NICE National Institute for Health and Care Excellence

Slides for projector – contains AiC

Galcanezumab for preventing migraine

Lead team presentation

Matt Bradley (cost), Gillian Ells (clinical), Malcolm Oswald (lay)

ERG: York Centre for Reviews and Dissemination

Technical team: Gary McVeigh, Omar Moreea, Caron Jones, Linda Landells

Company: Eli Lilly

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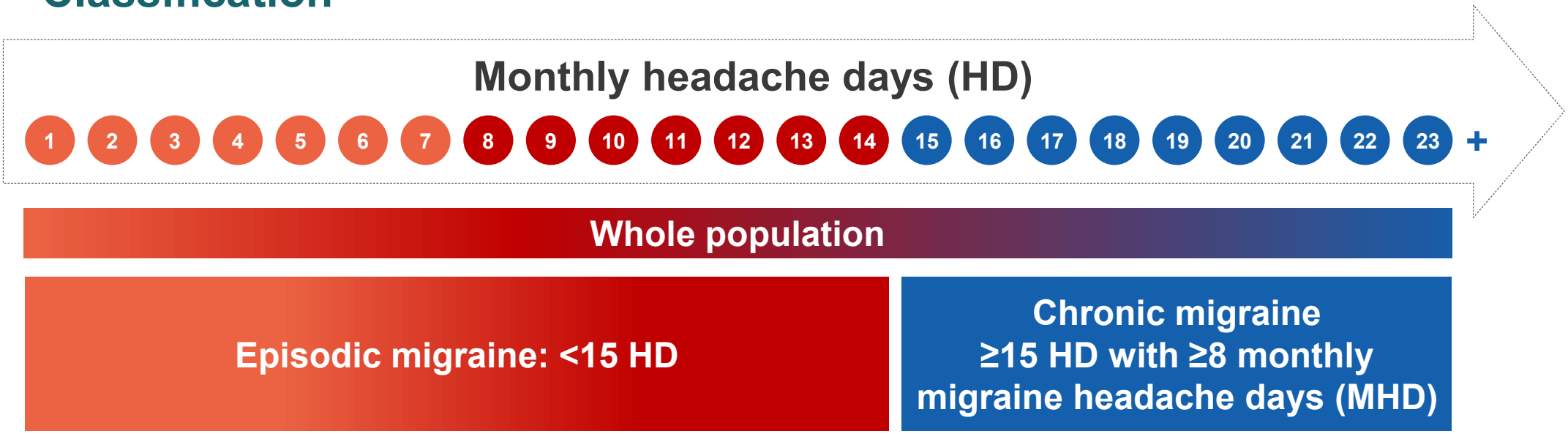
Key issues

- **Issue 2: High-frequency episodic migraine (HFEM)**
  - Should HFEM be considered separately to episodic and chronic migraine?
- **Issue 3: Position of galcanezumab in the treatment pathway**
  - Is galcanezumab an option after botulinum toxin A has failed?
- **Issue 4: Indirect treatment comparison for chronic migraine**
  - Should equal effectiveness or ITC results be used for galcanezumab vs botulinum toxin A?
- **Issue 6: Utility values applied to treatments**
  - Should differential or the same pooled utility values be used for all treatments?
- **Issue 7: Resource costs**
  - Should monitoring costs from 3-, 6- or 12-month reviews be included in the model?

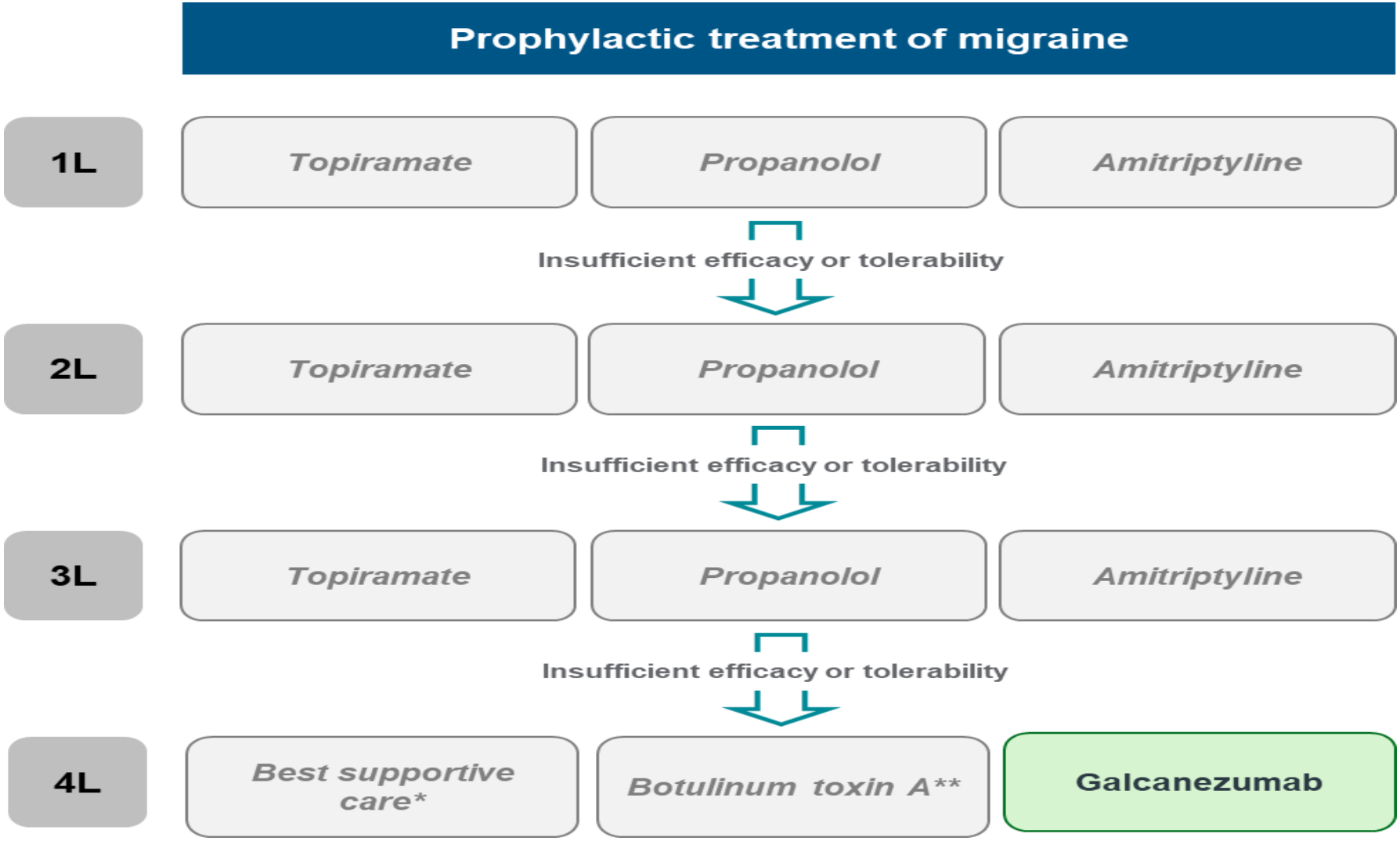
Migraine

- Headache disorder with recurring attacks usually lasting 4–72 hours
- Often accompanied by nausea, vomiting, sensitivity to light/sound
- Factors triggering attacks can include stress, change in sleep pattern, overtiredness, menstruation, caffeine/alcohol consumption
- Prevalence 5-25% in women; 2-10% in men

Classification



Migraine treatment pathway



*includes acute treatments such as triptans, analgesics and antiemetics
**licensed for the treatment of chronic migraine only

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Source: Company submission: section B.1.3.4.2 (page 22)

Galcanezumab (Emgality, Eli Lilly)

Description of technology	Galcanezumab (Emgality, Eli Lilly) is a humanised IgG4 monoclonal antibody that binds calcitonin gene-related peptide (CGRP) thus preventing its biological activity. Elevated blood concentrations of CGRP have been associated with migraine attacks.
Marketing authorisation	Galcanezumab indicated for the prophylaxis of migraine in adults who have at least 4 migraine days per month.
Dosage and administration	120 mg galcanezumab injected subcutaneously once monthly via autoinjector, with a 240 mg loading dose as the initial dose.
List price	The list price of galcanezumab is £386.50 per 120mg dose. Costs may vary in different settings because of negotiated procurement discounts.

Background

Comparators	Best supportive care (episodic migraine [EM] and chronic migraine [CM]) botulinum toxin A (CM only)
Subgroups	High-frequency episodic migraine (HFEM)
Main clinical trial	CONQUER (episodic and chronic migraine), REGAIN (chronic migraine), EVOLVE-1 (episodic migraine), EVOLVE-2 (episodic migraine)
Key results	[redacted]
Comparison with botulinum toxin A	Network meta-analysis in chronic migraine
Key result	[redacted]
Model	Semi-Markov model. 30 MHD health states → cost and utilities for each MHD health state
Technical team most plausible ICERs	EM (vs BSC): £22,573 CM (vs BSC): £8,838 CM (vs botulinum toxin A): £16,922

Key trial results (1)

Trial efficacy outcomes at 3 months (CONQUER) in people with ≥3 prior preventive medication failures.

Study	Outcome	CM: Effect (95% CI)	EM: Effect (95% CI)	HFEM: Effect (95% CI)
CONQUER	Change from baseline in mean migraine headache days	[redacted]	[redacted]	[redacted]
	Change from baseline in mean headache days	[redacted]	[redacted]	[redacted]
	≥ 50% reduction from baseline in migraine headache days	[redacted]	[redacted]	[redacted]
	≥ 30% reduction from baseline in migraine headache days	[redacted]	[redacted]	[redacted]

Source: based on company submission tables 27, 28, 30, 31, 33, 34 and 35

Key trial results (2)

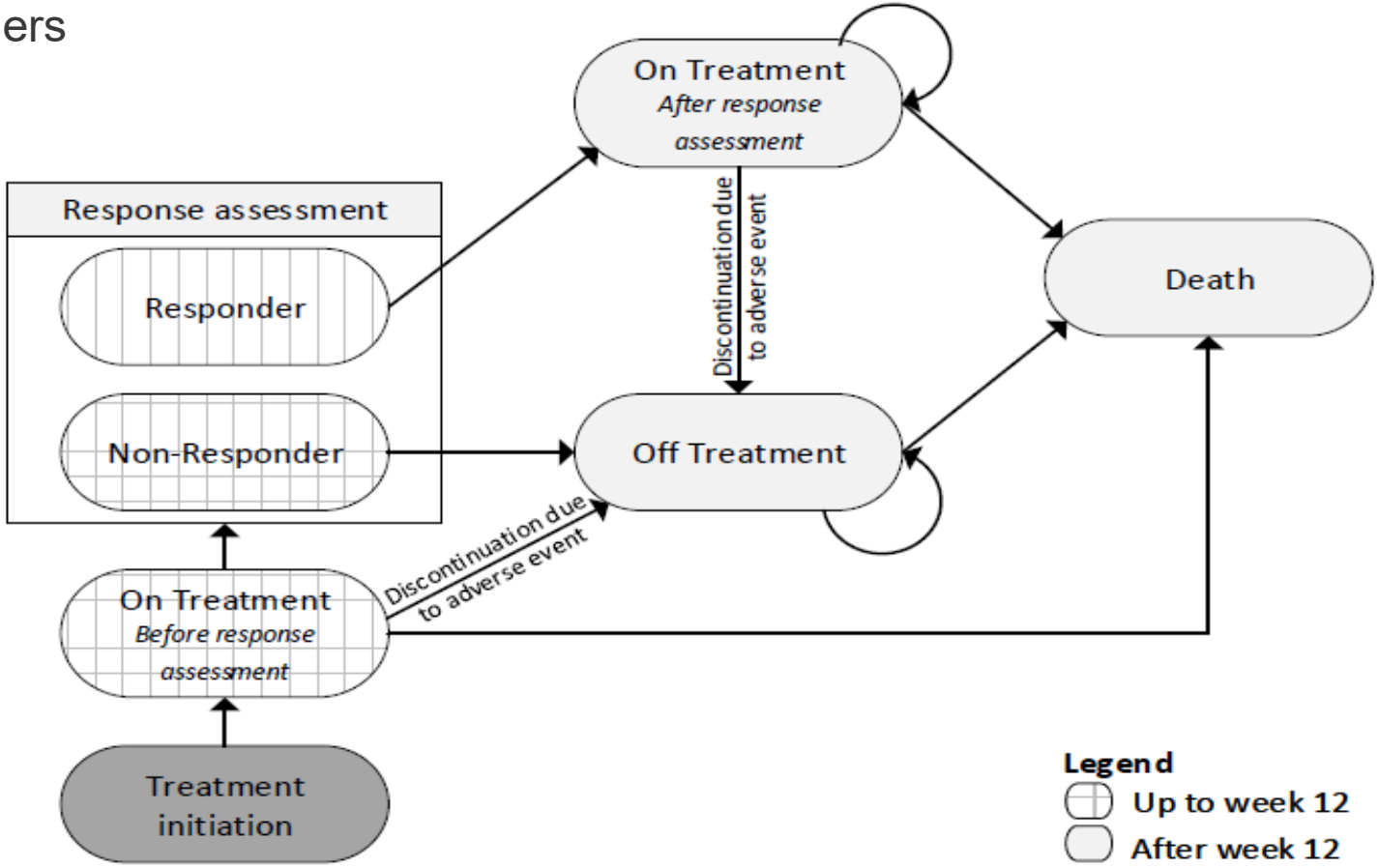
Trial efficacy outcomes at 3 months (REGAIN) and 6 months (EVOLVE-1 and EVOLVE-2) in people with ≥3 prior preventive medication failures.

Study	Outcome	CM: Effect (95% CI)	EM: Effect (95% CI)	HFEM: Effect (95% CI)
REGAIN	Change from baseline mean migraine headache days	[redacted]	-	-
	≥ 50% reduction from baseline in migraine headache days	[redacted]	-	-
EVOLVE 1 and 2 pooled	≥ 50% reduction from baseline in migraine headache days	-	[redacted]	-

Source: based on company submission tables 27, 28, 30, 31, 33, 34 and 35

Economic model

- Semi-Markov model
- Four health states; on-treatment, off-treatment due to non-response, off-treatment due to adverse events and death
- Assessment period (month 1 – 3) and post-assessment period (month 4 onwards)
- Each health state associated with a mean monthly MHD frequency
- Response assessment period allows differentiation between responders and non-responders



Patient and carer perspectives

Comments: Migraine Trust (based on over 2,000 responses from 3 recent surveys)

Migraine:

- Range of debilitating symptoms (e.g. fatigue, severe head pain, light sensitivity, difficulty concentrating, nausea, stiff neck or back, feeling down, sound sensitivity, 'background' headache, and visual aura)

Experience of living with the condition:

- Significant impact on work, family relationships, social life, mental health and wellbeing
- "I lost my job because of migraine". "I am not able to look after my child."
- People with migraine 3 times more likely than people without migraine to have depression

Current treatment experience

- No cure but numerous preventive treatments available
- Triptans (58%), lifestyle modifications (56%), painkillers (51%), and preventives (39%)
- Around 1/3 of patients satisfied with the care they receive for their migraine
- 70% of respondees had failed to respond to more than five different preventives
- 90% of respondees had adverse side-effects from migraine preventives, excluding CGRP
- Of patients who have had both, large majority prefer CGRP drugs over botulinum toxin A
- There is significant unmet need for patients who cannot tolerate currently available oral preventives and/or who have failed to respond to botulinum toxin A therapy

Patient and carer perspectives

Comments: Migraine Trust (based on over 1,800 survey responses)

Advantages of galcanezumab:

- Very tolerable side-effect profile
- Can be administered in the patient's own home
- 80% of respondees agree or strongly agree that CGRP drug has improved quality of life
- 73% of respondees report that they were able to stop or reduce their use of other migraine treatments while they were taking the CGRP medicine
- "My number of migraine days has reduced from up to 20 days per month to 5 days. Plus the migraines I still have are less severe"
- "My quality of life is transformed."

Disadvantages of galcanezumab:

- Few disadvantages but not all patients will respond to CGRP drugs
- Small minority of respondents identified disadvantages e.g. Injection site rashes, constipation

Clinician perspectives

Submissions:

- Association of British Neurologists (ABN)
- British Association for Study of Headache (BASH)

Current treatment experience

- Strongly believe there is very significant unmet need
- The condition is under-recognised, under-diagnosed and under-resourced
- Pharmacological options are limited
- Preventive options mostly repurposed and not designed for migraine
- Botulinum toxin A is option for chronic migraine after 3 failed treatments

Galcanezumab experience:

- A novel, easily self-administered, once monthly, well tolerated treatment
- Side effect profile is similar to placebo
- Improve patient compliance, empower the patient to manage own care
- Injection training for patients, perhaps through headache specialist nurses
- Equally effective in both episodic and chronic migraine but more need in chronic
- Easier to administer than botulinum toxin A

Issues resolved after technical engagement

	Summary	Technical engagement responses	Included in updated base case?
1	Company modelled a 25-year time horizon but technical team prefer lifetime (45-years).	*Stakeholder summary:* • 25 years could be sufficient, but lifetime is in line with previous appraisals • Lifetime may increase uncertainty in the model *Company:* • Agreed to increase the time horizon to 45 years	Company ✓ ERG ✓
5	Company assumed different treatment effect waning periods for galcanezumab and botulinum toxin A, also different periods for episodic and chronic migraine. Technical team prefer consistent treatment effect waning periods.	*Stakeholder summary:* • Small % will continue treatment indefinitely • Uncertainty in long-term efficacy & waning periods *Company:* • Indefinite treatment for responders is unrealistic • Positive discontinuation should not be included • No data to include restarting treatment Agreed to assume: • consistent waning periods for galcanezumab and botulinum toxin A • consistent waning periods between episodic and chronic migraine populations	Company ✓ ERG ✓

Issues resolved after technical engagement

	Summary	Technical engagement responses	Included in updated base case?
6	Company based utility values only from CONQUER trial. Technical team prefer use of relevant population from trials. In conjunction with the lifetime time horizon, age-related disutilities should be applied. There is uncertainty in the use of pooled or differential utilities between galcanezumab and comparators.	*Stakeholder summary:* • Utility values should be based on the relevant population • Appropriate to apply age-related disutility • Differential utilities not applied in previous appraisals *Company:* Updated model to: • Use all trials for relevant utility data • Apply age-related disutility • Use differential utilities between treatments	Company ✓ ERG ✓
7	Not everyone can self-administer galcanezumab. Technical team apply admin cost to 10% of people on treatment. Alternative resource cost generated from National Health & Wellbeing Survey (NHWS).	*Stakeholder summary:* • General agreement that 100% could not self-administer but exact figure not known • Appropriate to use NHWS data *Company:* • Agree to apply admin cost to 10% patients • Agree to use NHWS resource use data • Additional monitoring costs not included	Company ✓ ERG ✓

Outstanding issues after technical engagement

- **Issue 2:** High-frequency episodic migraine (HFEM)
  – Slide 16
- **Issue 3:** Position of galcanezumab in the treatment pathway
  – Slide 17
- **Issue 4:** Indirect treatment comparison for chronic migraine
  – Slide 18
- **Issue 6:** Utility values applied to treatments
  – Slide 19
- **Issue 7:** Resource costs – additional monitoring costs
  – Slide 20

Issue 2: High-frequency episodic migraine (HFEM)

Background

- Company defined this subgroup as patients with 8-14 monthly MHDs who suffer <15 headache days per month
- No clinical consensus on the definition
- HFEM is a high unmet need as botulinum toxin A is only used in CM

Stakeholder comments

Company:

- Similar burden of disease as CM
- Company sponsored clinical advisory group support HFEM as clinically distinct group

Professional groups:

- No consensus on definition of HFEM (8-14 or 10-14 MHD)
- Disability more similar to CM than EM

AbbVie:

- Experts suggest reclassifying CM as ≥8 MHDs/month

Novartis:

- Previous appraisals did not consider HFEM as distinct

Teva:

- No definition or inclusion of HFEM in ICHD-3

ERG comments

- Previous migraine appraisals judged that HFEM was not a clinically meaningful category
- Insufficient evidence that HFEM is a clinically distinct subgroup

Technical team judgement

- HFEM should not be considered as a distinct subgroup in the model or analysis

Should HFEM be considered separately to episodic and chronic migraine?

Issue 3: Position of galcanezumab in treatment pathway

Background

- Galcanezumab positioned as treatment after ≥3 failed previous therapies
- CONQUER trial included patients who received botulinum toxin A at different lines of treatment
- Some of these lines are not used in the NHS
- Is there evidence to support use after botulinum toxin A and/or as a 5th line treatment?

Stakeholder comments

Company:

- Post-hoc analysis after botulinum toxin A failed = significant decrease in MHDs (vs placebo)
- Analysis for 5th line used 4th line data from CONQUER as a proxy

Professional groups:

- Support galcanezumab (either 4th or 5th line) after botulinum toxin A

AbbVie:

- Disagree that access to botulinum toxin A is restricted
- Nurse-led botulinum toxin A administration reduces cost

Novartis:

- No evidence for galcanezumab before botulinum toxin A

Teva:

- Potential as 5th line but should be based on evidence

ERG comments

- No treatment sequencing in economic model is a limitation
- Lack of clinical evidence to support galcanezumab as 5th line

Technical team judgement

- Company evidence suggests galcanezumab may be effective after botulinum toxin A fails
- But, no cost-effectiveness evidence was presented to support this positioning

***Is galcanezumab an option after botulinum toxin A has failed*?**

Issue 4: Indirect treatment comparison for chronic migraine

Background

- ITC used for galcanezumab vs botulinum toxin A
- Key data missing for population with ≥3 previous treatments
- Company included 'all-comers' with <3 previous treatments
- ERG noted heterogeneity between studies but prefer to use these data
- Company assumed equal response rates and equal change from baseline MHDs, not ITC results

Stakeholder comments

Company:

- Acknowledged limitations of ITC
- Agreed to apply treatment effect estimated from ITC

Professional groups:

- No direct comparison but trials favour galcanezumab

AbbVie:

- Small sample size in ITC = uncertainty
- Long-term benefit of botulinum toxin A from several studies

Novartis:

- Assume equal effectiveness, in line with previous appraisals
- Use SMC report data for response rates

Teva:

- Scenario of equal effectiveness should be considered

ERG comments

- The ITC is sufficiently robust for use in the economic model
- Response rate data from SMC report not comparable with galcanezumab data

Technical team judgement

- Company agree with technical team preferences to use treatment effect estimates from ITC
- But, uncertainty remains and scenario of equal effectiveness should be considered

Should equal effectiveness or ITC results be used for galcanezumab vs botulinum toxin A?

Issue 6: Utility values applied to treatments

Background

- There is uncertainty in the way utility values are applied to the treatments
- The company used the same pooled utility values for all treatments
- The ERG considered there was evidence to use differential values
- However, the ERG approach is not consistent with previous migraine appraisals

Stakeholder comments

Company:

- At TE, updated model applied differential utilities
- Differential utilities account for different treatment effects
- Plausible that there are improvements in migraine severity beyond MHD (both during and between attacks)

Professional groups:

- Same values to be used but severity is also a factor

AbbVie:

- Several factors beyond MHD frequency impact HRQoL
- There is uncertainty in using differential utilities

Novartis:

- Same values to be used consistent with previous appraisals

Teva:

- Committee not previously accepted differential utilities

ERG comments

- Differential utilities allow capture of migraine severity beyond frequency of MHDs
- Unlike previous appraisals, data were presented to support the use of differential utilities

Technical team judgement

- New evidence to consider differential utilities but not consistent with previous appraisals
- Uncertainty remains and scenario of equal utility values to be considered

Should differential or the same pooled utility values be used for all treatments?

Issue 7: Resource costs – additional monitoring costs

Background

- Costs associated with monitoring people during treatment not included in company model
- Clinical advice suggested people on galcanezumab would be reviewed every 6-12 months

Stakeholder comments

Company:

- Additional monitoring costs should not be applied
- Including costs without benefits (positive discontinuation) is not appropriate
- The rule should also be applied to comparators

Professional groups:

- Costs of 3-, 6- & 12-month visits should be included

AbbVie:

- Include similar monitoring intervals as botulinum toxin A

Teva:

- Galcanezumab SmPC recommends regular evaluation
- Fremanezumab included 6-monthly review costs
- These costs would not apply to BSC or botulinum toxin A

ERG comments

- Additional monitoring costs not justified without also applying positive discontinuation
- Need to also apply benefits of monitoring or could lead to overestimates of ICERs

Technical team judgement

- The ERG and company both believe monitoring costs should be excluded in the absence of a positive stopping rule
- Stakeholders and previous appraisals support the inclusion of monitoring costs

Should monitoring costs from 3-, 6- or 12-month reviews be included in the model?

Additional areas of uncertainty

Issue	Why issue is important	Impact on ICER
Generalisability of trial results	• Some treatments not routinely used in NHS	Unknown impact on ICER
Systematic review	• The search criteria may have missed some relevant studies	Unknown impact on ICER
Extrapolation of data	• No long-term clinical effectiveness data beyond 90 days	Uncertainty could increase ICER

Cost effectiveness results (1)

Assumptions used in updated company base case with PAS*

Assumption	Episodic	Chronic	
	vs BSC	vs BSC	vs botulinum toxin A
ERG corrections to model	✓	✓	✓
Time horizon – 45 years	✓	✓	✓
Consistent waning period between EM & CM	✓	✓	✓
Consistent waning period between treatments	n/a	n/a	✓
Discontinuers wane back from responder MHDs	n/a	n/a	✓
Equivalent discontinuation rates across treatments	n/a	n/a	✓
Response rate differs (ITC) and Change from baseline in MHD differs (ITC)	n/a	n/a	✓
Alternative source used to generate HRQoL	✓	✓	✓
Differential utilities for galcanezumab and comparator	✓	✓	✓
Age-related disutility applied	✓	✓	✓
Galcanezumab administration cost for 10% of patients	✓	✓	✓
Alternative resource consumption rates	✓	✓	✓

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*Updated following technical engagement

Cost effectiveness results (2)

Technical team & updated company base case (probabilistic results)

Episodic migraine – galcanezumab vs BSC

Treatment	Total cost	Total life years	Total QALYs	Incremental cost	Incremental QALYs	ICER (£/QALY)
Galcanezumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£22,573
BSC	[redacted]	[redacted]	[redacted]	-	-	

Chronic migraine – galcanezumab vs BSC

Treatment	Total cost	Total life years	Total QALYs	Incremental cost	Incremental QALYs	ICER (£/QALY)
Galcanezumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£8,838
BSC	[redacted]	[redacted]	[redacted]	-	-	

Chronic migraine – galcanezumab vs botulinum toxin A

Treatment	Total cost	Total life years	Total QALYs	Incremental cost	Incremental QALYs	ICER (£/QALY)
Galcanezumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£16,922
Botulinum toxin A	[redacted]	[redacted]	[redacted]	-	-	

Cost effectiveness results (3)

Technical team & updated company base case (deterministic results)

Episodic migraine – galcanezumab vs BSC

Treatment	Total cost	Total life years	Total QALYs	Incremental cost	Incremental QALYs	ICER (£/QALY)
Galcanezumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£22,633
BSC	[redacted]	[redacted]	[redacted]	-	-	

Chronic migraine – galcanezumab vs BSC

Treatment	Total cost	Total life years	Total QALYs	Incremental cost	Incremental QALYs	ICER (£/QALY)
Galcanezumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£8,796
BSC	[redacted]	[redacted]	[redacted]	-	-	

Chronic migraine – galcanezumab vs botulinum toxin A

Treatment	Total cost	Total life years	Total QALYs	Incremental cost	Incremental QALYs	ICER (£/QALY)
Galcanezumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£15,636
Botulinum toxin A	[redacted]	[redacted]	[redacted]	-	-	

Cost effectiveness results (4)

Including scenario analyses to updated company base case (deterministic)

Scenario	Episodic (vs BSC)	Chronic (vs BSC)	Chronic (vs botulinum toxin A)
Updated company base case	**£22,633**	**£8,796**	**£15,636**
Issue 3: Nurse-led botulinum toxin A administration	-	-	£22,579
Issue 4: Equal effectiveness between galcanezumab and botulinum toxin A	-	-	£134,115
Issue 6: Equal utility values for galcanezumab and comparator	£41,218	£18,234	£21,879
Issue 7: Additional monitoring costs for galcanezumab	£23,211	£9,062	£16,776

Key issues

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  - Should HFEM be considered separately to episodic and chronic migraine?
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