisability of the trial
- Issue 2: Dose and dosing schedule
- Issue 3: Comparator treatments
- Issue 4: Disease progression
- Issue 5: HRQoL valuation
- Issue 6 : Other modelling assumptions
  - Discontinuation of treatment
  - Resource use multiplier
  - Adverse events

Generalisability of the trial – Issue 1

Background

- MYOMEX inclusion criteria:
  - Between age of 18 and 65
  - Genetically confirmed non-dystrophic myotonia disorders
  - Symptoms severe enough to justify treatment (symptoms affect >1 segment of the body and ≥3 daily activities)
- **Technical team judgement:** Some uncertainty about generalisability of age/severity of patients in the trial compared to NHS clinical practice – also linked to dose (see Issue 2)

Professional group comments – Association of British Neurologists (ABN)

- Patients are treated based on clinical severity and if their myotonia impacts on their activities of daily living – criteria broadly generalisable
- Not possible to fully evaluate severity criteria because they are not published
- 13% of non-dystrophic myotonia patients under a neurologist are over 65 years and the majority are on treatment (>92%)

Company response

- Clinical advisory board consider Activities of Daily Living (ADLs) to be most relevant criteria, but most NDM patients also match severity inclusion criteria

Generalisability of the trial – Issue 1

Potential for unblinding:

- [redacted] of patients in MYOMEX had previous treatment with mexiletine, recognisable side effects of mexiletine could have effectively unblinded patients to the treatment received
- In Statland et al. trial, 22% of patients had previous treatment with mexiletine and 79-80% of participants correctly guessed which treatment they received

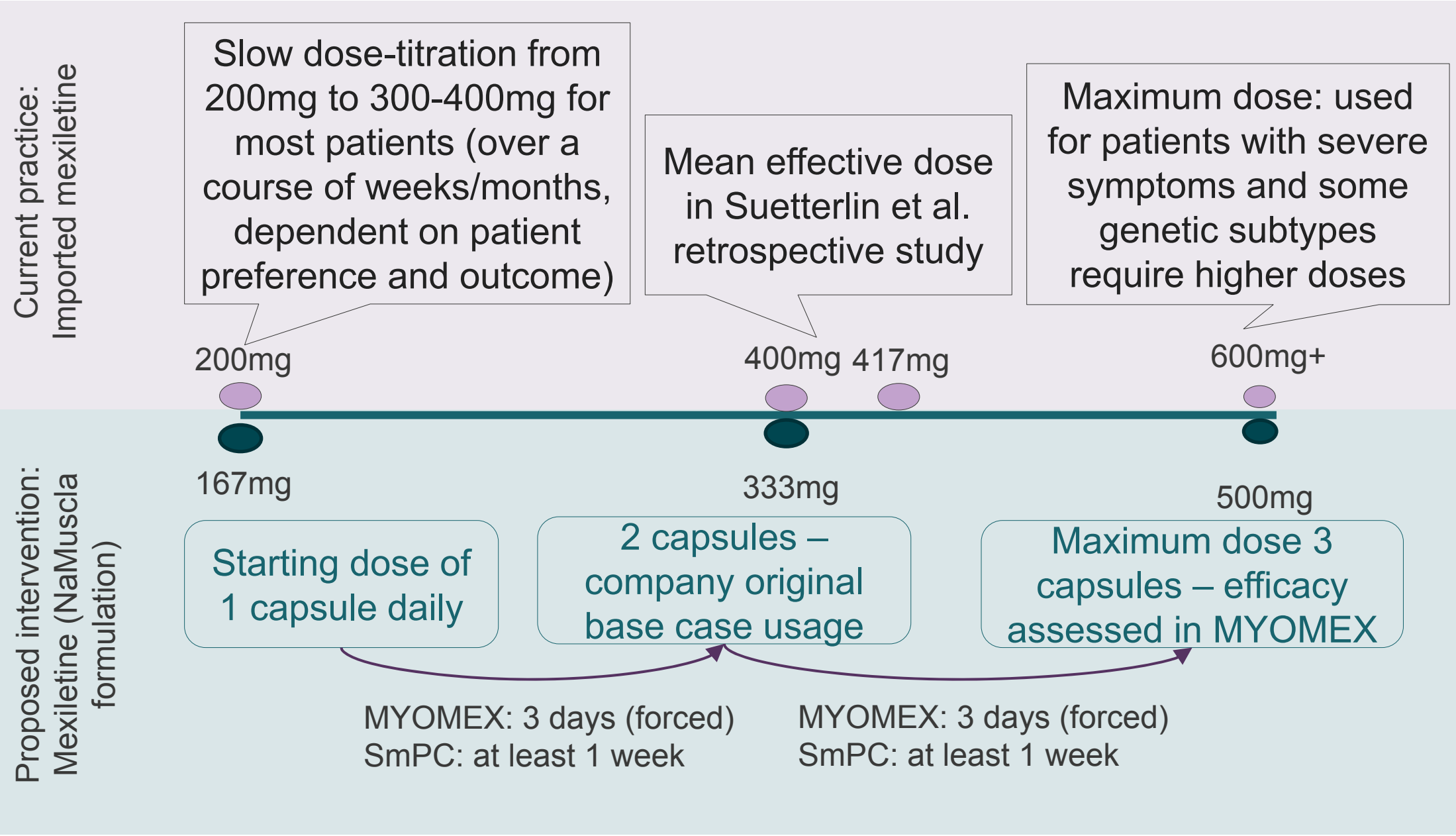
Potential carry-over effect:

- Crossover study designs can lead to carry-over effects if the wash-out period is not sufficiently long. Company analysis rejected a hypothesis of a crossover effect using the stiffness VAS outcome
- The analysis of stiffness in Statland et al. showed a significant carry-over effect (4 week treatment with 1-week wash-out period)

ERG comment

- For the reasons above, blinding was inadequate for MYOMEX and this could likely affect outcomes, particularly as key outcomes are patient-reported
- No statistical evidence of a carry-over effect in MYOMEX, although subject to uncertainty and underpowering

Dose and dosing schedule – Issue 2



Dose and dosing schedule – Issue 2

Technical team judgement: Not appropriate to separate the costs and the benefits of treatment. Adjustment is needed - appropriate to use the cost of the 600mg equivalent dose in the economic model. Importance of dosing schedule and titration is unclear.

Professional group comments – ABN

- 400mg/day is most common, very severe cases have 600-800mg/day
- On initiation, 100mg tablets are used slowly up-titrate mexiletine to minimise the side effects and reduce the risk of discontinuation due to gastric events
- When 100mg tablets are not available then 200mg tablets are used instead
- Patients who are not naïve to mexiletine will often tolerate faster titration using 200mg tablets.

Company response

- Consider Suetterlin et al. to be the mean ***effective*** dose and the optimal outcome for these patients - Updated base case to use 15 caps/week (429mg equivalent) from 14 caps/week
- In patients with dystrophic myotonia type 1, non-significant difference in hand-grip response time between 150mg TID vs 200mg TID
- EMA considered that the optimal dose regimen has been established
- The modelled rate of titration from the SmPC uses the costs of NaMuscla, which will capture the costs conservatively

ERG comments

- Applying mean doses stratified by genetic subgroup from Suetterlin et al. population to the Statland et al./MYOMEX population gives a mean effective dose of 467mg

Comparator treatments – Issue 3

At the scoping stage, it was considered that:

- Imported mexiletine could not be considered as a comparator despite being the preferred treatment option for more than 10 years
- Many antiarrhythmic and anti-epileptic medicines are used off-label for NDM (carbamazepine, acetazolamide, phenytoin, flecainide)
- Lamotrigine is increasingly used where mexiletine is not indicated (cardiac arrhythmias or pregnancy)

Final scope comparator:

Established clinical management without mexiletine, including but not limited to:
- lamotrigine
- best supportive care

Non-standard decision problem: Established clinical management without mexiletine cannot be observed

"Because the intervention is already established in clinical practice… In order to establish the true counterfactual scenario, the decision problem would need to consider what treatments [patients currently receiving mexiletine] would receive without mexiletine." (technical report)

Comparator treatments – Issue 3

[redacted]

Background

- Company considers lamotrigine is not established in clinical practice based on market research data and advisory board survey that shows limited current lamotrigine use
- For all other off-label treatments, the company consider these are unlicensed, no data to support their efficacy and that they have no additional benefit compared to placebo

Comparator treatments – Issue 3

Technical team judgement: Best supportive care as modelled in the company base case does not represent established clinical management without mexiletine

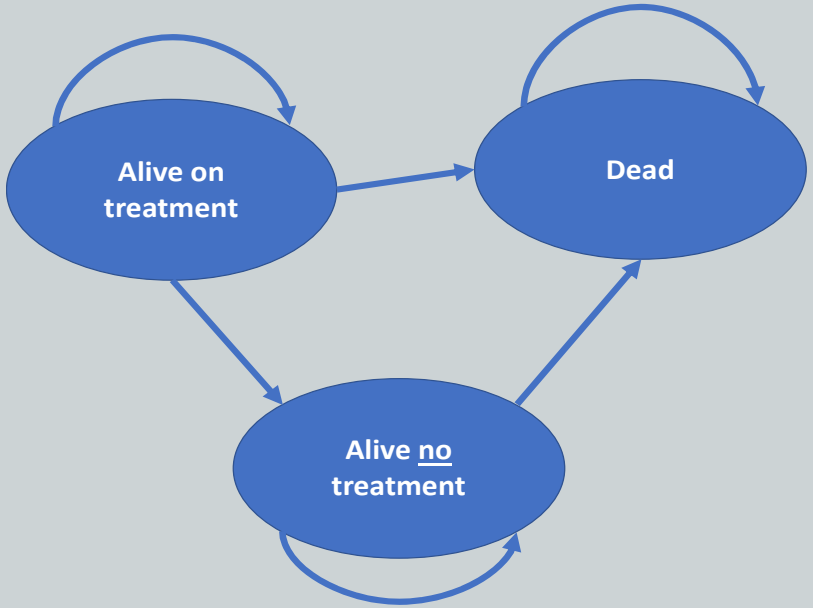
Professional group comments

- Lamotrigine is not established practice as only recent evidence has been published regarding its efficacy and its place in treatment pathway is uncertain
- Lamotrigine is currently used in patients who do not tolerate mexiletine, who have cardiac arrhythmias or in women trying to conceive
- Lamotrigine has some efficacy at high doses in this group of patients but takes significantly longer to titrate up
- Potential for side effects such as rash and Stevens-Johnson syndrome
- Other off-label treatments have significantly poorer efficacy and a more significant side effect profile to make their use rare in clinical practice.

ERG comments

- It is not surprising that there is little use of lamotrigine given that mexiletine has been available for much of the time (at a lower price than in this appraisal)
- ERG provides an indicative analysis assuming lamotrigine has a range of utility benefits between best supportive care and mexiletine

Economic model structure and assumptions

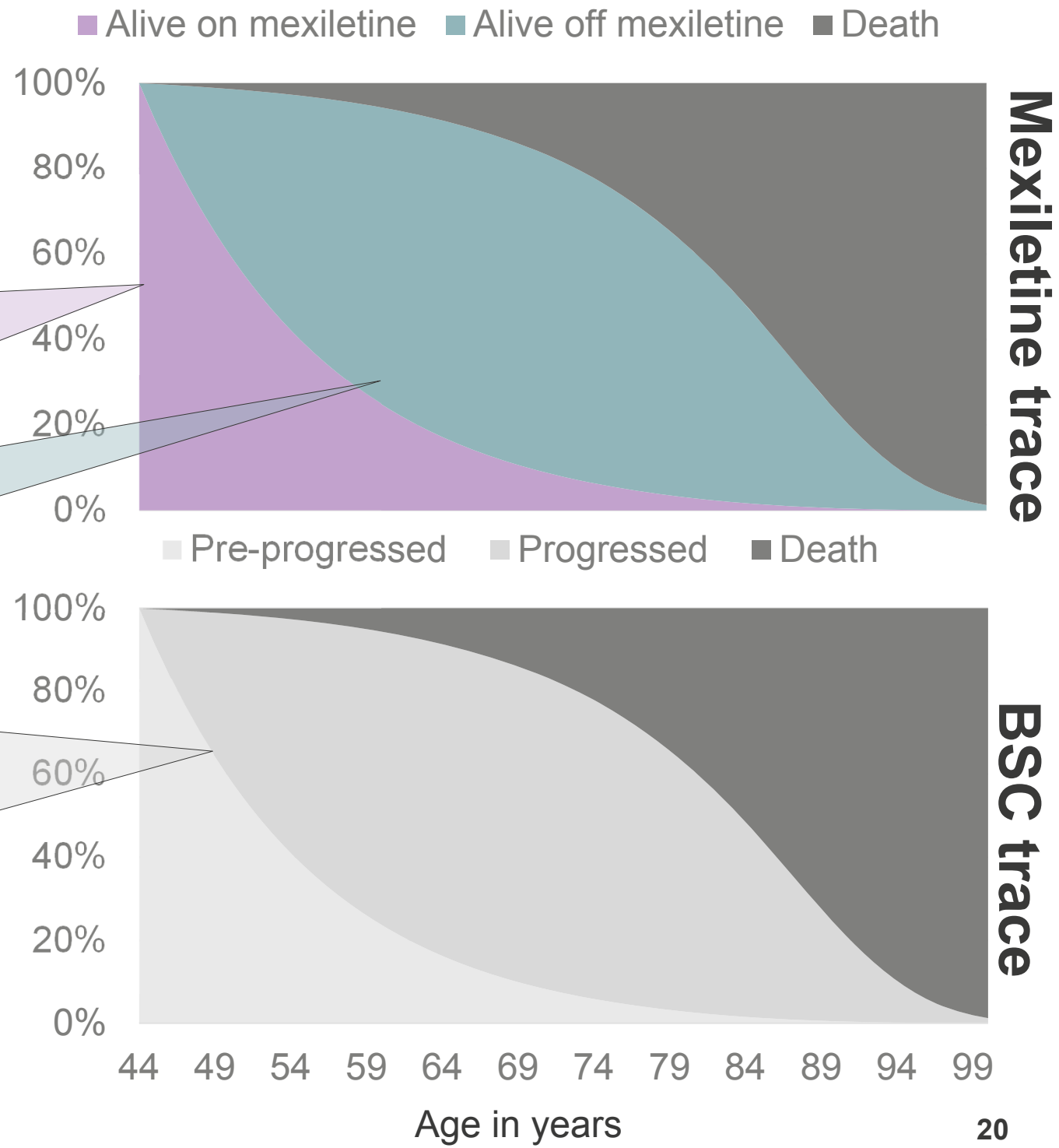
Model structure	
Transitions	Only transitions are based on discontinuation (see Issue 6) and general population mortality (no difference between arms)
Disease progression	A 15% reduction in quality of life is modelled in both treatment arms to reflect worsening of symptoms over time (see Issue 4)
Utility values	Derived from INQoL data from MYOMEX (see Issue 5)

Markov trace

Utility value of [redacted] whilst on mexiletine. Annual discontinuation rate transition to 'Alive off mexiletine'

Utility value of [redacted] (+15% reduction to account for disease progression).

Utility value of [redacted] initially. Upon progression, 15% reduction in utility is applied. Progression transition is [redacted] faster than mexiletine discontinuation curve



Disease progression differential – Issue 4

Background

- The natural history of NDM is not well characterised - whether symptoms of NDM worsen with age was discussed at technical engagement
- At technical engagement, the company agreed that the stated purpose of a worsening of symptoms with age was not implemented appropriately in the model
- In response, the company included a 'progression' event for both arms that reduced quality of life observed in the trial by 15% to represent this
- This 'progression' happened [redacted] faster in the control arm based on advisory board data
- **NB:** This is not applied as an annual discontinuation

Professional group comments

- The natural history of NDM is to show some worsening in older years and is likely the reason why a large proportion of older patients under a neurologist are on treatment (>92%)

ERG comments

- Implementation is still sub-optimal and surrounded by many uncertainties:
  - A single decrease in QoL is not likely to reflect the natural history of the condition, as it is more likely that patients experience a steady decline in QoL
  - The appropriateness of the 15% decline in QoL, on top of the differences in utility observed in the trial, is also questionable
- ERG base case removes this assumption with minimal impact on the ICER

Health-related quality of life – Issue 5
Measurement of HRQoL

Company approach

- HRQoL was measured in MYOMEX using the Individualized Neuromuscular Quality of Life Questionnaire (INQoL) at baseline, placebo (18 days) and mexiletine (18 days)
- INQoL is a condition-specific patient-reported outcome measure. INQoL is made up of 45 items, with 4 domains (symptoms, life domains, treatment effects and overall QoL)
- The company consider that generic measures of HRQoL, such as the SF-36 are unable to effectively capture muscle weakness and muscle locking and only measured INQoL in MYOMEX
- The company therefore measure only INQoL and completed valuation studies with conceptual mapping of INQoL to EQ-5D-3L utility values

ERG comments

- The company does not demonstrate that generic measures such as the EQ-5D or SF-36 are unable to measure the HRQoL of patients with NDM
- One of the benefits of using generic measures is that they are able to capture broader aspects of health such as comorbidities and the impact of AEs, which can be missed by condition-specific measures
- The ERG believes that a generic measure should have been included in line with the NICE reference case

Health-related quality of life – Issue 5
Measurement of HRQoL

SF-36 example

The following questions are about activities you might do during a typical day. In the past 1-week does your health limit you in these activities? If so, how much?

(Please circle one number on each line)

	ACTIVITIES	Yes Limited A lot	Yes Limited A little	No, Not Limited At All
3a:	Vigorous activities, such as running, lifting heavy Objects, participating in strenuous sports	1	2	3
3b:	Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	1	2	3
3c:	Lifting or carrying groceries	1	2	3
3d:	Climbing several flights of stairs	1	2	3
3e:	Climbing one flight of stairs	1	2	3
3f:	Bending, kneeling, or stooping	1	2	3
3g:	Walking more than one kilometre	1	2	3
3h:	Walking half a kilometre	1	2	3
3i:	Walking 100 metres	1	2	3

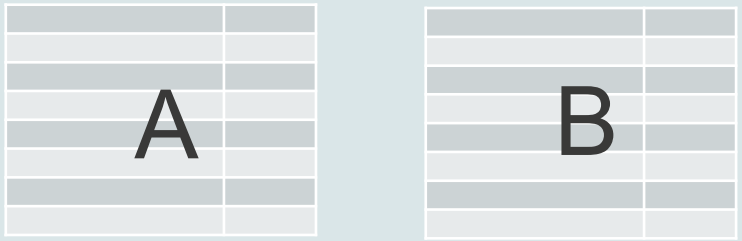
INQoL example

1. Do you have any muscle weakness due to your muscle condition?
   a) How much weakness would you say you have in the muscles affected by your condition? (1-7 Likert scale)
   b) Does your muscle weakness cause difficulties in your life at the moment? (0-6 Likert scale)
   c) How important to you are any difficulties caused by your muscle weakness? (0-6 Likert scale)
2. Do you have any ‘locking’ (seizing up) of your muscles as a result of your muscle condition?

Health-related quality of life – Issue 5
Valuation of HRQoL – company studies

Discrete choice experiment (DCE) study

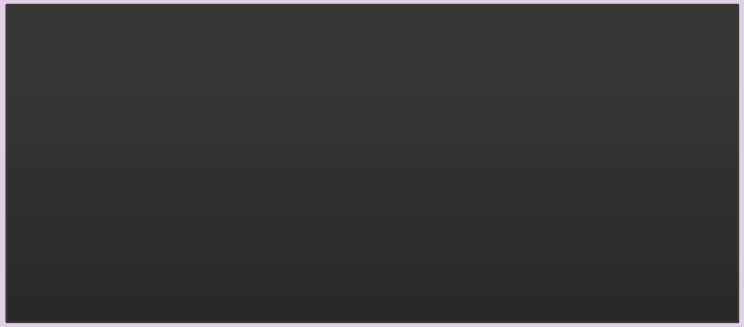
- 508 members of the UK general population completed an online survey comparing two hypothetical sets of health states drawn from a simplified version of the INQoL questionnaire (4 responses only)
- 8 attributes varied simultaneously
- Results were analysed using the conditional logit model to estimate a linear function



Which treatment is best A or B?

Vignette study

- 200 members of the UK general population completed 1-1 interviews using a time trade-off (TTO) exercise comparing vignettes of hypothetical health states
- Similar methodology to create vignettes as DCE methodology, also analysed to estimate linear function



Consider a choice between living in the health state described for 10 years or 10 minus [x] years in full health

Health-related quality of life – Issue 5
Valuation of HRQoL – ERG comments

Statland et al. QoL data

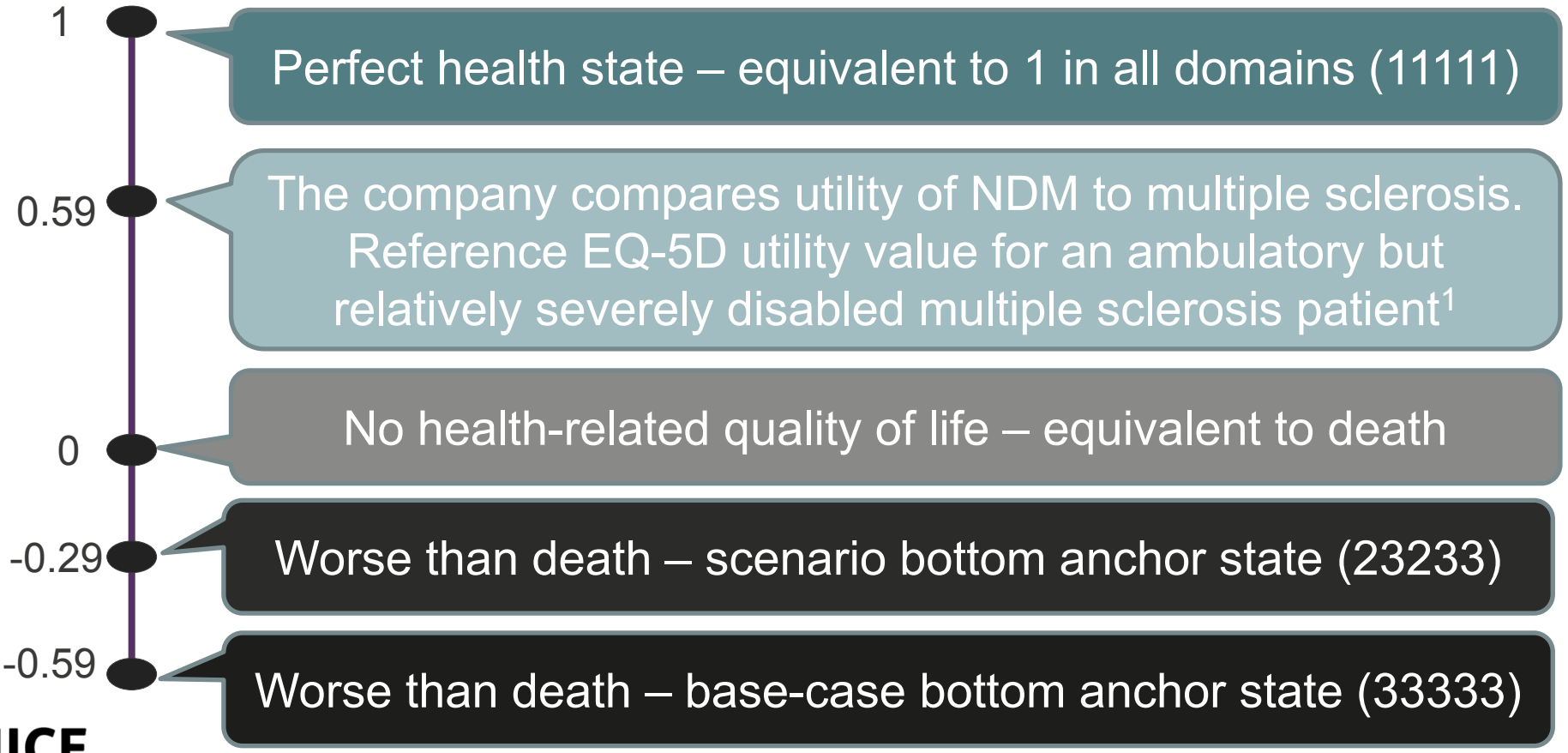
- The Statland et al. trial also reported SF-36 dimension scores across patients, for two trial periods (in line with the crossover trial design) combined for some dimensions and separately for the two periods for others.
- ERG provided as scenario mapping these to EQ-5D utility values using Rowen et al. algorithm

ERG comments

- The number of logical inconsistencies from the DCE study is a concern (e.g. some muscle weakness preferred to very little muscle weakness) – suggests widespread issues with DCE
- No clear monotonicity (preference of ordering, e.g. some, moderate)
- Also, some inconsistencies where this was not an issue suggests lack of understanding or attention to the task – ERG considers quality control checks were not complete
- 8 attributes varied simultaneously which may have been too complex for participants
- Anchoring to EQ-5D and conceptual mapping caused concerns (see next slides)
- ERG also has similar concerns for the vignette study – but also there was no explanation of health states, warm up exercises for participants or satisfactory quality control checks

Utility values – EQ-5D-3L scale

Domain	Mobility	Self-care	Usual activities	Pain/ discomfort	Anxiety/ depression
Level	1, 2 or 3	1, 2 or 3	1, 2 or 3	1, 2 or 3	1, 2 or 3



Conceptual mapping – bottom anchor state

Domain	Level	INQoL	EQ-5D-3L
Mobility	1	Very little muscle weakness in the muscles affected by your condition Very little muscle locking at the moment	No problems in walking about
	2	Some/moderate muscle weakness in the muscles affected by your condition Some/moderate muscle locking at the moment	Some problems in walking about
	3	Extreme amount of muscle weakness in the muscles affected by your condition Extreme amount of muscle locking at the moment	Confined to bed
Usual Activities	1	Muscle condition affects ability to do leisure activities not at all	No problems with performing usual activities
	2	Muscle condition affects ability to do leisure activities slightly or moderately	Some problems with performing usual activities
	3	Muscle condition affects ability to do leisure activities extremely	Unable to perform usual activities


Company base case – 33333 bottom anchor state


Company scenario analysis – 23233 bottom anchor state

NICE

Health-related quality of life – Issue 5

Individual patient data – Utility using DCE 33333 anchoring

NB: not indicative of treatment order received in MYOMEX

Health-related quality of life – Issue 5

Individual patient data – Utility using DCE 23233 anchoring

NB: not indicative of treatment order received in MYOMEX

Health-related quality of life – Issue 5

Utility source	Mexiletine utility value	BSC utility value	Treatment effect
DCE 33333 bottom anchor state (company revised base case)	[redacted]	[redacted]	[redacted]
DCE 23233 bottom anchor state	[redacted]	[redacted]	[redacted]
Vignette study (ERG base case)	[redacted]	[redacted]	[redacted]
Statland et al. scenario analysis	0.64	0.54	0.10

ERG comments

- The ERG raised multiple concerns regarding the design and limitations of the DCE study for valuation – including limitations of anchoring
- Different approaches produce very different results in terms of treatment effect – substantial uncertainty regarding the true utility values and treatment effect
- Statland et al. data used generic measures however ERG considers it should only be used for validation purposes because of limitations of the mapping algorithm
- ERG considers vignette study most appropriate because it uses TTO methodology and gives the most plausible outcomes of utility and treatment effect

Health-related quality of life – Issue 5
Carer quality of life – new since engagement

Company rationale

- The company consider there is a strong case for applying a carer disutility within the model because caregivers would be expected to have a significant negative impact on their QoL
- In the absence of NDM-specific carer utilities, the company assumed that for a severe NDM patient who is not on mexiletine treatment, a carer disutility would be 0.11 from the Duchenne muscular dystrophy evaluation (equivalent to non-ambulatory)
- This is applied for 20% of the population in the best supportive care arm only, there is no assumed carer disutility for those taking mexiletine

ERG comments

- The ERG does not disagree that carer disutility may be relevant in this condition
- It is uncertain if the assumption that 20% of patients will be severe and require the equivalent care of non-ambulatory Duchenne patients is reflective of the real-world situation
- No participants in MYOMEX required a wheelchair or walking aid, but approximately 44% in the placebo group did have moderate difficulties in walking, asking for occasional assistance
- Given the uncertainties in this area the ERG did not change the company base-case but did conduct scenarios around the assumed disutility and proportion of patients deemed severe.

Discontinuation of treatment – Issue 6

Background

- The rate of discontinuation is a key driver of the modelled outcomes (most impactful transition in the economic model) but not a key driver of the ICER
- Due to the very high correlation between incremental costs and benefits at any given time point, discontinuation rate has limited sensitivity to the final ICER
- The company used an annualised rate of discontinuation from Suetterlin et al. in their original base case. 15 out of 59 patients discontinued but 12 of these discontinuations were for lack of efficacy – so the appropriateness of an annualised discontinuation is uncertain

Study	Discontinuation rate
MYOMEX	[redacted] (revised base case)
Statland et al.	7%
Stunnenberg et al.	3%
Suetterlin et al.	5.15% (original base case)

Company response

- The Suetterlin et al study is most appropriate source of long-term discontinuation rates but because the discontinuation rate of MYOMEX is similar to Suetterlin et al, the company include MYOMEX in the revised base case

Resource use multiplier – Issue 6

Background

- The costs of health care resource use within each state were estimated by asking clinicians to estimate frequency of use within a category of disease severity (mild, moderate, severe) of the clinical myotonia rating scale (CMS).
- People in the 'alive with no treatment' health state were assumed to require 3 times the amount of health care resource.
- **Technical team judgement:** Further justification for a resource use multiplier is necessary because this is not based on evidence

Company response

- The company conducted a Delphi panel to estimate resource use
- It estimated [redacted] times more resource use visits required for patients on BSC, and for [redacted] times more patients than those on mexiletine
- The company multiplied these together ([redacted]) as validation for the 3 times multiplier in the original submission

ERG comments

- The ERG agrees that the Delphi panel is a better source of data than clinical estimation of the CMS rating scale
- The [redacted] figure already reflects the expected number of visits over all patients so it is inappropriate to multiply by the number of patients. experts were asked to estimate the frequency of resource use for adult NDM patients as the mean number of annual visits per patient per identified resource – this figure is included in the ERG base case

Cost-effectiveness results (proposed PAS price)

Intervention	Total costs (discounted)	Total QALYs (discounted)	Incr. costs	Incr. QALYs	ICER for mexiletine versus placebo (£/QALY)
Company revised base case (deterministic)					
BSC	[redacted]	[redacted]	-		
Mexiletine	[redacted]	[redacted]	[redacted]	[redacted]	£20,000-£30,000

ERG cumulative base case + scenarios

Scenario	Incr. costs	Incr. QALYs	ICER versus BSC (£/QALY)
Company base case	[redacted]	[redacted]	£20,000-£30,000
+ remove disease progression assumptions	[redacted]	[redacted]	£20,000-£30,000
+ vignette/TTO health state valuation	[redacted]	[redacted]	≥£30,000
+ [redacted] resource use multiplier	[redacted]	[redacted]	≥£30,000
ERG base case	[redacted]	[redacted]	≥£30,000
Further ERG scenario analysis on ERG base case			
600mg dose in MYOMEX trial	[redacted]	[redacted]	≥£30,000
Statland et al. utility values	[redacted]	[redacted]	≥£30,000
No carer disutility	[redacted]	[redacted]	≥£30,000
Company base case disease progression	[redacted]	[redacted]	≥£30,000
Company base case resource use multiplier (x3)	[redacted]	[redacted]	≥£30,000

ERG comparison with lamotrigine

Utility lamotrigine	Incr. QALYs	ICER (£) with 429mg dose	ICER (£) with 600mg dose
[redacted](U=BSC)	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted](U=mex)	[redacted]	[redacted]	[redacted]

Equality considerations

- Disability is a protected characteristic - people with NDM have a disability that could make travel to regional neurology centres for treatment more difficult.

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How will the decision impact people with NDM with regards to geographic access to treatment?

Key issues

- Issue 1: Generalisability of the trials
  - Potential unblinding and carry-over effects
- Issue 2: Dose and dose schedule
  - Outcomes do not align with dose used in modelling
  - Dosing schedule does not align with clinical practice
- Issue 3: Comparator treatments:
  - Established clinical management without mexiletine cannot be observed directly
- Issue 4: Disease progression differential
  - No data on natural history of the disease to inform modelling
- Issue 5: Health-related quality of life
  - Uncertainty in quality of life data presented