Glycopyrronium bromide cream for treating severe primary axillary hyperhidrosis [ID6487]

PART 1: For PROJECTOR – contains no confidential information

Technology appraisal committee B 2nd meeting [14 January 2026]

Chair: Charles Crawley

Lead team: Lisa Attrill, Vanessa Danielson, Nigel Westwood

External assessment group: BMJ Technology Assessment Group (BMJ-TAG)

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Company: Leith Healthcare

Draft guidance consultation

Glycopyrronium bromide 1% cream (Axhidrox)

- **Marketing authorisation (June 2025):** topical treatment for severe primary axillary hyperhidrosis in adults
- **List price:** anticipated list price CON, no PAS in place (not implementable in primary care)
- **Company positioning – GPB used after lifestyle advice and topical AL-based antiperspirants (ALAP)**
- **GPB Hyp1-18/2016 Phase 3a and 3b trials:**
  - <15% had prior treatment → GPB effectiveness may be overestimated
  - Primary outcome – sweat production, not Hyperhidrosis Disease Severity Scale (HDSS) used in economic model and comparator trials (clinically relevant)

*Link to Appendix – Background

RECAP

Preliminary recommendation

Glycopyrronium bromide (GPB) cream should not be used to treat severe primary axillary hyperhidrosis in adults

DG consultation responses

- **Company:** new evidence and analyses, updated base case with new assumptions
  - Did not respond to committee's requests for:
    - Utilities based on DLQI mapped onto EQ-5D-3L (DG, 3.13)
    - More detail about prior treatment with ALAP in Hyp-1-18 (DG, 3.5)
- **Professional organisations:** British Association of Dermatologists, Primary Care Dermatology Society

Abbreviations: AL, aluminium; ALAP, aluminium-based antiperspirants; botox, botulinum toxin; CON, confidential; DG, draft guidance; DLQI, Dermatology Life Quality Index; EQ-5D-3L, EuroQol-5 Dimensions-3 Level; GPB, glycopyrronium bromide 1% cream; HDSS, Hyperhidrosis Disease Severity Scale; PAHH, primary axillary hyperhidrosis; PAS, patient access scheme

Company positioning of GPB

Company

GPB used after lifestyle advice and ALAP:

- Primary care (majority) – alternative to oral anticholinergics (antimuscarinics)
- Secondary care (small prevalent population) – alternative to oral antimuscarinics or botox

Comments from The Primary Care Dermatology Society (PCDS)

Treatment pathway

- **Primary care:** ALAP widely prescribed at 1L, propantheline and oxybutynin (standard and modified-release)
  - Oral GPB: unlicensed special, rarely used – high cost and limited formulary inclusion
- **Botox referral:** usually not accepted until 1L, 2L and 3L treatments failed
  - Provision highly variable across ICBs (usually non-commissioned service)
  - Not curative (≤50% sweat reduction for 3–6 months; ongoing therapy needed after 2 cycles)
- **Topical compounded GPB:** unlicensed special, available in some trusts

GPB cream likely most appropriate:

- For PAHH when ALAP has failed or cannot be tolerated **(company's positioning)**
- As an adjunct to oral antimuscarinics when absorption or adverse effects are of concern
- After botox, as people who benefit often do not pursue costly private treatment. Majority referred to secondary care likely tried and failed ALAP (substantial cohort for whom GPB cream may be clinically appropriate)

Is company's positioning of GPB 1% cream appropriate in NHS primary and secondary care pathway?

Abbreviations: 1L/2L/3L, 1st/2nd/3rd line; ALAP, aluminium-based antiperspirants; botox, botulinum toxin; GPB, glycopyrronium bromide; ICB, Integrated Care Board; PAHH, primary axillary hyperhidrosis; PCDS, Primary Care Dermatology Society

Committee-preferred assumptions after ACM1 – company alignment

- **Comparators**: **Primary care** propantheline bromide. **Secondary care** MR oxybutynin and botox (DG, 3.3)
- **Botox**
  - Apply discontinuation at each admin timepoint, every 6 months (DG, 3.10)
  - Use company's approach for admin and monitoring costs – skin procedure and nurse time (DG, 3.14)
  - Assume botox OR for ≥1-point HDSS improvement is same as for ≥2-point improvement (DG, 3.16)
- **Monitoring frequencies for oral antimuscarinics:** closely at start and dose changes, then annually (DG, 3.14)
- **General population mortality:** ONS life tables from 2017 to 2019 (DG, 3.16)
- **Propantheline bromide costs in primary care model**
  - Drug Tariff price: £20.74 (DG, 3.16)
  - Company applied EAG scenario for admin costs in its updated base case: 90% primary care, 10% primary care + A&G services (1st appointment only) – not in DG (see Appendix slide)
- **Utilities**
  - Subsequent treatment: apply treatment-specific weighted average utility (DG, 3.11)
  - Company applied EAG scenario with HDSS utilities derived from Kamudoni et al.'s EQ-5D-5L data cross-walked to EQ-5D-3L in its updated base case
    - At ACM1, committee considered neither company base case nor EAG scenario provided appropriate utilities and requested scenario using DLQI from Hyp1-18 mapped onto EQ-5D-3L (not provided)

EAG comments: Corrections

- Accepts company's corrections to how treatment discontinuation of oral antimuscarinics was applied in EAG base case and company's updated costs (BNF prices and NHS reference costs for 2024-25)
- EAG corrected error in company's original ITC for GPB vs oral antimuscarinics

Abbreviations: A&G, advice and guidance; ACM, appraisal committee meeting; admin, administration; botox, botulinum toxin; DG, draft guidance; DLQI, Dermatology Life Quality Index; EQ-5D-3L/5L, EuroQol-5 Dimensions-3/5 Level; ITC, indirect treatment comparison; HDSS, Hyperhidrosis Disease Severity Scale; MR, modified release; ONS, Office for National Statistics; OR, odds ratio

Committee-preferred assumptions after ACM1: company deviations

Parameter	Committee's preferred assumption	Changes to company's updated base case	ICER impact
Relative effectiveness of antimuscarinics	Bucher ITCs for oxybutynin using Schollhammer et al. (2105) • no alternative ITC provided at ACM1	Assume oral antimuscarinics have same HDSS response rate as GPB • **New ITC vs methantheline bromide**	Large Slides 6-8
Subsequent treatment			
Distribution	EAG's distribution based on its clinical expert feedback	Distribution based on RWE and clinical expert survey	Large Slides 9-11
Modelling benefit	Not available	Revert to baseline HDSS if move to private treatment	Large Slide 12
Time horizon	2 years	5 years	Large Slide 13
Botox-waning effect	From 16 weeks	From 8 weeks	Large Slide 14
Treatment discontinuation	• GPB: constant rate from Hyp1-18 Phase 3b EAG's rates: • Antimuscarinics: 1/3 discontinued in 1st month, constant rate • Botox: rates from Lowe et al. (2007)	Clinical expert survey • Antimuscarinics and botox: % at 1, 2 and 5 years • GPB: long-term same as antimuscarinics	Large Slides 15-16
AE costs	Excluded (covered in monitoring costs)	Clinical expert survey • Add 10 mins pharmacist time per AE	Large Slide 17

Key issue (primary care): Relevant antimuscarinics and ITCs – oxybutynin or methantheline bromide

Large ICER impact

Company: new Bucher ITC GPB (Hyp1-18/2016 Phase 3a) vs methantheline bromide (Muller et al. 2013 trial)

- Key antimuscarinic comparator: **propantheline bromide**
- **Company original ITC:** vs **oxybutynin** (Schollhammer et al. (2015); only study reporting HDSS response rates)
  - Limitations: mainly generalised hyperhidrosis; non-site-specific HDSS measurement; oxybutynin comparator
- **Company new ITC:** vs **methantheline bromide** (isopropyl analogue of propantheline)
  - Closer clinical proxy for propantheline than oxybutynin; not used in UK
  - Muller et al. (2013): statistically significant HDSS improvements with methantheline vs placebo at 4 weeks, similar in magnitude to GPB data
  - Company derived HDSS response rates **indirectly** via review (Wade et al. 2017) that simulated ≥2-point HDSS rates from Muller's continuous HDSS data → used for Bucher ITC
- Company: GPB cream is likely at least as effective as oral antimuscarinics, with targeted delivery, reduced systemic exposure and less frequent dosing after induction. RWE show high HDSS response rates with GPB in PAHH than those for antimuscarinics
  - Company updated base case: assume equal efficacy between GPB and oral antimuscarinics
  - Scenario: apply methantheline-based OR to both propantheline bromide and modified-release oxybutynin

Is methantheline bromide used in the UK for PAHH?

Which oral antimuscarinic provides the most appropriate proxy for NHS primary care practice in PAHH: oxybutynin or methantheline bromide?

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Abbreviations: GPB, glycopyrronium bromide; HDSS, Hyperhidrosis Disease Severity Scale; ITC, indirect treatment comparison; OR, odds ratio; PAHH, primary axillary hyperhidrosis; RWE, real world evidence

ITCs: GPB vs antimuscarinics

Large ICER impact

EAG comments on ITC GPB vs methantheline bromide (Muller et al. 2013 trial)

- Limitations of Muller et al. trial and methantheline ITC
  - Few baseline characteristics reported (conducted in Germany) → generalisability of population unclear
  - Analysis populations from Muller and GPB trials not aligned → Muller population (not all randomised who had ≥1 study treatment dose) vs GPB mITT FASa population
    - EAG conducted ITC using mITT from Muller assuming missing patients show non-response
  - Simulated HDSS response data from Wade et al. → more uncertainty; reliability of analysis unclear
- EAG results broadly consistent with company's analyses; ORs [redacted]
  - All analyses: CIs [redacted], results [redacted], [redacted]

#	Treatment	Source of data	Timepoint	HDSS response	Company OR (95% CI)	EAG OR (95% CI)
1	**GPB**	**FASa**	**Day 29**	**≥2**	[redacted]	[redacted]
	Oxybutynin	**Schollhammer 2015**	**6 weeks**	**≥2**		
4	GPB	FASa	Day 29	≥2	[redacted]	[redacted]
	Oxybutynin	Wade 2017	4 weeks	≥2		
17	**GPB**	**FASa**	**Day 29**	**≥2**	[redacted]	[redacted]
	Methantheline	**Muller 2013 (Wade 2017)**	**Day 28 ± 1**	**≥2**		
18	GPB	FASa	Day 29	≥2	[redacted]	[redacted]
	Methantheline	Muller 2013 (Wade 2017) mITT	Day 28 ± 1	≥2		

[a]Schollhammer: all randomised and had allocated treatment (30 oxybutynin vs 30 placebo). Missing patients = non-response
[b]Muller: all randomised and had allocated treatment (171 methantheline vs 168 placebo). Missing patients = non-response

Abbreviations: CI, confidence interval; FASa, full analysis set Phase 3a; GPB, glycopyrronium bromide; HDSS, Hyperhidrosis Disease Severity Scale; ITC, indirect treatment comparison; mITT, modified intention-to-treat; NA, not available; OR, odds ratio

Large ICER impact

Key issue (primary care): Relevant antimuscarinics and ITCs – oxybutynin or methantheline bromide

EAG comments on ITC GPB vs methantheline bromide (Muller et al. 2013 trial)

- Consider company original ITC using Schollhammer et al. more robust than Muller methantheline
- Lack of statistical significance is not sufficient evidence to conclude clinical equivalence
- Scenario: committee preferred base case after ACM1 and estimates from company's methantheline ITC

Which ITC provides most robust evidence on the clinical effectiveness of GPB vs antimuscarinics? Schollhammer oxybutynin or Muller methantheline bromide?

Which analytical approach is preferred? EAG's with matched trial populations or company's analyses?

Does the evidence support an assumption of equal clinical effectiveness for GPB and antimuscarinics?

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Abbreviations: ACM, appraisal committee meeting; GPB, glycopyrronium bromide; ITC, indirect treatment comparison

Key issue: Modelling subsequent treatments

Large ICER impact

Background

- At ACM1, distribution of subsequent treatments had small impact on ICER (DG 3.14)
- DG 3.16 states committee preferred assumption of using EAG's basket of subsequent treatments

Company's original model

- All subsequent treatments assumed to occur in secondary care
- One-off cost applied for basket of subsequent treatments (distribution based on initial treatment)
- No benefits assumed: patients revert to baseline HDSS scores and accrue utilities for that health state

EAG critique

- Costs without benefits bias results against comparators (key ICER driver)
- Antimuscarinics and botox assumed to have higher discontinuation rates, with longer time in subsequent treatment health state over lifetime horizon

Alternative assumptions

- Company scenario: applied treatment-weighted average utility for subsequent treatment health state rather than reverting to baseline HDSS scores (EAG and committee-preferred assumption – see slide 4)
- EAG clinical expert informed distribution of basket of subsequent treatments and advised that around 1/3 of secondary-care patients without further NHS care would seek private healthcare
- EAG scenario: used its clinical expert's distribution and assumed that 2/3 of patients without further NHS or private care would revert to baseline HDSS scores

Abbreviations: ACM, appraisal committee meeting; botox, botulinum toxin; DG, draft guidance; GPB, glycopyrronium bromide; HDSS, Hyperhidrosis Disease Severity Scale; ICER, incremental cost-effectiveness ratio

Key issue: Distribution of subsequent treatments

Large ICER impact

Company

- EAG assumptions based on limited expert opinion and may not reflect UK clinical practice
- Collected new UK RWE and clinician feedback of 10 UK dermatologists treating PAHH:
  - ~45% PAHH patients could access botox as subsequent therapy (42 ICBs policy review)
  - Fewer patients have botox than assumed in EAG base case (10 UK dermatologists survey)
  - 1,047 PAHH botox treatments over 12 months across 36 trusts (Hospital Episode Statistics)
  - ~3,435 patients per month use propantheline bromide on repeat (all indications) [NHS prescription data]
- EAG's clinical expert estimate of botox use as subsequent treatment may be overestimated
- Company updated base case: cap botox use at 45.4% and apply clinician-derived distributions where consistent with this cap (proportionally rescaling where needed)

EAG comments

- ICB data: insufficient to determine how many eligible PAHH patients actually had botox
- HES data: data not specific to PAHH and did not report patient numbers. PAHH prevalence unknown, so data too incomplete to draw conclusions on access to treatment in patients with PAHH
- NHS prescription data on propantheline: not PAHH-specific and unknown prevalence, so conclusions on access to treatment cannot be made
  → Evidence too incomplete to draw conclusions on access
- Maintains EAG-preferred assumption of using its clinical expert's distribution of subsequent treatments

Abbreviations: botox, botulinum toxin; HES, Hospital Episode Statistics; ICB, Integrated Care Board; PAHH, primary axillary hyperhidrosis; RWE, real world evidence

Distribution of subsequent treatments

Large ICER impact

Subsequent treatment – primary care model	Committee preferred distribution after ACM1 Source: EAG clinical expert		Updated company base case Source: RWE and 10 UK dermatologists	
	GPB	Antimuscarinics	GPB	Antimuscarinics
Antimuscarinics (primary care)	0%	0%	14%	3.2%
Antimuscarinics (primary care and A&G)	0%	0%	12%	8%
Antimuscarinics (secondary care)	20%	10%	26.6%	22.3%
Botox (secondary care)	80%	90%	33.9%	45.4%
Unlicensed GPB (secondary care)	0%	0%	1.9%	4.2%
Private treatment	0%	0%	5.1%	7.3%
No further treatment	0%	0%	6.5%	9.6%

Subsequent treatment – secondary care model	Committee preferred base case after ACM1 Source: EAG clinical expert			Updated company base case Source: RWE and 10 UK dermatologists		
	GPB	Antimuscarinics	Botox	GPB	Antimuscarinics	Botox
Antimuscarinics (primary care)	0%	0%	0%	2.1%	1.7%	11%
Antimuscarinics (primary care and A&G)	0%	0%	0%	3.3%	0%	3%
Antimuscarinics (secondary care)	10%	10%	25%	31%	9.3%	18.5%
Botox (secondary care)	80%	63%	0%	45.4%	45.4%	0%
Unlicensed GPB (secondary care)	0%	2%	25%	3.2%	7.7%	8.5%
Private treatment	3.3%	8.3%	16.7%	6.5%	12.7%	29.5%
No further treatment	6.7%	16.7%	33.3%	8.5%	23.2%	29.5%

Which subsequent treatment distributions are most plausible and reflective of NHS clinical practice?

Abbreviations: A&G, advice and guidance; ACM, appraisal committee meeting; botox, botulinum toxin; GPB, glycopyrronium bromide; RWE, real world evidence

Key issue: Subsequent treatment benefit and costs

Large ICER impact

Company

- EAG assumption that people having botox privately get full clinical benefit at no NHS cost is inappropriate
  - In EAG primary care model, private or no treatment not modelled. But, when clinician-derived distributions are applied, some patients move to these states without assigned outcomes (incomplete modelling)
  - In EAG secondary care model, EAG assumed: no further NHS costs for private or no treatment; reversion to baseline HDSS for no treatment; continued benefit for private treatment from prior NHS therapy
- Company considers EAG's approach is methodologically and ethically flawed, as it:
  - Biases results towards pathways that move patients out of NHS care
  - Treats private care as a zero-cost, full-benefit option
  - Conflicts with NICE equity principles by assuming equal ability to self-fund care
- Company updated base case: patients having private treatment revert to baseline HDSS (strict NHS perspective)
- Scenario analyses: alternative assumptions of average benefit across therapies and EAG's original approach

EAG comments

- Company private-care assumption removes all treatment benefit
- Considers costs and benefits should be accounted for as patients have them (benefits but not costs attributed to patients in private healthcare)
- EAG scenario: assumes patients have benefit of treatment in private care, but model assumes this is paid for by NHS. Recognises this is a strong assumption, EAG considers it to be preferable to company's assumption that patients revert to their baseline HDSS health state

Should patients who no longer have treatment on the NHS revert to baseline HDSS score?

Abbreviations: A&G, advice and guidance; ACM, appraisal committee meeting; botox, botulinum toxin; GPB, glycopyrronium bromide; HDSS, Hyperhidrosis Disease Severity Scale; RWE, real world evidence

Key issue: Time horizon

Large ICER impact

Committee considerations at ACM1

- Clinical experts: treatment response occurs early, remains stable; so costs and benefits captured in first 2 years
- Longer time horizon compounds modelling assumptions that are biased against comparators

Company

- Some patients remain on treatment (GPB, antimuscarinics, botox) beyond 2 years
  - % on treatment at 2 years: 61% GPB, 48% antimuscarinics, 70% botox
- Propose 5-year horizon that captures sustained benefits while limiting influence of subsequent treatments
  - % on treatment at 5 years: 39% GPB, 31% antimuscarinics, 46% botox
- Company's updated base case: 5-year time horizon

EAG comments

- Prefer 2-year horizon because mortality is unchanged, health-state transitions stop after week 72, and treatment responses occur early and remain stable
- Trial data are only available up to 72 weeks and no further health-state transitions are modelled thereafter
- Company has not provided strong justification to change 2-year horizon

What is the most appropriate time horizon for modelling GPB and comparators? 2 or 5 years?

Abbreviations: ACM, appraisal committee meeting; botox, botulinum toxin; GPB, glycopyrronium bromide

Key issue: Treatment-effect waning of botox

Large ICER impact

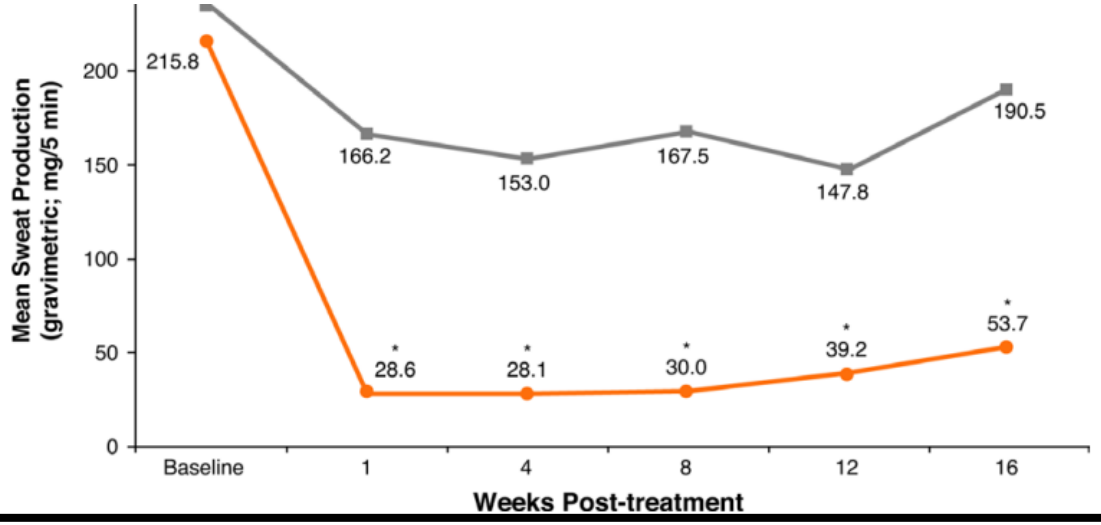
Committee considerations at ACM1: botox-effect waning from week 16 (clinical opinion)

Company updated base case: treatment-effect waning of botox from week 8

- Original company base case: peak efficacy at 4 weeks with waning to no effect by 6 months (Lowe et al. 2007)
- Published literature: peak efficacy between 4 and 16 weeks (upper limit of treatment effect)

Figure 1. HDSS improvement for botox (blue) vs placebo (orange) in PAHH (Lee et al). All p values 0 at weeks 4 to 1
Decline from week 8

Figure 2. Sweat production with botox (orange) vs placebo (grey) [Lowe et al.]. Decline from week 12



EAG comments

- Most evidence >20 years, may not reflect current practice; variable peak efficacy
  - Lee et al: no CIs or p-values; EAG considers changes likely not statistically significant
  - Lowe et al: weak correlation between sweat production and HDSS → not supportive of earlier waning
- Clinical experts (EAG's and at ACM1) aligned that botox waning should be applied from week 16

When should botox treatment-effect waning be applied in the model? From 8 weeks or from 16 weeks?

Key issue: Treatment discontinuation for antimuscarinics and botox

Large ICER impact

Committee considerations at ACM1

- GPB: constant discontinuation rate from GPB Hyp1-18 Phase 3b
- Antimuscarinics: 1/3 discontinued in 1st month, then slower rate thereafter (~10%) (EAG clinical experts)
- Botox: discontinuation rates from Lowe et al. (2007) using EAG's approach
- Requested further validation of treatment discontinuation for antimuscarinics and botox

Company

- Identified and corrected modelling errors in applying EAG's preferred discontinuation rates (EAG accepted)
- Notes differing recollections of clinical expert views on discontinuing antimuscarinics at ACM1, with emphasis on high early discontinuation and few long-term users, though not necessarily ≥90% by 2 years
- Company conducted literature review and survey of 10 UK dermatologists in Nov 2025: discontinuation estimates at 1, 2 and 5 years
- Company updated base case: uses estimates from clinician survey for antimuscarinics and botox. For GPB beyond 72-week trial period, assumed discontinuation is aligned with stabilised antimuscarinic at 2 and 5 years

EAG comments

- Company's 10 expert feedback broadly supports committee's preferred assumptions at ACM1
- Disagrees with assuming equal discontinuation rates for antimuscarinics and GPB (discontinuation reasons differ between topical and systemic treatments)
- Scenarios using company's updated discontinuation assumptions and retaining committee's preferred GPB rates

Abbreviations: ACM, appraisal committee meeting; botox, botulinum toxin; GPB, glycopyrronium bromide; Nov, November

Treatment discontinuation rates

Large ICER impact

Time point	Company original base case			EAG's base case		Company's survey Average clinician responses		Company updated base case	
	GPB	Anti-muscarinics	Botox	Anti-muscarinics	Botox	Anti-muscarinics	Botox	Anti-muscarinics	Botox
Source of rates	Hyp1-18	Wolosker et al. 2014	Lowe et al. 2007[a]	1 clinical expert	Lowe et al. 2[b]	10 UK dermatologists who treat PAHH			
6 months	12%	52%	32%	36%	10%	-	-	22%	7%
1 year	22%	76%	54%	38%	21%	38%	14%	38%	14%
2 years	39%	94%	78%	43%	37%	52%	30%	52%	30%
5 years	61%	99%	97%	56%	69%	69%	55%	69%	54%

[a]All patients who formally discontinued and 50% who completed study without further treatment
[b]Patients who formally discontinued only

Which treatment discontinuation assumptions for antimuscarinics and botox are most plausible?

Abbreviations: ACM, appraisal committee meeting; botox, botulinum toxin; GPB, glycopyrronium bromide; Nov, November

Key issue: Cost of managing adverse events

Large ICER impact

Committee considerations at ACM1

- Clinical experts: AEs generally mild and managed through dose reduction or stopping treatment
- GPB, topical treatment, likely to have fewer side effects
- AE costs covered by routine monitoring; only AE-related disutilities should be included

Company

- Assuming costs of AEs are covered by monitoring underestimates impact of AEs
- Survey of 10 UK dermatologists on managing mild or moderate AEs
  - Only 3/10 clinicians reported no additional resource use
  - 5/10 indicated AEs would need pharmacist or GP input in primary care
  - 2/10 expected additional secondary-care resource use, possibly extra appointments and tests
- Company updated base case: added cost of 10 minutes of pharmacist time (£9.17, PSSRU) per AE

EAG comments

- Reviewed company's clinical experts' feedback and found it largely aligned with committee's view that most AEs are mild and managed within routine care
- Consider company's survey evidence does not justify including additional AE management costs

Should additional cost of managing adverse events be included?

Abbreviations: ACM, appraisal committee meeting; AE, adverse event; GP, general practitioner; GPB, glycopyrronium bromide; PSSRU, Personal Social Services Research Unit

Other issues: Clinical effectiveness of GPB

Large ICER impact

Company: Long-term efficacy of GPB (Hyp1-18/2016) vs botox (Lowe et al.)

- Considers DG understates uncertainty in long-term relative efficacy of botox: limitations in ITC HDSS responder definitions between Hyp1-18 and Lowe et al. botox study. FDA, trial and RWE of Lowe et al. suggest GPB and botox have broadly comparable sustained response rates over 1 year based on naïve comparison
- Company scenarios: impact of different OR assumptions (OR =1, 2 & 3, data from Wade et al. 2017) for GPB vs botox
  - Applied to company updated base case for secondary care model; minimal impact on ICERs

Underestimated QoL benefit of GPB

- Hyp1-18 showed statistically significant improvements vs placebo across 3 validated QoL measures (HDSS absolute change, HidroQoL and DLQI) at Days 15 and 29, with only 1 HDSS responder outcome narrowly missing significance. Sustained improvements up to Week 72 for all 3 outcomes

EAG comments

- ITC responder definition not an issue: patients on botox had to relapse before retreatment; ongoing use of GPB
  - Agree any differences in responder definitions unlikely to affect outcomes at 4 weeks used in ITCs (botox's long median duration of effect ~200 days)
- Suggest caution on company's naïve comparison: GPB data from open-label, single-arm study; botox data from double-blind, placebo-controlled RCT; uncertain if outcome definitions were comparable; GPB outcome appeared to be based on a post hoc analysis
  - Company's scenarios less robust than committee's preferred base case and no further analyses needed

Abbreviations: botox, botulinum toxin; DG, draft guidance; DLQI, Dermatology Life Quality Index; FDA, U.S. Food and Drug Administration; GPB, glycopyrronium bromide; HDSS, Hyperhidrosis Disease Severity Scale; HidroQoL, Hyperhidrosis Quality of Life Index; ICER, incremental cost-effectiveness ratio; ITC, indirect treatment comparison; OR, odds ratio; QoL, quality of life; RCT, randomised controlled trial; RWE, real world evidence

Summary of assumptions in committee's preferred base case after ACM1 and company's updated base case

Parameter	Committee's preferred assumption	Changes to company's updated base case
Relative effectiveness of antimuscarinics	Bucher ITCs for oxybutynin using Schollhammer et al. (2105)	Assume oral antimuscarinics have same HDSS response rate as GPB
Subsequent treatment		
Distribution (slide 11)	EAG's distribution based on its clinical expert feedback	Distribution based on RWE and clinical expert survey
Modelling benefit	Not available	Private treatment revert to baseline HDSS
Time horizon	2 years	5 years
Botox-waning effect	From 16 weeks	From 8 weeks
Treatment discontinuation (Slide 16)	• GPB: constant rate from Hyp1-18 Phase 3b EAG's rates: • Antimuscarinics: 1/3 discontinued in 1st month, constant rate • Botox: rates from Lowe et al. (2007)	Clinical expert survey • Antimuscarinics and botox: % at 1, 2 and 5 years • GPB: long-term same as antimuscarinics
AE costs	Excluded (covered in monitoring costs)	Clinical expert survey • Add 10 mins pharmacist time per AE

Abbreviations: ACM, appraisal committee meeting; AE, adverse event; botox, botulinum toxin; GPB, glycopyrronium bromide; HDSS, Hyperhidrosis Disease Severity Scale; ITC, indirect treatment comparison; RWE, real world evidence

Cost-effectiveness results

All ICERs are reported in PART 2 slides because they include confidential comparator discounts

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Abbreviations: ICER, incremental cost-effectiveness ratio

Summary of key issues

- Is company's positioning of GPB 1% cream appropriate in NHS primary and secondary care pathway? (Slide 3)
- Is methantheline bromide used in the UK for PAHH? (Slide 6)
- Which oral antimuscarinic provides the most appropriate proxy for NHS primary care practice in PAHH: oxybutynin or methantheline bromide? (Slide 6)
- Which ITC provides most robust evidence on the clinical effectiveness of GPB vs antimuscarinics? Schollhammer oxybutynin or Muller methantheline bromide? (Slide 6)
- Which analytical approach is preferred? EAG's with matched trial populations or company's analyses? (Slide 8)
- Does the evidence support an assumption of equal clinical effectiveness for GPB and antimuscarinics? (Slide 8)
- Which subsequent treatment distributions are most plausible and reflective of NHS clinical practice? (Slide 11)
- Should patients who no longer have treatment on the NHS revert to baseline HDSS score? (Slide 12)
- What is the most appropriate time horizon for modelling GPB and comparators? 2 or 5 years? (Slide 13)
- When should botox treatment-effect waning be applied in the model? From 8 weeks or from 16 weeks? (Slide 14)
- Which treatment discontinuation assumptions for antimuscarinics and botox are most plausible? (Slide 16)
- Should additional cost of managing adverse events be included? (Slide 17)
- Are there any uncaptured benefits?
- Are there any equality issues to consider?

Abbreviations: botox, botulinum toxin; GPB, glycopyrronium bromide; HDSS, Hyperhidrosis Disease Severity Scale; ITC, indirect treatment comparison; PAHH, primary axillary hyperhidrosis

Appendix

Background

Primary axillary hyperhidrosis: excessive sweating in armpits, more than needed to maintain normal body temperature, no known cause, improves with age

- Severe PAHH: 3 or 4 on Hyperhidrosis Disease Severity Scale (HDSS); severe or intolerable on Primary Focal Hyperhidrosis (PFH) severity
- Significant impact on people's quality of life, emotional wellbeing, and self-esteem. Affects daily activities can cause anxiety and embarrassment
- **Treatment pathway and positioning of GPB:**
    - Primary care (main population): lifestyle advice → 20% ACH preparations → oral anticholinergic (antimuscarinics) **or GPB** → refer to secondary care
    - Secondary care: lifestyle advice, 20% ACH preparations **or GPB** → oral antimuscarinics or botox → surgery
- **Equality considerations:** PAHH usually self-managed with significant out of pocket costs, variation in availability of botox on the NHS

***Link to Draft guidance consultation**

Abbreviations: ACH, aluminium chloride hexahydrate; botox, botulinum toxin; GPB, glycopyrronium bromide; HDSS, Hyperhidrosis Disease Severity Scale; PAHH, primary axillary hyperhidrosis; PFH, Primary Focal Hyperhidrosis

Administrative cost for oral antimuscarinics

Company base case at ACM1

- Admin cost for oral antimuscarinics: 25% primary care; 25% primary care + A&G services

EAG comments

- EAG scenario: 90% primary care, 10% primary care + A&G services (1st appointment only)
  - Justification:
    - Company states GPB will be used in primary and secondary care. Analysis reflects primary care setting
    - Propantheline bromide is only antimuscarinic with marketing authorisation for PAHH and GPs are less likely to use A&G services. Cost of A&G services is applied to smaller proportion and is a one-off appointment and not ongoing support

Company updated base case in response to DG

- Accepted EAG scenario for admin cost of oral antimuscarinics

***Committee-preferred assumptions after ACM1 – company alignment**

Abbreviations: A&G, advice and guidance; ACM, appraisal committee meeting; admin, administration; DG, draft guidance; PAHH, primary axillary hyperhidrosis

Company model

Markov model with 6 health states, 4 based on HDSS, a subsequent therapy health state and death

Figure: Company's model structure

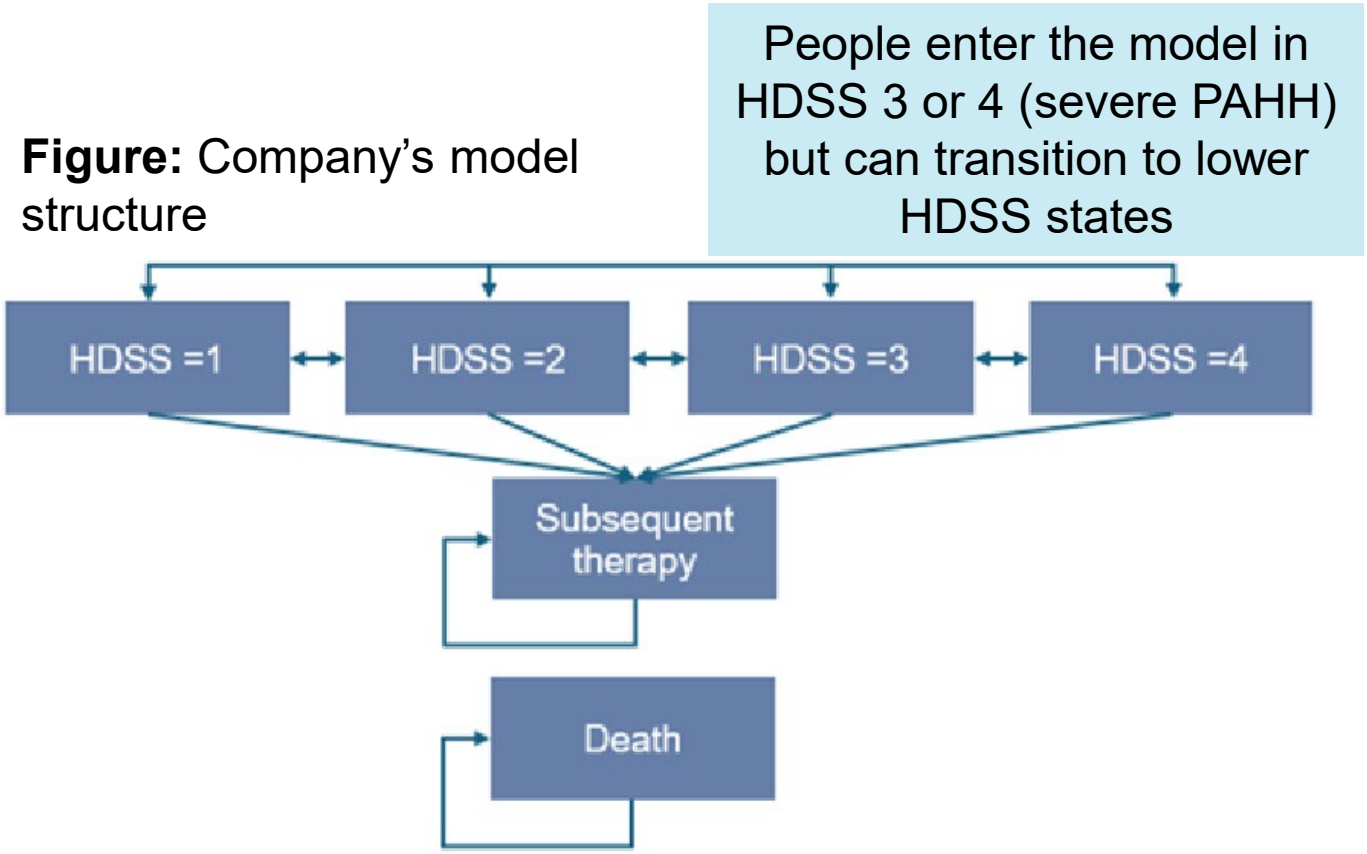

Table: Company's model features

Model features	
Cycle length	2 weeks
Half-cycle correction	Applied
Time horizon	65 years
Perspective	UK NHS
Discount rates	3.5%

Abbreviations: HDSS, Hyperhidrosis Disease Severity Scale; PAHH, primary axillary hyperhidrosis.

Company dispute on recollection of clinical experts feedback at ACM1 on treatment discontinuation

At the first Committee meeting, 2 clinical experts provided input on antimuscarinic discontinuation.

"*One clinical expert explained that around a third to a half of people would stop taking oral anticholinergics in the first 2 months, followed by slower discontinuation rates. The other clinical expert explained that in secondary care, they would not expect to see anyone on oral anticholinergic treatment after 2 years. … So, the committee agreed that the company's discontinuation of 94% at 2 years for oral anticholinergics was too high*." (DG, section 3.10)

Company notes this interpretation does not fully reflect the clinicians' views.

- One clinician observed that many patients discontinue due to side effects or intolerability, and only a small proportion continue beyond 2 years, estimating that "more than 6–10% of patients may remain on antimuscarinics beyond this point." The second clinician initially agreed with the 94% discontinuation rate but later clarified that although discontinuation is common, the proportion is not ≥90%.

Company and EAG scenarios

Company scenarios:

- **Relative efficacy of propantheline bromide.** Apply range of alternative ORs e.g. from Müller et al. (2013) and Wade et al. (2017) in Bucher ITC framework, fixed ORs of 3 and 4, and ORs from Schollhammer et al. (2015). Except for Schollhammer et al. (2015) scenario, all analyses assume same OR for both ≥2-point and ≥1-point HDSS improvement
- **Relative efficacy of botox.** Explore ORs from Wade et al. (2017) ITC and fixed ORs of 1, 2, and 3. All scenarios apply same OR for both ≥2-point and ≥1-point HDSS improvement
- **Modelling subsequent treatments.** Explore alternative assumptions about treatment benefit when patients move to privately funded care e.g. assuming patients having privately funded care accrue benefits equal to average of all treatments, and EAG's original approach to modelling private treatment outcomes

EAG scenarios:

- OR based on company's ITC for methantheline bromide vs GPB
- 5-year time horizon
- Botox costs applied to patients on privately funded treatment
- Company clinician survey feedback on treatment discontinuation for oral antimuscarinics and botox

Abbreviations: botox, botulinum toxin; GPB, glycopyrronium bromide; HDSS, Hyperhidrosis Disease Severity Scale; ITC, indirect treatment comparison; OR, odds ratio