Public observer slides

NICE National Institute for Health and Care Excellence

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

Chair's presentation – second meeting

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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
- Main subgroups are myotonia congenita (chloride channelopathies) and paramyotonia congenita (sodium channelopathies) but all NDMs have 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 potential to fall – episodes can last from seconds to minutes
- Triggers for myotonic episodes include:
  - Cold weather
  - Stressful situations
  - Using stairs

Mexiletine (NaMuscla, Lupin)

Mechanism	• Blocks sodium channels in muscle cells that are involved in 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 167mg (1 capsule equivalent to 200mg imported mexiletine). Can be increased to 333mg (2 capsules, 400mg equivalent) after at least 1 week with increase to 500mg (3 capsules, 600mg equivalent) after at least 1 further week (based on clinical response)
List price	• £5,000 per pack of 100 capsules (~£60,000 annual cost) • Confidential patient access scheme available – has been updated since the first meeting
History of off-label use	• For more than 10 years, pharmacological management of NDM has involved using mexiletine off-label • Since marketing authorisation, Lupin has provided mexiletine at a confidential interim price discount

Key issues from ACM1

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

Summary committee conclusions – clinical evidence

Topic	Conclusion	ACD
Comparator	Clinical and patient experts confirmed that another sodium channel blocker would be used if mexiletine was not available.	3.3
Evidence base	Main evidence from MYOMEX with support from 3 other studies. Evidence suggests mexiletine is effective but has not been compared with an active comparator.	3.4
Generalisability to NHS clinical practice	MYOMEX included people aged 18 to 65 with confirmed NDM severe enough for treatment. Evidence was broadly generalisable but with limitations in inclusion criteria.	3.5
Trial design	Concerns about unblinding due to recognisable effects of mexiletine treatments, short wash-out period, small population, and short trial duration contribute substantial uncertainty to MYOMEX.	3.6
Dose and dosing schedule	Mexiletine dosing schedule is based on clinical response in NHS practice to avoid side effects. In MYOMEX, patients were forcibly titrated to 600mg within a week. Short trial duration may have masked some adverse events. Company used cost data from an average (417mg) dose and efficacy data from MYOMEX (600mg dose) in modelling. Using 600mg for both cost and efficacy was considered more appropriate.	3.7

Summary committee conclusions – economic modelling

Topic	Conclusion	ACD
Model structure	Company's economic model does not represent clinical practice. Patients unlikely to be 'alive with no treatments' because other treatments are available. Discontinuation rate underestimated due to the source of information.	3.8
Disease progression	No evidence for disease worsening in people receiving BSC.	3.9
QoL instruments	Generic QoL instruments, like SF-36 data from Statland et al. (2012), are suitable for use in NDM and this appraisal.	3.10
DCE utility values	Utility values from company's DCE valuation implausible and the DCE studies had several issues.	3.11
Preferred utility values	SF-36 values from Statland et al. preferred to company's TTO values but both highly uncertain.	3.12
Carer disutility	Not enough evidence to justify including consideration of carer quality of life and it is highly uncertain.	3.13
Resource use	BSC resource use overestimated in company's model.	3.14
ICER values	ICERs comparing mexiletine with BSC indicated mexiletine not cost-effective, and likely to be even less cost-effective if an active comparator was used.	3.15

BSC: Best supportive care; DCE: Discrete choice experiment; ICER: Incremental Cost-Effectiveness Ratio; QoL: Quality of Life; SF-36: Short Form – 36 questions; TTO: Time Trade-Off

Overview of consultation comments from people with NDM

- Many commentators shared positive experiences with mexiletine treatment:

"Gained my independence back, the ability to look forward to events and enjoy time with family and outdoors"

"Makes everyday activities so much more manageable"

"Able to laugh with my loved ones without having to hide the agony I was in"

- Concerns about supply of mexiletine if approval not granted
- Some expressed concerns that they had previously tried other sodium channel blockers and treatment had been unsuccessful
- Some commenters noted increased risk of falls and accidents if mexiletine were to be withdrawn
- Concerns about side effects of lamotrigine, particularly mental health consequences

At consultation, company provided supporting information:
Clinical elicitation for utility comparisons and comparators
Utility valuation analysis
Updated company deterministic base case and scenario analyses

Main issues after consultation

- Comparison to sodium channel blockers
- Use of special import mexiletine hydrochloride, longer term dosing and dose titration
- Health-related quality of life
  - Suitability of utilities from SF-36 from Statland et al. trial
  - Methodologies to value health status
- Caregiver disutilities
- Impact of removal of mexiletine

Comparison to sodium channel blockers (1)

Committee concluded that comparison of mexiletine with BSC not appropriate. People would be offered other active treatments like lamotrigine/other sodium channel blockers if mexiletine unavailable, and other active treatments would likely be more effective than BSC.

Company

- Lamotrigine should **not** be considered a comparator as it is **not in established clinical practice** to treat people with NDM, does not have marketing authorisation for this population
- Research conducted by company shows approx. **1%** of people with NDM being treated or have ever been treated with lamotrigine in UK
- Lamotrigine limited for use in adults with NDM:
  - *No long-term safety or efficacy data to support safe use of high doses of lamotrigine in population.*
  - *Much **longer titration period and intensive monitoring** to reach required higher doses.*
  - *Well-known **serious and life-threatening side-effects**, requiring immediate treatment withdrawal in all those who develop a common lamotrigine-related rash, and other common undesirable side effects.*

Comparison to sodium channel blockers (2)

Association of British Neurologists
Not reasonable to consider lamotrigine/other sodium channel blockers equivalent to or comparator for mexiletine.

- People do not stay on drugs like carbamazepine, flecainde or phenytoin long term - lack of efficacy, side effects.
- **Lamotrigine** rarely used at present
  - **Not as effective**, high doses over 150mg a day to see effect
  - Number of people with NMD report not having any symptom improvement, **high discontinuation** rate

ERG view at consultation:
- Company doesn't present any new evidence
- Agree with committee that most appropriate comparator is what people currently taking mexiletine would have if mexiletine was not available. So comparators should include, as outlined in the NICE scope: "Established clinical management without mexiletine, including but not limited to: lamotrigine and best support care".

Comparison to sodium channel blockers (3)

Consultation comments indicated that:
Direct comparator trial of mexiletine and lamotrigine being set up, but results likely to take several years (*Association of British Neurologists, stakeholder*) No evidence to show lamotrigine superior/equal to mexiletine in an RCT (*clinical expert*)
Lamotrigine not considered first line treatment (may take many months to be effective, risk of serious side-effects), carbamazepine and phenytoin considered clinically ineffective (*web comment, British Myology Society Council*)
Other sodium channel blockers used in very small number of people to date, efficacy less well established Clinical effectiveness of lamotrigine as alternative treatment over-stated (*web comment, neuromuscular specialist*)
People on mexiletine at our neuromuscular centre have already tried other sodium channel blockers. The reason for refusing mexiletine seems to be that it was not compared with cheaper alternatives – most of us are mindful of this and will try other sodium channel blocker first (*web comment, consultant neurologist*)

Has the committee's view on a comparison to sodium channel blockers such as lamotrigine being considered as part of the decision making changed since the ACD?

Use of special import mexiletine hydrochloride

Company
Believe that special unlicensed mexiletine very rarely used alone or instead of NaMuscla to treat myotonia symptoms in adults with NDM. Concerned for patient welfare in the event of a negative recommendation for NaMuscla as special unlicensed mexiletine would not be a suitable alternative.

Longer term dosing

Company
Reiterated argument that evidence from clinical experts, Suetterlin et al. and MYOMEX trial follow-up suggests long term mean mexiletine dosage in clinical practice will be around 400mg daily. Provided evidence to support view that evidence exists for effectiveness of mexiletine over long term with lower doses than those in MYOMEX.

Dose titration

Company
Acknowledge some people will be titrated using 100mg special import mexiletine hydrochloride, but report that majority of clinicians now titrate with NaMuscla. Acknowledge that some people will be titrated at more cautious rate than in NaMuscla SmPC. Fastest titration (as per MYOMEX) ICER [redacted], slowest titration ICER [redacted].

SmPC: Summary of Product Characteristics

Use of special import mexiletine hydrochloride, longer term dosing and dose titration

ERG views at consultation:

- If committee prefers to use 600mg dose, to be consistent with the dosage given in the MYOMEX trial, on which the model efficacy is based, then this is their prerogative.
- Scenario for more cautious titration uses cost of NaMuscla rather than price of imported mexiletine so won't reflect the true current cost of more cautious titration in 100mg steps. However, if the cost of imported mexiletine would be lower, this would lower the ICER further.

Should the 400mg or 600mg longer term dose be used for the MYOMEX trial?

Health-related quality of life (1)

- Many uncertainties remain around utilities used in model
- ERG and company still disagree on which HRQoL valuation approach to use in the base-case, with the company now preferring their hybrid analysis of DCE and TTO data (provided at consultation), while the ERG prefer to use the vignette/TTO approach

Suitability of utilities derived from SF-36 from the Statland et al. trial

Committee concluded that the generic SF-36 data from the Statland et al. trial could be included in its considerations.

Company

Reiterated that ERG noted extensive limitations associated with its crude mapping of SF-36 values from Statland et al. to EQ-5D-3L utilities. Highlighted limitations including:

- Mean scores rather than patient level data from Statland; mapping algorithm not designed/validated in NDM
- Literature suggests use of SF-36 not supported in NDM – instead, INQoL is validated method of quantifying QoL in neuromuscular diseases, appears to correlate with clinical severity in myotonia

ERG views at consultation:

- Given limitations of this mapping analysis, ERG did not (and continue not to) use these values in their base-case.
- A less strong correlation for SF-36 does not mean it is not sufficiently correlated to capture changes in health.

INQoL: Individualized Neuromuscular Quality of Life Questionnaire; SF-36: Short Form – 36 questions

Health-related quality of life (2)

Valuation methodologies

Company's approach at consultation
DCE and vignette TTO separate valuation methodologies independently reviewed by 3 experts, none of whom suggested that the valuation exercises or results were highly uncertain
Argument for the similarity in the results of the two methods - when anchored to the same range, the utilities produced correlate very highly (R^2=0.96), and this validates and gives confidence and credence to the two datasets and methodologies
New hybrid modelling approach combined data from the DCE and vignette TTO studies into a single model (see Appendix 2a of company's ACD response)

ERG views at consultation:

- Consider the hybrid modelling analysis well conducted, modellers have done their best to limit the impact of the limitations in the data of the original studies.
- Linking the data from the two studies resolves the anchoring issues for the DCE. But reanalysis of data derived from a DCE study with design issues will not resolve those issues or improve quality of the data on which results are based
- Still prefer to use utility values produced by vignette/TTO study to avoid use of the DCE data

DCE: Discrete choice experiment; TTO: Time Trade-Off

Health-related quality of life (3)

Valuation methodologies (continued)

Utility values obtained from different valuation methods:

ERG's preferred approach

Method (bottom anchor state)	Mexiletine (Alive on treatment)	BSC (Alive not on treatment)	Treatment effect	EQ-5D-3L UK average general population utility value (aged 44)
Original Company Valuation studies				0.8896
DCE (33333)	[redacted]	[redacted]	[redacted]	
DCE (23223)	[redacted]	[redacted]	[redacted]	
DCE (23333)	[redacted]	[redacted]	[redacted]	
Vignette/TTO	[redacted]	[redacted]	[redacted]	
Statland mapping				
Period 1	0.67	0.54	0.13	
Period 2	0.61	0.53	0.08	
Averaged periods	0.64	0.54	0.10	
Hybrid DCE TTO modelling				
Hybrid 1	[redacted]	[redacted]	[redacted]	
Hybrid 2	[redacted]	[redacted]	[redacted]	
BSC = best supportive care; DCE = discrete choice experiment				

Company's new preferred approach

Health-related quality of life (4)

Valuation methodologies (continued)

Scenarios for utility value approaches (with updated PAS) run by ERG:

Utility values	Incr. QALYs
HRQoL valuation approach	
DCE approach anchored to 33333 and 1	[redacted]
Vignette/TTO approach (ERG BC)	[redacted]
Hybrid 1 (company BC)	[redacted]
Hybrid 2	[redacted]
ERG mapping utility validation	
Statland period 1 utilities	[redacted]
Statland averaged period utilities	[redacted]

Should the generic SF-36 data from the Statland et al. trial still be considered in decision making?

Is the company's updated preferred approach to health-related quality of life valuation appropriate?

Caregiver disutilities (1)

Committee had not seen enough evidence to justify including consideration of carer quality of life, inclusion of this assumption is highly uncertain and should be removed.

Web comment:
If funding for mexiletine is withdrawn, then I **am faced with a lifetime of care**, helping my partner get up from a chair, or move about the house for fear of falling. **Could lead to me having to give up my job to be a full time carer** for my partner, I may have to claim benefits, yet another cost. We have together a much better quality of life with mexiletine in our lives

Company:

Planned to present results from caregiver survey, but remains ongoing due to ethical approval delays

Conducted scenarios using Acaster et al. study, that examined carer disutilities for carers of people with multiple sclerosis (MS) against patient determined disease scores (PDSS). Believe this score could be used as proxy for someone with NDM having BSC.
PDSS 3.0 = *"Gait Disability: MS does interfere with my activities, especially my walking. I can work a full day, but athletic or physically demanding activities are more difficult than they used to be. I usually doesn't need a cane or other assistance to walk, but I might need some assistance during an attack.*

- Disutility for caregiver of person with MS with PDSS score of 2.0 to 3.0 is -0.045. Suggests company base case value used previously (average -0.022) may be conservative. No base case change made.

Caregiver disutilities (2)

ERG view at consultation:
Unclear whether assumption that all people with NDM would score 2 or 3 on PDSS appropriate, or if some would score 1 (some minor noticeable symptoms from MS, small effect on lifestyle). Disutility -0.002 for carers of people with score 1 so company's disutility -0.045 would be overestimate.
Company scenarios based on caregiver studies for Duchenne muscular dystrophy (DMD) and MS. DMD disutility -0.11 includes carers of both ambulatory and non-ambulatory people. • More severe than NMD population - non-ambulatory NDM very rare, clinical expert had only ever seen 1 person who needed to use a wheelchair. Unclear whether application of overestimated disutility to [redacted] of NMD population appropriate.
Would be impact on carers, but unclear what disutility would apply, to what proportion of people with NMD. • Substantial uncertainties remain unresolved, so **ERG removed this disutility from their updated base-case.**

Should caregiver disutility be considered as part of the modelling, and if so, are any of the company's approaches acceptable?

Impact of possible removal of mexiletine (1)

ACD 1.2, this guidance does not require that patients having treatment with mexiletine (NaMuscla) that was started in NHS through interim agreement for use as a 'pass through' drug for patients within specialised neurosciences centres, should continue to receive treatment with NaMuscla.

Multiple comments from people with myotonia and clinicians highlighted that suddenly stopping treatment with mexiletine worsens symptoms for a prolonged period, means careful withdrawal regimen needs to be worked out for each individual.

Confusion over what a negative recommendation would mean in terms of prescribing, and whether or not people would still be able to access imported generic mexiletine.

Public comments

- If I was unable to have this medication, without suitable alternative that delivered same results, I would not be able to live any kind of normal life.
- Going to cause problems for many who have been functioning at a level they consider significantly higher compared to no treatments/other alternatives.
- Possible job losses due to process of adapting to new medication.

Association of British Neurologists

- Unethical to recommend discontinuation of mexiletine for people already established on treatment, concerned that they would be **left worse off**.

Impact of possible removal of mexiletine (2)

Muscular Dystrophy UK

- Concerned that removal of effective well-tolerated treatment would be **unfair and unethical**, precedent setting
- Concerned negative recommendation would mean people successfully managing condition with NaMuscla would no longer have access. Wrong to suggest there's a supply of mexiletine readily available from alternative sources that patients could access instead.
- Likely **widespread anxiety** from uncertainty of supply of other forms of mexiletine from alternative sources, places onus on clinicians to source.

Clinical expert

- Not be able to justify prescribing an unlicensed, unproven drug when licensed drug available, puts us in very difficult uncertain position.

NICE has been asked to assess the clinical and cost effectiveness of mexiletine (NaMuscla)

Other issues

Issue	Company	ERG
Clinical trial design	Evidence accepted by EMA for licensing. Potential carry over effect and unintentional blinding not evidenced in MYOMEX trial, no risk of bias found. Do not believe that relevant evidence provided above has been taken into account	Agrees with committee on potential for unblinding and carry-over effects, short trial duration and few patients contribute substantial uncertainty to MYOMEX results as per original ERG report
Resource use	Clarified that questions used in Delphi study to elicit resource use multiplier clear in asking percentage of patients who would use each type of resource and of those who use the resource, how often would they use it per year	Given limited impact of assumed resource use multiplier on ICER, no ERG base-case change made
Disease progression	Given uncertainty of natural history of the disease, removed any disease progression assumptions from base and scenario economic cases	Agrees with this choice
Adverse events	Provided scenario on updated base-case (using Hybrid Model 1 utilities), ICER using MYOMEX AEs is [redacted] and ICER with Suetterlin et al. AEs is [redacted]	Scenario shows that choice has a very minor impact on results, not a key issue
EQ-5D-3L	From literature review, EQ-5D has never been used in this disease area, therefore suitability of tool in capturing quality of life in this population unknown	If no evidence that EQ-5D does not perform well in this population, should have been used by company. If EQ-5D not collected in patient population, company could have performed mapping study, removed need for conceptual mapping and uncertainties introduced into analysis by INQOL/DCE/TTO studies.

Potential equalities issues raised during consultation

Sex-based differences in alternative treatment suitability (alternatives include lamotrigine, phenytoin, carbamazepine, flecainde):

- Physiological changes during pregnancy may affect lamotrigine levels and/or therapeutic effect (section 4.6 SmPC)
- Increased risk of major congenital malformations and possibility of adverse effects on neurodevelopment in pregnancy have been seen with phenytoin
- Interaction between lamotrigine and hormonal birth control
- Oestrogen reduces levels of lamotrigine in blood, meaning a higher dose of lamotrigine is needed

Further views on possible impact of guidance on people who have disabilities:

"Draft guidance if finalised unaltered will deny known effective treatment for those disabled by myotonia and prevent them from having a much fuller life than is possible."

"It is a discrimination against the disabled to take away the drugs that allow them to lead a normal life"

SmPC: Summary of Product Characteristics

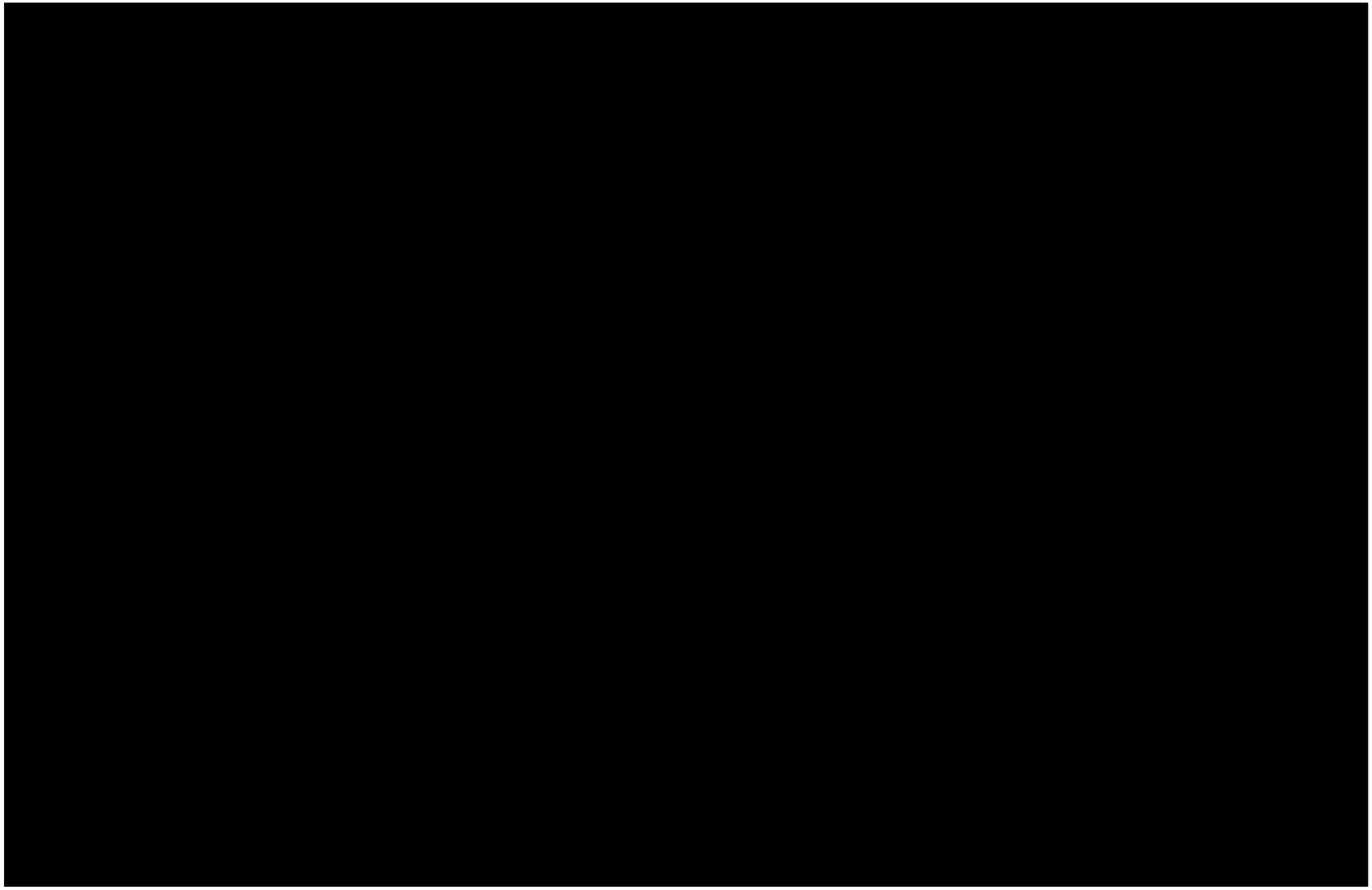
Cost-effectiveness results (updated PAS)

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]	[redacted]

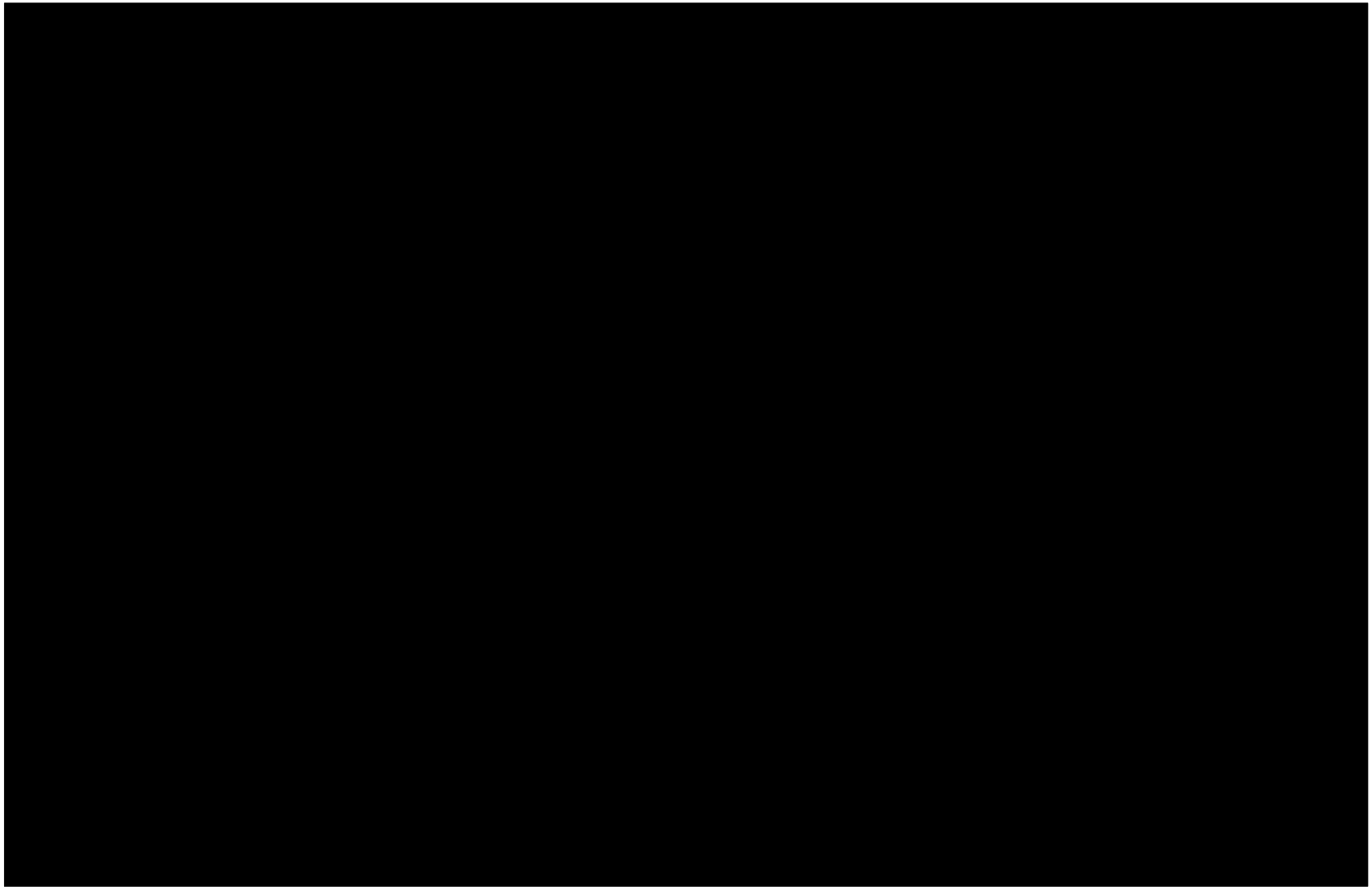
ERG cumulative base case (updated PAS)

Scenario	Incr. costs	Incr. QALYs	ICER versus BSC (£/QALY)
Company base case	[redacted]	[redacted]	[redacted]
+ maintenance dose 600mg	[redacted]	[redacted]	[redacted]
+ vignette/TTO health state valuation (instead of Hybrid 1)	[redacted]	[redacted]	[redacted]
+ no carer disutility	[redacted]	[redacted]	[redacted]
+ [redacted] resource use multiplier (instead of company's 3)	[redacted]	[redacted]	[redacted]
ERG base case	[redacted]	[redacted]	[redacted]
ERG scenario analysis			
429mg dose in MYOMEX trial (company preferred)	[redacted]	[redacted]	[redacted]

ERG base case DSA tornado diagram (updated PAS)



ERG base case CEAC (updated PAS)



ERG comparison with lamotrigine (updated PAS)

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=mexiletine)	[redacted]	[redacted]	[redacted]

[redacted]

ERG utility value scenarios (updated PAS) (1)

Utility values	Incr. Costs (£)	Incr. QALYs	ICER (£/QALY)
HRQoL valuation approach			
DCE approach anchored to 33333 and 1	[redacted]	[redacted]	[redacted]
Vignette/TTO approach (ERG BC)	[redacted]	[redacted]	[redacted]
Hybrid 1 (company BC)	[redacted]	[redacted]	[redacted]
Hybrid 2	[redacted]	[redacted]	[redacted]
ERG mapping utility validation			
Statland period 1 utilities	[redacted]	[redacted]	[redacted]
Statland averaged period utilities	[redacted]	[redacted]	[redacted]

ERG utility value scenarios (updated PAS) (2)

Utility values	Incr. Costs (£)	Incr. QALYs	ICER (£/QALY)
Carer disutilities			
Carer disutility of 0.11 applied to [redacted] of NDM placebo patients and patients off mexiletine (company BC)	[redacted]	[redacted]	[redacted]
Carer disutility of 0.06 applied to [redacted] of NDM placebo patients and patients off mexiletine	[redacted]	[redacted]	[redacted]
Carer disutilities of 0.045 for all placebo patients and patients off mexiletine	[redacted]	[redacted]	[redacted]
No carer disutility (ERG BC)	[redacted]	[redacted]	[redacted]

Questions for committee

- Should the 400mg or 600mg longer term dose be used for the MYOMEX trial?
- Should the generic SF-36 data from the Statland et al. trial still be considered in decision making?
- Is the company's updated preferred approach to health-related quality of life valuation appropriate?
- Should caregiver disutility be considered as part of the modelling, and if so, are any of the company's approaches acceptable?
- Other considerations?