# Single Technology Appraisal

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

# Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

# SINGLE TECHNOLOGY APPRAISAL

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

**Contents:**

The following documents are made available to stakeholders:



*Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.*

NICE National Institute for Health and Care Excellence

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

## Draft guidance comments form

**Consultation on the draft guidance document – deadline for comments** by the end of 5 December 2025. Please submit via NICE Docs.

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| **Organisation name – Stakeholder or respondent** (if you are responding as an individual rather than a registered stakeholder please leave blank): | Leith Healthcare |
| **Disclosure**<br>Please disclose any funding received from the company bringing the treatment to NICE for evaluation or from any of the comparator treatment companies in the last 12 months. [Relevant companies are listed in the appraisal stakeholder list.]<br>Please state:<br>• the name of the company<br>• the amount<br>• the purpose of funding including whether it related to a product mentioned in the stakeholder list<br>• whether it is ongoing or has ceased. | N/A |
| Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry. | Nothing to disclose |
| **Name of commentator person completing form:** | [redacted] |

## Response to Draft Guidance

The Company thanks NICE for the opportunity to respond to the Draft Guidance document, and provide further evidence relating to key uncertainties discussed during the first Appraisal Committee Meeting (ACM). To do this we reassessed the evidence identified in the systematic literature review (SLR), sought and obtained published information relating to oral antimuscarinic therapies that were not specified in the NICE scope but may provide helpful data for decision making, made Freedom of Information requests to obtain information about the availability of treatment for hyperhidrosis in the UK from NHS England and the NHS Business Services Authority, and carried out primary market research through a survey of 10 UK dermatologists.

Below we outline our comments on the Draft Guidance document and detail the additional evidence we have obtained to address the areas of uncertainty. Following this, we present an updated Company base case

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which uses the new evidence provided in this document and aims to provide a plausible base case for NICE decision making.

For orientation within the table below, our responses relate to the following topics:

- **Comment 1:** Efficacy of GPB 1% cream compared to oral antimuscarinics
- **Comment 2:** Efficacy of GPB 1% cream compared to botulinum toxin (BTX)
- **Comment 3:** Waning of BTX
- **Comment 4:** Distribution of subsequent therapies (a) and benefits accrued to private treatments (b)
- **Comment 5:** Time horizon (2 years vs 5 years)
- **Comment 6:** Discontinuation rates for oral antimuscarinics (a) and BTX (b)
- **Comment 7:** Cost of management of adverse events
- **Comment 8:** Impact of GPB 1% cream on patient health-related quality of life (HRQoL)
- **Comment 9:** Updated reference costs

| Comment number | Comments |
|---|---|
| 1 | Following the Committee's discussion at the first Appraisal Committee Meeting (ACM) and the Draft Guidance, we would like to clarify and revisit the evidence underpinning the relative efficacy comparison between GPB 1% cream and oral antimuscarinics.<br><br>To date, the Company has relied on indirect treatment comparisons (ITCs) combining GPB 1% cream data from the Hyp1-18/2016 phase 3a trial with oxybutynin data from Schollhammer et al. (2015).[1] Schollhammer et al. (2015) was selected because it was the only placebo-controlled study identified in the systematic literature review (SLR) that included a relevant oral antimuscarinic comparator and reported HDSS responder rate outcomes. During the development of the submission, oral antimuscarinics were considered broadly as a therapeutic class for PAHH, and oxybutynin was therefore used as a pragmatic representative of that class. The Committee accepted these ITCs for decision making, while highlighting substantial uncertainty and methodological limitations. The Committee also noted that no alternative analyses had been presented. |

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| | **Why we are re-visiting this now**<br><br>First, in the original submission, the assumed relative efficacy between GPB 1% cream and oral antimuscarinics was not a key driver of cost-effectiveness. As such, the uncertainty surrounding the existing ITCs was less critical to the overall decision. At that time, we acknowledged the limitations of the evidence and adopted a conservative position by accepting a numerical, but non-significant, advantage in favour of oral antimuscarinics. However, under the Committee's preferred assumptions this parameter has now become a major driver of cost-effectiveness results in both primary and secondary care models. Given its new influence on model outcomes, we do not consider the evidence underpinning the original ITCs to be sufficiently robust for decision-making, and therefore we have explored alternative approaches in this response.<br><br>Second, in the Draft Guidance, the Committee concluded that the most relevant comparators to GPB 1% cream are propantheline bromide in primary care and modified-release oxybutynin and BTX in secondary care. Because GPB 1% cream is expected to be used mostly in the primary care setting, and the Committee has clarified that propantheline bromide is the main comparator, we have revisited the comparative evidence to ensure greater relevance to the decision problem. In doing so, we identified evidence on methantheline bromide (the isopropyl analogue of propantheline bromide), which may provide a closer pharmacological and clinical proxy than oxybutynin and help address several of the concerns previously associated with the Schollhammer et al. (2015) comparison.<br><br>This evidence was not included in the original ITCs because methantheline bromide is not used in UK clinical practice and therefore did not meet the initial criteria for inclusion. At that time, the objective was to represent the broader antimuscarinic class, and oxybutynin was selected as a pragmatic proxy for agents used in the UK. However, given (i) the substantial uncertainty identified in the ITC based on Schollhammer et al. (2015), (ii) the fact that relative efficacy has now become a key driver of the results, and (iii) the Committee's clarification that propantheline bromide is the relevant comparator specifically in primary care, we have re-examined the available evidence accordingly. |

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| | **Recap of the limitations associated with the ITCs using Schollhammer et al. (2015)**<br><br>As highlighted in the Draft Guidance, the ITCs based on Schollhammer et al. (2015) have several fundamental limitations – as summarised below.<br><br>Limitations of the Schollhammer data:<br><br>• The study population consisted predominantly of people with generalised hyperhidrosis rather than axillary hyperhidrosis (50 of 60 patients; 83%). Sweating was reported across multiple sites (palmar [36], plantar [39], axillary [45], facial [19], and truncal [26]).<br><br>• Measurement of sweating severity also differed: in the GPB 1% cream trial (Abels et al. 2021), patients rated underarm-specific sweating, whereas in Schollhammer et al. (2015) patients rated sweating severity without specifying a site using the HDSS tool.<br><br>• Oxybutynin is not the comparator for GPB 1% cream in primary care.<br><br>**Evidence from methantheline bromide as a more relevant comparator**<br><br>As noted above, we have identified evidence for methantheline bromide (the isopropyl analogue of propantheline), which is likely to be a closer pharmacological and clinical proxy for propantheline bromide than oxybutynin. Two relevant studies were found in the SLR: Muller et al. (2013) and Hund et al. (2004), but only Muller et al. (2013) reported HDSS outcomes.[2,3]<br><br>Muller et al. (2013) was a prospective, placebo-controlled clinical trial evaluating methantheline bromide for axillary and palmar hyperhidrosis. Baseline HDSS was 3.2 in both arms. In the methantheline group, mean HDSS fell to 2.6 at day 14 and 2.4 at day 28. In the placebo group, HDSS decreased to 2.8 at day 14 and 2.7 at day 28. The differences between treatments were statistically significant at both time points (P = 0.02 and P = 0.002). These reductions are very similar to the week-4 HDSS changes observed with GPB 1% cream in the Phase IIIa and IIIb trials (shown in Table 1). |

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**Table 1: A comparison of absolute change in HDSS from baseline (mean values) from the GPB 1% cream data and the methantheline bromide data**[3,4]

| | GPB 1% PIII | | | Methantheline bromide PIII | |
|---|---|---|---|---|---|
| | **PIIIa GPB 1% cream** | **Placebo** | **GPB 1% cream PIIIb newly recruited population** | **Methantheline bromide 50mg three times daily** | **Placebo** |
| HDSS at baseline | [redacted] | [redacted] | [redacted] | 3.2 | 3.2 |
| Change from baseline at day 14 or 15 | [redacted] | [redacted] | [redacted] | -0.6 | -0.4 |
| Change from baseline at day 28 or 29 | [redacted] | [redacted] | [redacted] | -0.8 | -0.5 |

Abbreviations: GPB, glycopyrronium bromide; HDSS, Hyperhidrosis Disease Severity Scale.

Unfortunately, Muller et al. (2013) did not report HDSS responder rates, meaning the data are not directly usable within a Bucher ITC framework. However, in Wade et al. (2017),[5] the authors addressed this limitation by simulating the ≥2-point HDSS response rates based on the available continuous HDSS data. This method introduces additional uncertainty and required the assumption of a unimodal distribution across all response levels, which is fully described in Wade et al. (2017). Nevertheless, it provides responder estimates aligned with the 4-week timepoint of the GPB 1% cream trials which can be used in the Bucher ITC framework.

Wade et al. (2017) estimated that 4/128 patients receiving methantheline bromide and 1/139 patients receiving placebo achieved a ≥2-point HDSS improvement (Table 14 of Wade et al. 2017).[5] Using these estimates in our Bucher ITC, the odds ratio for methantheline bromide vs GPB 1% cream is [redacted] (95% CI [redacted]). While the confidence intervals remain wide, this comparison is methodologically more appropriate and better aligned with the key comparator used in the economic model than analyses relying on Schollhammer et al. (2015).

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| | **Pharmacological plausibility and updated assumptions**<br><br>We acknowledge that the current evidence base comparing GPB 1% cream with oral antimuscarinics is limited and uncertain. The data available to date, including the ITCs previously submitted, show very wide confidence intervals, meaning that the results are uncertain and it is difficult to draw firm conclusions from them.<br><br>GPB 1% cream and oral antimuscarinics both work by inhibiting the action of acetylcholine at muscarinic receptors and reducing eccrine sweat gland production. GPB 1% cream is applied directly to the axillae,[6] where there is a high volume of eccrine sweat glands located in the dermis of the skin. Antimuscarinics taken orally reach the glands through the bloodstream, which results in the well characterised adverse events from the action of the antimuscarinic at muscarinic receptors throughout the body. Frequent dosing is required to maintain any effect (up to three times daily) as the effects persist for relatively short time e.g., propantheline peak plasma levels at 2 hours and duration of effect of 6 hours.[7]<br><br>The main challenge in developing topical antimuscarinics has been to provide sufficient cutaneous concentrations to facilitate anhidrosis, with minimal systemic absorption, that results in antimuscarinic adverse events. This has been achieved with GPB 1% cream,[6] to such an extent that after the initial treatment period of 4 weeks, the dosing frequency can be reduced to a minimum of twice weekly application.<br><br>There is no reason to expect that the efficacy of GPB 1% cream directly applied to the axillae will be lower than the efficacy of oral antimuscarinics for people with PAHH. Indeed, real-world data from 68 people with axillary and/or extra-axillary primary hyperhidrosis (published since the initial Company submission to NICE) demonstrates high real-world responder rates for GPB 1% cream.[8] For the 31 patients with PAHH only, HDSS responder rate at week 4 was 76% and at week 12 was 70%. The patients followed a defined tapering schedule, applying the cream four times a week for 1 week, followed by three times a week for the next week, and ultimately transitioning to a maintenance frequency of two times a week. These responder rates are considerably higher than those reported in Schollhammer (2015), Muller et al. (2013) and Wade et al. (2017).[1,3,5]<br><br>Accordingly, we have updated our base case to assume no difference in efficacy between GPB 1% cream and oral antimuscarinics. In a key scenario, we apply the OR derived from |

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| | Muller et al. (2013) to both the propantheline bromide and modified-release oxybutynin comparisons. |
| 2 | We are concerned that the Draft Guidance does not adequately reflect the uncertainty surrounding the relative long-term efficacy of GPB 1% cream versus BTX for the treatment of PAHH. In addition to the limitations of the data and the ITCs already detailed in the submission documents, we have identified a further flaw in the evidence underpinning the ITC versus BTX, which we detail below.<br><br>Following the first ACM, additional information was identified regarding the Lowe et al. (2007) study reported in the FDA submission.[9] The data provided at 4-weeks from the FDA submission aligns with those included in our Bucher ITCs. However, new information clarified endpoint definitions. The criteria for defining HDSS responders in the GPB 1% cream studies were more stringent than in the BTX study. For GPB 1% cream, a responder was defined as a patient achieving a ≥2-point reduction from baseline at any time point and patients had to have maintained this response through to the next response assessment timepoint. In contrast, in the BTX study, patients could have achieved a ≥2-point reduction from baseline at any time point and lost this response, but still be counted as a responder in the analysis. This definition mismatch is unlikely to affect the Bucher ITC based on the 4-week timepoint, since patients are unlikely to achieve a ≥2-point HDSS improvement and then lose it within this period. Therefore, we have not updated our Company base case and it remains as per the EAG's and NICE Committee's base case.<br><br>There was one more additional piece of information in the FDA submission which may be useful for the submission, and this is the proportion of responders at week 52. Following a protocol amendment, removing eight patients who had an initial ≥2-point improvement response but subsequently had HDSS 3 or 4 but were not eligible for a second injection because of their sweat production being too low, 49/104 (47.1%) patients were considered responders at 52 weeks based on their definition of ≥2-point HDSS improvement in the Lowe et al. (2007) study. To explore what the relative efficacy of GPB 1% cream vs. BTX may look like at later timepoints, we have extracted data from the Phase 3b study based on defining a HDSS response as a patient with a ≥2-point change at any time during the study who spent most of the study period (52 -72 weeks) with an HDSS score of 1 or 2;[10] these data show that [redacted] of patients were considered responders based on this definition of ≥2-point HDSS improvement. As this is very similar to the 52-week data from Lowe et al. (2007), it |

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| | suggests that the long-term relative efficacy between GPB 1% cream and BTX may be similar. Indeed, as described above, real-world responder rates (≥2-point HDSS improvement) for GPB 1% cream have been reported to be as high as 76% at 4 weeks and 70% at 12 weeks.[8]<br><br>Given the long-term nature of PAHH, and our more complete understanding of the BTX study following review of the FDA submission document, we have provided additional scenarios based on efficacy comparisons outside of the week-4 HDSS responder rate comparison from the ITC. |
| 3 | We are concerned that the waning effect assumptions for BTX used in the Committee's preferred base case don't align with all the available evidence. To address this issue, Leith presents additional evidence supporting an earlier timepoint of peak efficacy than the 16 weeks assumed in the Committee's preferred base case. Before outlining this evidence, we first summarise the background to the issue.<br><br>In Section 3.3.2 of the CS, it was described that the Company base case modelled peak efficacy for BTX at 4 weeks, followed by a decline to no effect by 6 months. This timepoint was based on the available data from Lowe et al. (2007),[11] and was explored in scenario analyses. In the Clarification Questions (B4), the EAG highlighted that their clinical experts considered that the assumption of treatment waning from week 4 for BTX was clinically implausible and requested a scenario where treatment waning was applied from 16 weeks. Whilst this scenario was presented by the Company in response to the EAG's question, additional literature evidence from four studies was also provided showing that waning is variable and can occur anytime between week 2 and week 16, with week 16 representing the latest point at which waning was observed.[12–15] It should be noted that in Section 4.2.3.3 of the EAG report, the EAG comments on only two of the four studies submitted by the Company.<br><br>The data from Heckmann et al. (2005) were excluded on the basis that the study's outcome measure did not correspond to the HDSS used in the Company's model. The EAG's discussion focuses primarily on Lee et al. (2022), which they cite as evidence that BTX effectiveness remains relatively stable over 16 weeks. However, this study reports the highest HDSS improvement at week 12 (78.53%), followed by a decline at week 16 (73.01%), suggesting that waning may begin around week 12. Importantly, the study evaluates Neu-BoNT/A (Meditoxin®), a formulation of botulinum toxin A not used in the UK, limiting its |

relevance to the comparator of interest. Whilst the Company presented this study alongside others due to the limited evidence base, this limitation should be recognised.

The Company also submitted two additional studies. Naumann et al. (2001) reported a decline in efficacy occurring between 4 and 16 weeks, and Odderson et al. (2002) suggested that waning may begin at approximately 4 months, although this study had a small sample size. Therefore, even excluding Heckmann et al. (2005), the broader literature indicates that peak efficacy is likely reached between 4 and 16 weeks, with 16 weeks representing the upper bound of the observed range.

In the Draft Guidance, the Committee noted that the modelling of the treatment-effect waning for BTX had a moderate impact on the results, and that they preferred the EAG's approach for modelling treatment-effect waning for BTX, because it applied waning after week 16 in line with clinical expert feedback rather than linearly from week 4 to week 26.

Following the first ACM, we explored further sources of information on waning and were able to identify the supplementary application for BTX to the USA FDA from 2004.[9] These data include HDSS outcomes from the clinical study that informed the Lowe et al. (2007) publication used in the ITC. The HDSS distributions show a reduction in the proportion of patients reporting scores of 1 or 2 at week 12 compared with week 4, and at week 8 compared with week 4, in the 50 IU arm after both the first and second treatments (see **Error! Reference source not found.** and **Error! Reference source not found.**). This demonstrates that waning of effect occurred as early as week 8 in the dataset underpinning the Lowe et al. (2007) study.

**Table 2: HDSS frequency distribution of raw scores by visit, treatment session 1 from the FDA submission for BTX[9]**

| Visit | | BTX 75U (n=110) | BTX 50U (n=104) | Placebo (n=108) |
|---|---|---|---|---|
| Baseline | n | 110 | 104 | 108 |
| | 1 | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| | 2 | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| | 3 | 55 (50.0%) | 54 (51.9%) | 58 (53.7%) |
| | 4 | 55 (50.0%) | 50 (48.1%) | 50 (46.3%) |
| Week 1 | n | 103 | 100 | 104 |
| | 1 | 49 (47.6%) | 42 (42.0%) | 9 (8.7%) |
| | 2 | 32 (31.1%) | 32 (32.0%) | 29 (27.9%) |
| | 3 | 19 (18.4%) | 23 (23.0%) | 43 (41.3%) |
| | 4 | 3 (2.9%) | 3 (3.0%) | 23 (22.1%) |

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| Week 4 | n | 110 | 104 | 108 |
| | 1 | 65 (59.1%) | 63 (60.6%) | 7 (6.5%) |
| | 2 | 33 (30.0%) | 31 (29.8%) | 49 (45.4%) |
| | 3 | 10 (9.1%) | 7 (6.7%) | 32 (29.6%) |
| | 4 | 2 (1.8%) | 3 (2.9%) | 20 (18.5%) |
| Week 8 | n | 100 | 88 | 86 |
| | 1 | 53 (53.0%) | 52 (59.1%) | 6 (7.0%) |
| | 2 | 32 (32.0%) | 27 (30.7%) | 29 (33.7%) |
| | 3 | 15 (15.0%) | 8 (9.1%) | 33 (38.4%) |
| | 4 | 0 (0.0%) | 1 (1.1%) | 18 (20.9%) |
| Week 12 | n | 97 | 94 | 54 |
| | 1 | 38 (39.2%) | 42 (44.7%) | 7 (13.0%) |
| | 2 | 39 (40.2%) | 33 (35.1%) | 23 (42.6%) |
| | 3 | 20 (20.6%) | 17 (18.1%) | 16 (29.6%) |
| | 4 | 0 (0.0%) | 2 (2.1%) | 8 (14.8%) |

Abbreviations: BTX, botulinum toxin type A; HDSS, Hyperhidrosis Disease Severity Scale.

**Table 3: HDSS frequency distribution of raw scores by visit, treatment session 2 from the FDA submission for BTX[9]**

| Visit | | BTX 75U (n=53) | BTX 50U (n=48) | Placebo (n=68) |
|---|---|---|---|---|
| Pre-injection 2 score | n | 53 | 48 | 68 |
| | 1 | 0 (0.0%) | 0 (0.0%) | (0.0%) |
| | 2 | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| | 3 | 49 (92.5%) | 38 (79.2%) | 45 (66.2%) |
| | 4 | 4 (7.5%) | 10 (20.8%) | 23 (33.8%) |
| Week 1 | n | 51 | 44 | 60 |
| | 1 | 34 (66.7%) | 27 (61.4%) | 7 (11.7%) |
| | 2 | 12 (23.5%) | 13 (29.5%) | 16 (26.7%) |
| | 3 | 4 (7.8%) | 4 (9.1%) | 21 (35.0%) |
| | 4 | 1 (2.0%) | 0 (0.0%) | 16 (26.7%) |
| Week 4 | n | 53 | 48 | 68 |
| | 1 | 28 (52.8%) | 29 (60.4%) | 7 (10.3%) |
| | 2 | 19 (35.8%) | 19 (39.6%) | 27 (39.7%) |
| | 3 | 5 (9.4%) | 0 (0.0%) | 19 (27.9%) |
| | 4 | 1 (1.9%) | 0 (0.0%) | 15 (22.1%) |
| Week 8 | n | 46 | 33 | 55 |
| | 1 | 26 (56.5%) | 21 (63.6%) | 7 (12.7%) |
| | 2 | 16 (34.8%) | 12 (36.4%) | 17 (30.9%) |
| | 3 | 3 (6.5%) | 0 (0.0%) | 20 (36.4%) |
| | 4 | 1 (2.2%) | 0 (0.0%) | 11 (20.0%) |
| Week 12 | n | 38 | 31 | 29 |
| | 1 | 16 (42.1%) | 10 (32.3%) | 0 (0%) |
| | 2 | 12 (31.6%) | 12 (38.7%) | 15 (51.7%) |
| | 3 | 10 (26.3%) | 9 (29.0%) | 7 (24.1%) |
| | 4 | 0 (0.0%) | 0 (0.0%) | 7 (24.1%) |

Abbreviations: BTX, botulinum toxin type A; HDSS, Hyperhidrosis Disease Severity Scale.

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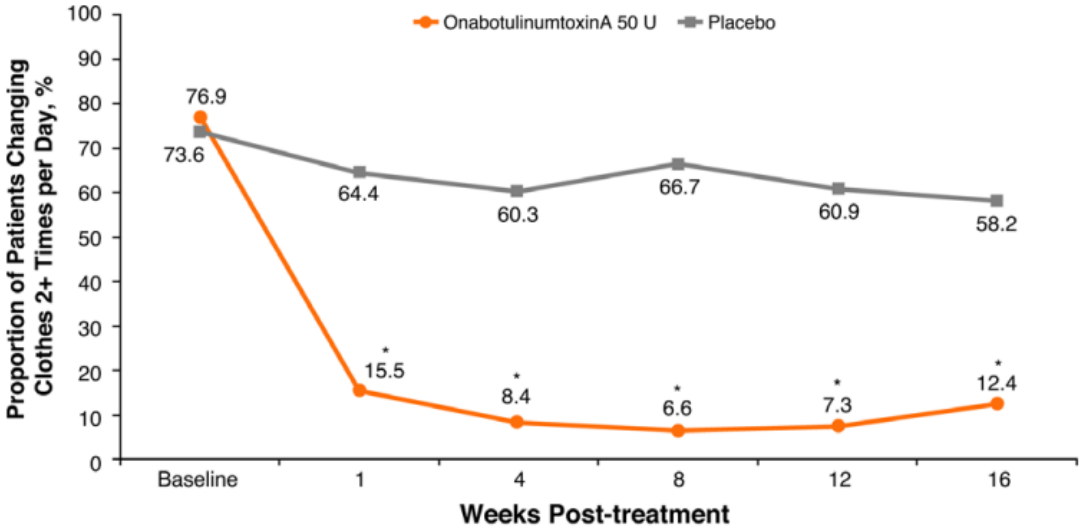
Lowe et al. (2023), in their review of the development of BTX, present additional data from the clinical development programme showing patterns consistent with an earlier waning of treatment effect.[16] Specifically, the proportion of patients with PAHH who needed to change their clothes two or more times per day decreased from 76.9% at baseline to a low of 6.6% at week 8, before rising to 7.3% at week 12 and 12.4% at week 16 (Figure 1). They also report mean sweat production results, which show a peak effect at week 1 post-treatment followed by a progressive decline, with a more pronounced reduction in efficacy from week 12 onwards (Figure 2). While these outcomes are not directly aligned with the HDSS endpoint used in the modelling, they nevertheless support the conclusion that treatment effect begins to wane earlier than 16 weeks.

**Figure 1: Proportion of patients changing clothing ≥2 times per day because of excessive sweating from hyperhidrosis from Lowe et al. (2023)[16]**




| n/N | Baseline | 1 | 4 | 8 | 12 | 16 |
|---|---|---|---|---|---|---|
| OnabotA 50 U | 176/229 | 36/233 | 19/226 | 15/227 | 16/218 | 28/225 |
| Placebo | 53/72 | 47/73 | 44/73 | 48/72 | 42/69 | 39/67 |

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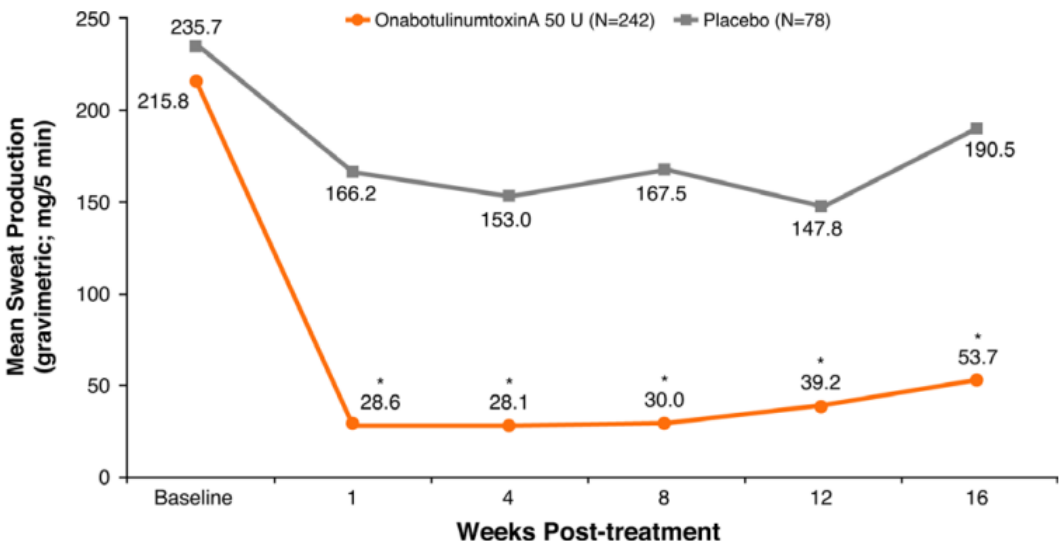
| | **Figure 2: Effect on sweat production of BTX type A versus placebo from Lowe et al. (2023)[16]**<br>  <br><br>Abbreviations: BTX, botulinum toxin type A.<br>Taken together, the available evidence indicates that week 16 represents the latest possible point at which waning may begin, while the data underpinning the Lowe study suggest that waning may start as early as week 8. To remain aligned with the evidence base used in the ITC that informs the economic model, the updated base case assumes peak efficacy for BTX at week 8 and applies waning from that point onward. |
| 4a | The distribution of subsequent therapies was identified as an area of uncertainty at the first ACM. Changes in these assumptions can have a material effect on the ICER, so Leith sought additional information to ensure that the Committee's decision is based on data reflecting actual UK clinical practice. At the first meeting, estimates were derived from assumptions and limited expert opinion. During the consultation period, we have been able to gather more robust evidence. Leith has now collected new data from UK real-world sources and feedback from UK clinicians to provide a more accurate characterisation of the distribution of subsequent therapies within the NHS. Before presenting this evidence, we first outline the background to the issue.<br><br>Table 4 and Table 5 show the distribution of subsequent therapies applied in the EAG's base case (reflecting Table 57 of the EAG report) in the primary care and secondary care setting, |

respectively. Leith's subsequent therapy assumptions were similar to the EAG's and in the Draft Guidance, the Committee stated that they preferred using the EAG's basket of subsequent therapies in the base case. However, it was stated that there was a limited impact on the ICERs. Although the subsequent therapy distributions were not initially considered a key driver (and were thought to have no material impact on the results) it became clear, during the generation of additional evidence for the other key data uncertainties, that the figures used in the original analysis were not representative of UK practice and when more representative data are applied, the assumptions around subsequent therapy distributions become more influential.

**Table 4: Distribution of subsequent therapies in primary care model | EAG's and Committee preferred base case**

| | EAG's and Committee preferred base case | |
|---|---|---|
| | **After GPB 1% cream** | **After propantheline bromide** |
| Antimuscarinics (primary care) | 0.0% | 0.0% |
| Antimuscarinics (primary care and A&G) | 0.0% | 0.0% |
| Antimuscarinics (secondary care) | 20.0% | 10.0% |
| BTX (secondary care) | 80.0% | 90.0% |
| Unlicensed GPB (secondary care) | 0.0% | 0.0% |
| Private treatment | 0.0% | 0.0% |
| No further treatment | 0.0% | 0.0% |

Abbreviations: A&G, advice and guidance; BTX, botulinum toxin type A; EAG, External Assessment Group; GPB, glycopyrronium bromide.

**Table 5: Distribution of subsequent therapies in secondary care model | EAG's and Committee preferred base case**

| | EAG's and Committee preferred base case | | |
|---|---|---|---|
| | **After GPB 1% cream** | **After oxybutynin** | **After BTX** |
| Antimuscarinics (primary care) | 0.0% | 0.0% | 0.0% |
| Antimuscarinics (primary care and A&G) | 0.0% | 0.0% | 0.0% |

| | | | |
|---|---|---|---|
| Antimuscarinics (secondary care) | 10.0% | 10.0% | 25.0% |
| BTX (secondary care) | 80.0% | 63.0% | 0.0% |
| Unlicensed GPB (secondary care) | 0.0% | 2.0% | 25.0% |
| Private treatment | 3.3% | 8.3% | 16.7% |
| No further treatment | 6.7% | 16.7% | 33.3% |

Abbreviations: A&G, advice and guidance; BTX, botulinum toxin type A; EAG, External Assessment Group; GPB, glycopyrronium bromide.

**Review of NHS access to BTX through policy and formulary document assessment**

Firstly, on the high proportion of BTX use in the subsequent therapy distribution (63–90%). The Final Scope for this appraisal previously noted that BTX is only commissioned in some parts of the UK.[17] Leith noted that in the most recently available 'Dermatology Acute Services Specification' (Acute-Dermatology-Service-Specification.pdf) hyperhidrosis is listed within the 'Service Restrictions' category.[18] The direction to providers is as follows: "The Provider will not undertake procedures excluded by the ICS/Service Restriction Policy". A review of the hyperhidrosis and formulary policies of the 42 ICBs showed that by policy, 55% of the population of England across 24 ICBs does not have access to BTX for PAHH.[19] We classified "not having access" to mean that the ICB does not routinely fund BTX outside of an individual funding request. This is a likely underestimate as we recorded an ICB as providing access to BTX even if there are severe restrictions on access, such as a patient having had to self-fund iontophoresis prior to being eligible for BTX. Therefore, as a maximum, only 45% of patients with PAHH in England could get access to BTX as a subsequent therapy.

**Dermatologist survey conducted in November 2025**

To further strengthen the evidence base for representative subsequent therapy distributions, Leith also conducted a clinician survey in November 2025.[20] Respondents included UK dermatologists (N=10) with experience of treating patients with hyperhidrosis referred to them from primary care. Respondents were asked about:

1. the distribution of subsequent therapies after discontinuing GPB 1% cream or antimuscarinics in the primary care setting, and

2. the distribution of subsequent therapies after discontinuing GPB 1% cream, antimuscarinics, or BTX in the secondary care setting.

Table 6 presents the mean values across 10 responses for the distribution of subsequent therapies after discontinuing GPB 1% cream or antimuscarinics in the primary care setting. Key differences from the EAG's and the Committee's preferred base case include:

- some patients remain in primary care for subsequent treatment rather than moving directly to secondary care;
- far fewer patients receive BTX in secondary care; and
- a proportion of patients discontinue NHS treatment altogether, either transitioning to private care or receiving no further treatment.

Of note, the proportion of patients receiving BTX after discontinuing antimuscarinics in the primary care setting still exceeds the 45.4% highlighted in the ICB data. This likely indicates that the proportion of subsequent BTX use may still be somewhat overestimated in the UK clinician feedback, as the respondents (UK dermatologists working in secondary care) may not have full visibility of treatment patterns across both primary and secondary care in the UK.

Table 7 presents the mean values across 10 responses for the distribution of subsequent therapies after discontinuing GPB 1% cream, antimuscarinics, or BTX in the secondary care setting. Key differences from the EAG's and the Committee's preferred base case include: some patients return to primary care for subsequent treatment rather than remaining in secondary care, and fewer patients receive BTX as a subsequent therapy. Note that, as with the primary care setting, the proportion of patients receiving BTX after discontinuing GPB 1% cream or antimuscarinics in secondary care still exceeds the 45.4% reported in the ICB data. As before, this suggests that subsequent BTX use may remain somewhat overestimated in the UK clinician feedback.

**Table 6: Average of clinician responses | Distribution of subsequent therapies after discontinuing GPB 1% cream or antimuscarinics in the primary care setting[20]**

| | GPB 1% cream | Oral antimuscarinic |
|---|---|---|
| Antimuscarinics (primary care) | 14.0% | 3.0% |
| Antimuscarinics (primary care and A&G) | 12.0% | 7.5% |
| Antimuscarinics (secondary care) | 26.6% | 21.0% |
| BTX (secondary care) | 33.9% | 48.5% |

| | | |
|---|---|---|
| Unlicensed GPB (secondary care) | 1.9% | 4.0% |
| Private treatment | 5.1% | 6.9% |
| No further treatment | 6.5% | 9.1% |

Abbreviations: A&G, advice and guidance; BTX, botulinum toxin type A; GPB, glycopyrronium bromide.

**Table 7: Average of clinician responses | Distribution of subsequent therapies after discontinuing GPB 1% cream, antimuscarinics, or BTX in the secondary care setting[20]**

| | GPB 1% cream | Oral antimuscarinics | BTX |
|---|---|---|---|
| Antimuscarinics (primary care) | 2.0% | 1.5% | 11.0% |
| Antimuscarinics (primary care and A&G) | 3.2% | 0.0% | 3.0% |
| Antimuscarinics (secondary care) | 29.6% | 8.0% | 18.5% |
| BTX (secondary care) | 45.5% | 54.0% | 0.0% |
| Unlicensed GPB (secondary care) | 3.1% | 6.6% | 8.5% |
| Private treatment | 6.2% | 10.9% | 29.5% |
| No further treatment | 8.1% | 20.0% | 29.5% |

Abbreviations: A&G, advice and guidance; BTX, botulinum toxin type A; GPB, glycopyrronium bromide.

**Hospital Episode Statistics data on BTX use for PAHH**[21]

We also sought additional evidence from the Hospital Episode Statistics (HES) to understand the use of BTX for HH within the NHS. The data show that patients with a recorded diagnosis of hyperhidrosis received an axillary injection consistent with BTX treatment 1,047 times in the 12-month reporting period. Treatment took place in 36 Trusts/clinics but only 13 Trusts representing 1,010 of the treatments, had numbers of treatments high enough that their figures were able to not be suppressed.

It is important to note that HES does not reliably capture outpatient diagnoses, and around 90% of outpatient records have the diagnosis field left blank. As a result, these data represent an incomplete picture. However, even with this limitation, the findings indicate that BTX is used very infrequently for the treatment of HH in the NHS. This supports the conclusion that earlier estimates of the proportion of patients receiving BTX as a subsequent therapy were overstated.

**NHS England prescription data on propantheline bromide**[22]

We requested from the NHS Services Business Authority information on the number of propantheline prescriptions over the last 2 years, including details of whether the prescription was a repeat prescription. This data was requested to provide an upper limit for the number of patients in England regularly using propantheline bromide, across all diseases. The limitation of this methodology is that propantheline bromide is also used for other conditions, such as myasthenia gravis. In the last 12 months, each month an average of 3,435 patients are using propantheline bromide on a recuring basis.[22] This shows that propantheline bromide is utilised at a low level as an ongoing treatment for patients with PAHH in the UK given the number of eligible patients.

**Conclusion**

Based on these data, we believe we now have a more accurate representation of subsequent therapy distribution that better reflects UK clinical practice. Therefore, we have updated our base case to incorporate both the ICB data and the clinician feedback. The ICB data are used to set an upper limit on BTX use of 45.4%. Where the clinician feedback is consistent with this level, the clinician-derived distributions are applied directly, where required these have been proportionally re-scaled to ensure the total sums to 100%. Where the clinician feedback suggests higher BTX use, BTX is capped at 45.4% and the remaining therapies are proportionally re-scaled to ensure the total sums to 100%. The resulting distributions applied in the updated Company base case are presented in Table 8 for the primary care setting and Table 9 for the secondary care setting.

**Table 8: Updated Company base case | Distribution of subsequent therapies after discontinuing GPB 1% cream or antimuscarinics in the primary care setting**

| | GPB 1% cream | Oral antimuscarinic |
|---|---|---|
| Antimuscarinics (primary care) | 14.0% | 3.2% |
| Antimuscarinics (primary care and A&G) | 12.0% | 8.0% |
| Antimuscarinics (secondary care) | 26.6% | 22.3% |
| BTX (secondary care) | 33.9% | 45.4% |
| Unlicensed GPB (secondary care) | 1.9% | 4.2% |
| Private treatment | 5.1% | 7.3% |
| No further treatment | 6.5% | 9.6% |

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

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<table>
<tr><td></td><td>
Abbreviations: A&G, advice and guidance; BTX, botulinum toxin type A; GPB, glycopyrronium bromide.<br><br>
Table 9: Updated Company base case | Distribution of subsequent therapies after discontinuing GPB 1% cream, antimuscarinics, or BTX in the secondary care setting
<table>
<tr><th></th><th>GPB 1% cream</th><th>Oral antimuscarinics</th><th>BTX</th></tr>
<tr><td>Antimuscarinics (primary care)</td><td>2.1%</td><td>1.7%</td><td>11.0%</td></tr>
<tr><td>Antimuscarinics (primary care and A&G)</td><td>3.3%</td><td>0.0%</td><td>3.0%</td></tr>
<tr><td>Antimuscarinics (secondary care)</td><td>31.0%</td><td>9.3%</td><td>18.5%</td></tr>
<tr><td>BTX (secondary care)</td><td>45.4%</td><td>45.4%</td><td>0.0%</td></tr>
<tr><td>Unlicensed GPB (secondary care)</td><td>3.2%</td><td>7.7%</td><td>8.5%</td></tr>
<tr><td>Private treatment</td><td>6.5%</td><td>12.7%</td><td>29.5%</td></tr>
<tr><td>No further treatment</td><td>8.5%</td><td>23.2%</td><td>29.5%</td></tr>
</table>
Abbreviations: A&G, advice and guidance; BTX, botulinum toxin type A; GPB, glycopyrronium bromide.
</td></tr>
<tr><td>4b</td><td>
We don’t believe that the cost-effectiveness base case is a reasonable interpretation of the evidence because it assumes that private treatment carries no cost to the NHS while still delivering full clinical benefit.<br><br>
In the EAG’s base case for the primary care setting, no patients were assumed to receive either no treatment or private treatment as a subsequent therapy. As a result, the assumptions governing how benefits should accrue for these options were not relevant within that framework. However, when the updated subsequent-therapy distributions from the clinician surveys are applied to the EAG’s primary care model, some patients do transition to no treatment or private treatment, yet they are not assigned any HDSS score. This results in incomplete and inconsistent modelling of patient outcomes.<br><br>
In the EAG’s secondary care base case, a proportion of patients were assumed to receive no treatment or private treatment as subsequent therapy. The EAG’s approach was to apply no further NHS costs to these patients; to revert those receiving no treatment to their baseline
</td></tr>
</table>

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| | |
|---|---|
| | HDSS; and to assume that patients receiving private treatment continued to accrue the clinical benefit of their previous NHS-funded therapy.<br><br>Neither of these approaches is consistent with good economic-modelling practice or with equity principles.<br><br>From an NHS perspective, it is neither methodologically appropriate nor equitable to assume that patients who exit NHS-provided care and receive privately funded treatment incur no cost to the system while continuing to accrue the same health benefits as if they were still receiving NHS-funded therapy.<br><br>First, this creates a structural bias in favour of pathways that push patients out of NHS treatment, because the model effectively treats private therapy as free to the NHS, and equally (or more) beneficial than the publicly funded alternatives. Under these assumptions, the model will consistently show that it is “better” for patients to abandon NHS care altogether, an outcome that is inconsistent with the principles of a publicly funded health system and the remit of NICE technology appraisal, which is to assess cost-effectiveness within the NHS.<br><br>Second, modelling private treatment as a zero-cost, full-benefit option violates the equity principles central to NICE guidance. It implicitly assumes that all patients have equal ability to pay for private care, which is not the case. Allowing a treatment pathway to appear favourable purely because it relies on patients self-funding their care creates an artificial and inequitable advantage for technologies whose NHS treatment effect wanes earlier or whose discontinuation directs patients to private options.<br><br>For these reasons, in the updated Company base case we revert patients receiving private treatment to their baseline HDSS state, ensuring that the NHS perspective is maintained and that no artificial benefit is introduced through self-funded care. Scenario analyses are explored where patients receiving private treatment are assumed to experience the average benefit across therapies and the EAG’s original approach. |
| 5 | We don’t believe that the cost-effectiveness base case is a reasonable interpretation of the evidence given its 2-year time horizon, which does not fully capture the full benefits anticipated with GPB 1% cream. |

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

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| | Originally, the Company's base case used a lifetime (65-year) time horizon, while the EAG preferred a 2-year horizon. The EAG's rationale was that mortality does not differ between treatment arms and, after week 72, no further transitions occur between HDSS health states for GPB cream or oral antimuscarinics. As a result, patients spend most of the time horizon in the subsequent-treatment health state in the model. Clinical experts also noted that treatment response is typically evident early, often within the first month, and remains stable thereafter. The committee therefore concluded that the key differences in costs and benefits between GPB 1% cream and comparators would largely be captured within 2 years, and that the Company's lifetime horizon exacerbated modelling assumptions that favoured the intervention.<br><br>While we agree that the time horizon must balance capturing the full benefits of GPB 1% cream with avoiding undue influence of subsequent therapies, we consider 2 years to be too short to reflect the duration of treatment benefit. At 2 years, 61% of patients remain on GPB 1% cream, and substantial proportions continue treatment with antimuscarinics (48%) or BTX (70%). Note: these estimates are based on the updated Company base case. This indicates that many patients remain on their initial therapy well beyond the 2-year period used by the EAG.<br><br>A lifetime horizon would more fully capture the potential long-term benefits of GPB 1% cream, as some patients may remain on effective treatment for many years. However, we acknowledge that extending the horizon increases the weight given to subsequent therapies, which then risks distorting comparative outcomes.<br><br>For these reasons, a 5-year time horizon represents a pragmatic compromise. It is sufficiently long to capture meaningful, sustained differences in costs and benefits between GPB 1% cream and its comparators, while still limiting the disproportionate influence of subsequent therapies on the model results. At 5 years, 39%, 31%, and 46% of patients remain on treatment with GPB 1% cream, antimuscarinics, and BTX, respectively. Note: these estimates are based on the updated Company base case.<br><br>It should also be noted that the Company has accepted the revisions proposed in the EAG's clarification questions and has updated the model to ensure that the benefits associated with subsequent therapies are fully and appropriately captured. As a result, the assumptions that were previously considered to bias against the comparators no longer apply. |

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

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| | |
|---|---|
| | Therefore, the updated Company base case considers a 5-year time horizon. |
| 6a | We recognise that in the Draft Guidance, the Committee requested further validation of the discontinuation assumptions for antimuscarinics. In response to this request, Leith have conducted a clinician survey and presented additional information from the literature to support decision making. Before presenting this evidence, we first outline the background to the issue.<br><br>Section 3.3.3 of the CS outlines how treatment duration for GPB 1% cream and antimuscarinics was modelled in the Company's base case. These estimates were informed by data from the Phase 3b clinical trial for GPB 1% cream and by Wolosker et al. (2014) for antimuscarinics.[4,23,24] In the Clarification Questions (B19), the EAG's clinical experts advised that most discontinuations of antimuscarinics occur within the first month of treatment, with approximately one-third of patients stopping during this period. Beyond the first month, those who continue are assumed to respond well, with an overall discontinuation rate of around 10% over time. Table 10 compares the resulting modelled discontinuation proportions at two years for the Company's and EAG's base cases, and Figure 3 provides a graphical illustration of these differences.<br><br>Note: Two errors were identified in the model regarding the application of the EAG's preferred discontinuation rates in response to Clarification Question B19. These have now been corrected in both the primary and secondary care models. The errors related to the timing of when one-third of patients discontinue antimuscarinics and the calculation of the instantaneous discontinuation rate thereafter. After applying these corrections, the EAG's base case ICER in the primary care setting changes from [redacted] (NMB [redacted]) to [redacted] (NMB [redacted]), and in the secondary care setting from [redacted] (NMB [redacted]) to [redacted] (NMB [redacted]) for GPB 1% cream vs. oxybutynin and from [redacted] (NMB [redacted]) to [redacted] (NMB [redacted]) for GPB 1% cream vs. BTX. These corrections are incorporated into the Company's updated base case, and all numbers presented in this response reflect these adjustments. |

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

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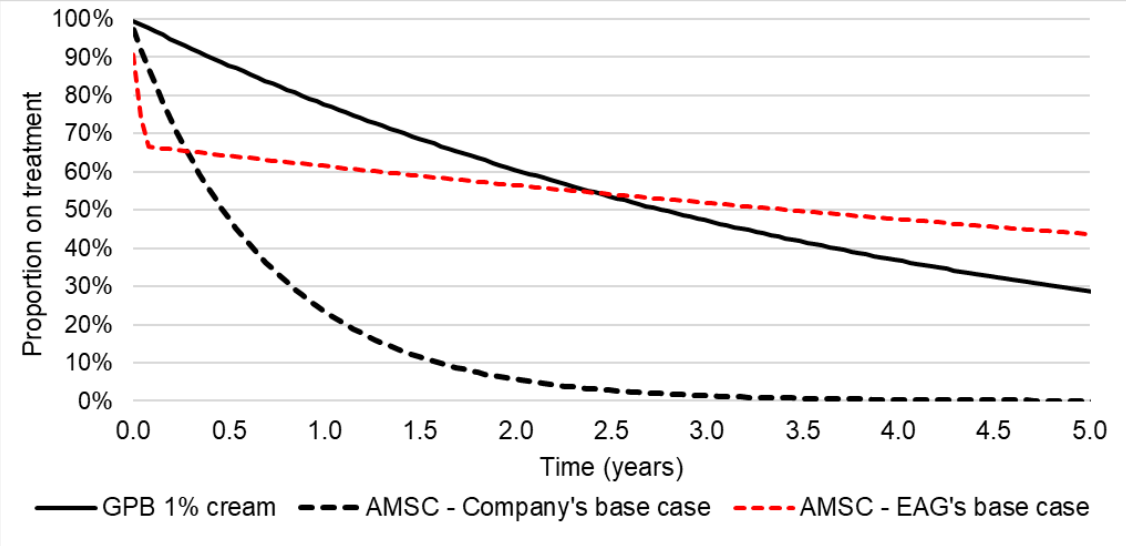
**Table 10: Proportion of patients who have discontinued GPB 1% cream and antimuscarinics over time | A comparison of the Company's base case and the EAG's base case**

| | Company's base case | | EAG's base case | |
|---|---|---|---|---|
| | GPB 1% cream | Antimuscarinics | GPB 1% cream | Antimuscarinics |
| 6 months | 12% | 52% | 12% | 36% |
| 1 year | 22% | 76% | 22% | 38% |
| 2 years | 39% | 94% | 39% | 43% |
| 5 years | 71% | 99% | 71% | 56% |

Abbreviations: EAG, External Assessment Group; GPB, glycopyrronium bromide.

**Figure 3: Proportion of patients who have discontinued GPB 1% cream and antimuscarinics over time | A comparison of the Company's base case and the EAG's base case**




Abbreviations: AMSC, antimuscarinics; EAG, External Assessment Group; GPB, glycopyrronium bromide.

At the first Committee meeting, the two clinical experts provided comments on the discontinuation rates for antimuscarinics. The Committee's interpretation of this expert feedback is outlined in the Draft Guidance:

> "*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. The committee reflected on this variation in clinical expert opinion about discontinuation of oral anticholinergics. It interpreted this to mean that most people having oral anticholinergics would have their condition managed in primary, rather than secondary, care by 2 years. The committee thought that some people who start oral anticholinergics would stop because of side effects, but a substantial proportion would also be expected to continue long term. So, the committee agreed that the company's discontinuation of 94% at 2 years for oral anticholinergics was too high.*"<br><br>We would like to highlight that this interpretation does not fully reflect the Company's recollection of the first ACM. One clinician observed that many patients discontinue oral antimuscarinics, primarily due to intolerability or side effects, and only a small proportion of patients tolerate treatment for more than two years. The clinician noted that while more than 6–10% of patients may remain on antimuscarinics beyond this point, this group may include patients with stable disease or those taking medication for a one-off event.<br><br>The other clinician initially agreed with the Company's 94% discontinuation rate, noting that very few patients continue antimuscarinics beyond two years. However, they later clarified that although many patients discontinue, the proportion is not ≥90%.<br><br>In the Draft Guidance, the Committee concluded that the EAG's approach to modelling discontinuation was more appropriate, albeit associated with uncertainty. The Committee also requested further validation of the discontinuation assumptions, including scenario analyses exploring alternative discontinuation rates for oral antimuscarinics to assess the impact on cost-effectiveness estimates.<br><br>In response to the Committee's request, Leith conducted a clinician survey to identify more evidence on discontinuation rates for antimuscarinics. The survey was conducted in November 2025. Respondents included UK dermatologists (N=10) with experience of treating patients with hyperhidrosis referred to them from primary care.[20] Respondents were asked about the expected proportion of patients to have discontinued oral antimuscarinics at 1 year, 2 years and 5 years. On average, clinicians anticipated 38% of patients would discontinue treatment with oral antimuscarinics by 1 year, 52% by 2 years, and 69% by 5 years. This is in comparison to the 38%, 43%, and 56% assumed in the EAG's base cases, respectively. |

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**Table 11: Average of clinician responses | Proportion of patients who have discontinued with oral antimuscarinics**

| | 1 year | 2 years | 5 years |
|---|---|---|---|
| Oral antimuscarinics | 38% | 52% | 69% |

In addition to the literature already presented in the CS (Section 3.3.3) or in the Clarification Questions response (B19), three additional papers have been identified which provide information on the discontinuation rates for antimuscarinics in clinical practice:

- Wolosker et al. (2020)[25] conducted a large retrospective review of patients with primary hyperhidrosis treated with oral oxybutynin. For the subgroup whose hyperhidrosis primarily affected the axillae (n = 569), the median treatment duration was 238 days, with a minimum of 21 days and a maximum of 4,213 days.

- Briatico et al. (2021)[26] conducted a retrospective cohort study of patients with severe hyperhidrosis (HDSS 3 or 4) treated with oral oxybutynin. Most patients (80.6%, n = 50) had only one body site affected, with 42 cases involving the axillae, seven the hands, and one the feet. The study reported a median treatment duration of nine months (IQR: 6–12 months), with no significant differences between the 5 mg/day and 10 mg/day therapy groups (n = 62).

- Almedia et al. (2020)[27] conducted a real-world, long-term study of 30 patients with primary hyperhidrosis and an HDSS score of ≥2. Patients completed a questionnaire capturing demographic data, HDSS, and oxybutynin side effects. The most common hyperhidrosis sites were axillary (n = 15, 50.0%), cranio-facial (n = 11, 36.7%), palmoplantar (n = 8, 26.7%), and trunk (n = 5, 16.7%). Median treatment duration was 2.4 years (range 1–6 years; SD 1.3). All patients used oxybutynin for at least one year, with 30% continuing for 2 years, 20% for 3 years, 17% for 4 years, and 3% for 6 years.

Table 12 summarises all available data on antimuscarinic discontinuation after two years and median treatment duration, drawing from the Company's base case, the EAG's base case, the clinician survey, and the literature. While not reporting these exact endpoints, Wolosker et al. (2014),[24] used in the Company's base case, observed 50.9% of patients discontinuing within the first six months, and Millán-Cayetano et al. (2017), explored in a Company scenario

analysis, reported 35% discontinuing within the first year. Overall, the available evidence on antimuscarinic discontinuation is variable, with 30–52% of patients discontinuing by two years and a median treatment duration ranging from 0.65–2.4 years.

Consistent with the updated subsequent therapy data, the Company's updated base case incorporates the new clinician feedback to model antimuscarinic treatment duration, assuming that 38% of patients have discontinued by one year, 52% of patients have discontinued by two years, and 69% of patients have discontinued by five years.

The model uses discontinuation data for GPB 1% cream up to 72 weeks from the Phase 3b clinical trial.[23] Beyond the trial period, in the absence of direct data, the probability of discontinuation was initially assumed to remain constant. However, using the same rationale applied to oral antimuscarinics, we would expect long-term discontinuation of GPB 1% cream to slow over time. By 72 weeks, patients who remain on treatment are likely satisfied and will continue therapy. There is also no reason to expect the long-term discontinuation rate for GPB 1% cream to differ from patients stabilised on oral antimuscarinics. Accordingly, the model uses the trial data for GPB 1% cream up to 72 weeks and then applies the longer-term discontinuation rates estimated from 2- and 5-year clinician survey data for oral antimuscarinics for the remainder of the model time horizon.

Table 12 presents the proportion of patients who have discontinued GPB 1% cream and antimuscarinics in the updated base case; Figure 4 depicts these proportions over time.

**Table 12: Comparison of the proportion of patients who have discontinued antimuscarinics at 2 years and the median treatment duration across all evidence sources[20,24–28]**

| | % discontinued treatment at 2 years | Median treatment duration (years) |
|---|---|---|
| Company's base case | 94% | 0.5 |
| EAG's base case | 43% | 3.4 |
| Clinician survey | 52% | NA |
| Wolosker et al. (2020) | NA | 0.65 |
| Briatico et al. (2021) | NA | 0.75 |
| Almedia et al. (2020) | 30% | 2.4 |
| Wolosker et al. (2014) | 50.9%* | NA |
| Millán-Cayetano et al. (2017) | 35%** | NA |

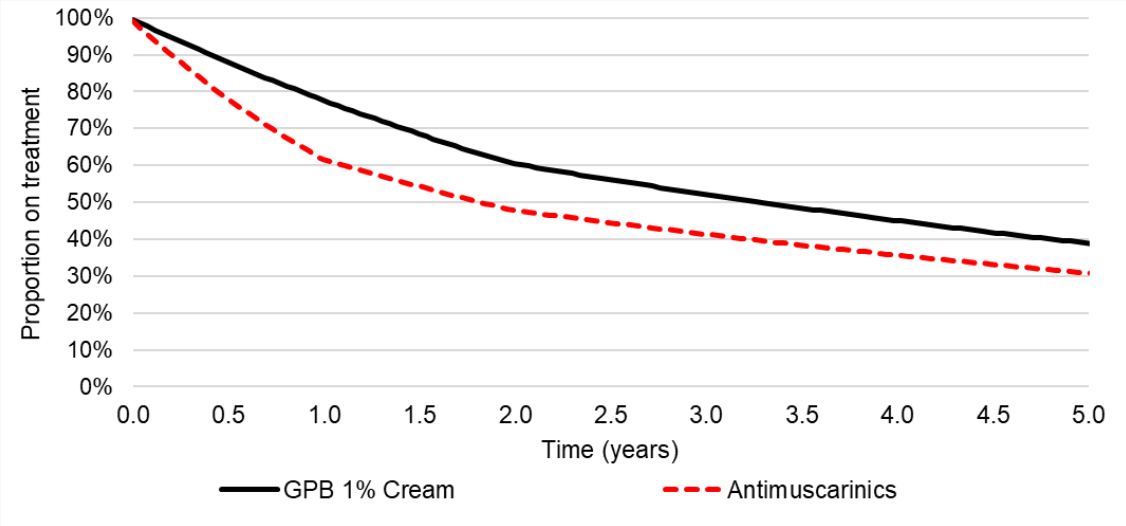
Abbreviations: EAG, External Assessment Group
*Timepoint does not align with 2 years. Wolosker et al. (2014) reported 50.9% of patients discontinuing during the first six months.
** Timepoint does not align with 2 years. Millán-Cayetano et al. (2017) reported 35% discontinuing during the first year.

**Table 13: Proportion of patients who have discontinued GPB 1% cream and antimuscarinics over time | Updated Company base case**

| | Updated Company's base case | |
|---|---|---|
| | **GPB 1% cream** | **Antimuscarinics** |
| 6 months | 12% | 22% |
| 1 year | 22% | 38% |
| 2 years | 39% | 52% |
| 5 years | 61% | 69% |

Abbreviations: GPB, glycopyrronium bromide.

**Figure 4: Proportion of patients who have discontinued GPB 1% cream and antimuscarinics over time | Updated Company base case**




Abbreviations: GPB, glycopyrronium bromide.

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| 6b | We recognise that in the Draft Guidance, the Committee requested further validation of the discontinuation assumptions for BTX. In response to this request, Leith have conducted a clinician survey and presented additional information from the literature to support decision making. Before presenting this evidence, we first outline the background to the issue. |

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

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| | |
|---|---|
| | Section 3.3.3 of the CS outlines how treatment duration for BTX was modelled in the Company's base case. These estimates were informed by data from Lowe et al. (2007) – the study reported data on those who had completed study with no further treatment, another BTX procedure, and discontinued. The Company base case assumed all patients who formally discontinued, along with half of those who completed the study without further treatment, are true discontinuers. In the Clarification Questions (B20), the EAG considered that data on study completion from Lowe et al. 2007, should not inform treatment discontinuation (as has been included in the Company base case) as the trial design was such that based on monitoring during the trial, patients were only eligible for retreatment with BTX A if they had a HDSS score of 3 or 4 and at least 50 mg of spontaneous resting axillary sweat over 5 minutes in each axilla. Therefore, the EAG understands that patients who completed the study were those who were not eligible for retreatment due to maintained response to previous treatment. Based on this the EAG assumed only those who had formally discontinued from Lowe et al. (2007) should inform the model and that it would be more appropriate to apply discontinuation in the model at the timepoint of each administration (every 6 months).<br><br>Table 14 compares the resulting modelled discontinuation proportions at two years for the Company's and EAG's base cases, and Figure 5 provides a graphical illustration of these differences.<br><br>Note, as described above, two errors were identified in the model regarding the application of the EAG's preferred discontinuation rates in response to Clarification Question B19. These have now been corrected in both the primary and secondary care models. The errors related to the timing of when one-third of patients discontinue antimuscarinics and the calculation of the instantaneous discontinuation rate thereafter. After applying these corrections, the EAG's base case ICER in the primary care setting changes from [redacted] (NMB [redacted]) to [redacted] (NMB [redacted]), and in the secondary care setting from [redacted] (NMB [redacted]) to [redacted] (NMB [redacted]) for GPB 1% cream vs. oxybutynin and from [redacted] (NMB [redacted]) to [redacted] (NMB [redacted]) for GPB 1% cream vs. BTX. These corrections are incorporated into the Company's updated base case, and all numbers presented in this response reflect these adjustments. |

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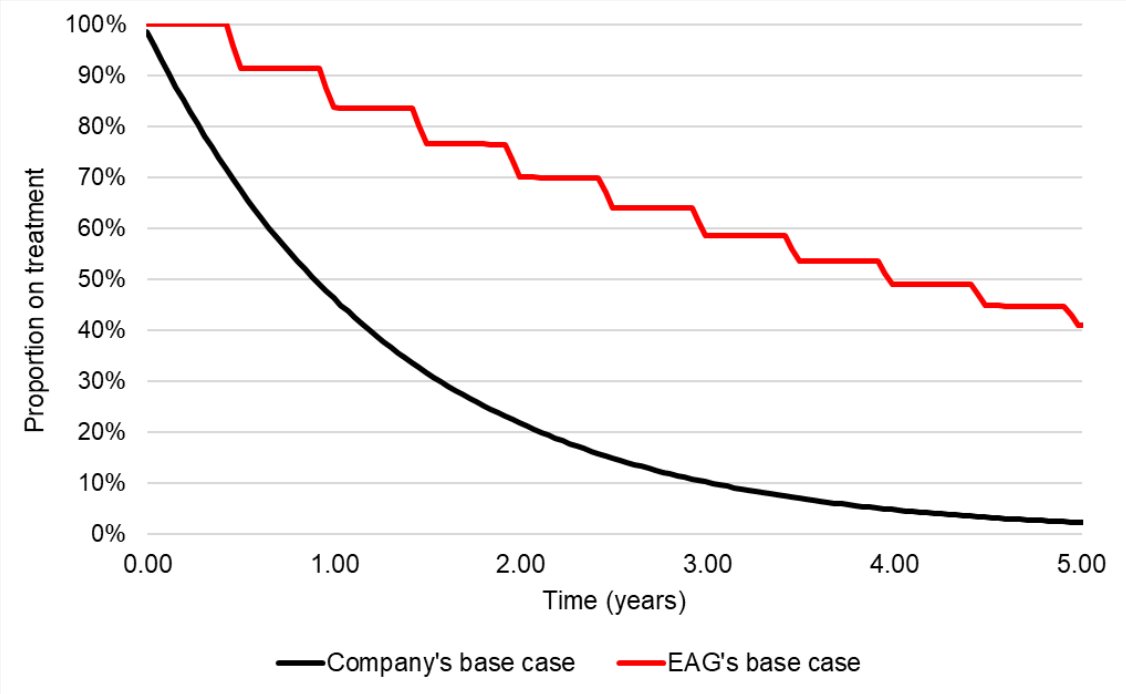
**Table 14: Proportion of patients who have discontinued BTX over time | A comparison of the Company's base case and the EAG's base case**

| | Company's base case | EAG's base case |
|---|---|---|
| | BTX | BTX |
| 6 months | 32% | 10% |
| 1 year | 54% | 21% |
| 2 years | 78% | 37% |
| 5 years | 97% | 69% |

Abbreviations: BTX, botulinum toxin type A; EAG, External Assessment Group

**Figure** 5: Proportion of patients who have discontinued BTX over time | A comparison of the Company's base case and the EAG's base case




Abbreviations: BTX, botulinum toxin type A; EAG, External Assessment Group.

In the Draft Guidance, the Committee concluded that the company's discontinuation of 78% at 2 years was too high for an effective treatment option such as BTX and that the EAG's approach to modelling discontinuation was more appropriate, albeit associated with uncertainty. The Committee also requested further validation of the discontinuation

assumptions, including scenario analyses exploring alternative discontinuation rates for BTX to assess the impact on cost-effectiveness estimates.

In response to the Committee's request, Leith conducted a clinician survey to identify more evidence on discontinuation rates for BTX in November 2025.[20] Respondents included UK dermatologists (N=10) with experience of treating patients with hyperhidrosis referred to them from primary care (DOF). Respondents were asked about the expected proportion of patients to have discontinued BTX at 1 year, 2 years and 5 years. On average, clinicians anticipated 14% of patients would discontinue in year 1, 30% would discontinue in year 2, and 55% would have discontinued by year 5. This is in comparison to the 21%, 37%, and 69% in the EAG's base case, respectively.

**Table 15: Average clinician responses | Proportion of patients who discontinued with BTX**

| | 1 year | 2 years | 5 years |
|---|---|---|---|
| BTX | 14% | 30% | 55% |

Abbreviations: BTX, botulinum toxin type A.

Consistent with the updated subsequent therapy and antimuscarinic discontinuation data, the Company's updated base case incorporates the new clinician feedback to model BTX treatment duration, assuming that 14% of patients have discontinued by one year, 30% of patients have discontinued by two years, and 55% have discontinued by 5 years.

Table 16 presents the proportion of patients who have discontinued BTX in the updated base case; Figure 6 depicts these proportions over time.

**Table 16: Proportion of patients who have discontinued BTX over time | Updated Company base case**

| | Updated Company base case |
|---|---|
| | BTX |
| 6 months | 7% |
| 1 year | 14% |
| 2 years | 30% |
| 5 years | 54% |

Abbreviations: BTX, botulinum toxin type a.

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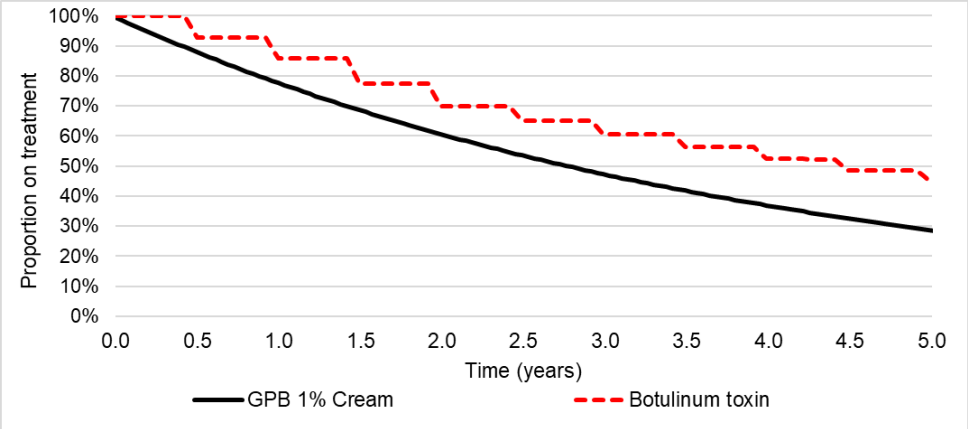
| | |
|---|---|
| | **Figure 6: Proportion of patients who have discontinued BTX over time \| Updated Company's base case**<br>  <br><br>Abbreviations: BTX, botulinum toxin type a. |
| 7 | We are concerned that the impact of adverse events from treatment of PAHH are not being fully reflected within the Committee's base case. In response to this concern, Leith have conducted a clinician survey to support decision making. Before presenting this evidence, we first outline the background to the issue.<br><br>The Company's base case included costs and utility decrements of adverse events for all treatments. The EAG's clinical experts advised that the adverse events included in the company's economic model would not be severe enough to be treated. Instead, they would be managed through dose reductions or stopping treatment. So, the EAG did not include the impact of adverse events in its model base case. At the ACM, the clinical experts agreed that adverse events would not be severe and would be managed by dose reductions and stopping treatment. But the Company explained that many people choose to remain on oral antimuscarinics despite having adverse events if the treatment is working. It explained that the GP and pharmacy visit costs included for treating adverse events in the model were minimal. The Committee noted that as GPB cream is a topical treatment, it would be expected to have fewer side effects than oral antimuscarinics, so it was important to capture the cost and utility impact of this in the model. The Committee thought that costs included in the model for monitoring would already capture the costs of managing adverse events. So, the Committee agreed to include a utility decrement for adverse events for people continuing treatment but not the costs of managing adverse events. |

In response to our concern that the impact of adverse events from treatment of PAHH are not being fully reflected within the economic model, Leith conducted a clinician survey in November 2025 to identify more evidence on the treatment of adverse events in patients with PAHH.[20] Respondents included UK dermatologists (N=10) with experience of treating patients with hyperhidrosis referred to them from primary care. Respondents were asked:

1. In your experience, do patients experiencing mild or moderate adverse events, particularly with oral antimuscarinics, typically require additional resource use beyond the scheduled monitoring? If so, can you describe this resource use?
2. Even if these mild or moderate adverse events are managed within the routine monitoring schedule, would they trigger any additional resource use e.g., a new or amended prescription, or any other form of healthcare contact?

Table 17 summarises the responses from the 10 clinicians. Although the responses varied, only three of the ten clinicians indicated that no additional resource use would be required. Five reported that any required resource use would be manageable within primary care, handled by a pharmacist or GP. The remaining two clinicians anticipated higher resource needs, potentially involving extra secondary-care appointments, coordination with primary care, and possibly laboratory testing.

Based on this feedback, we have updated our base case to include a pharmacy cost of £9.17 for all adverse events. We believe this approach remains conservative, as only 3/10 respondents indicated that no additional resource would be required. Most respondents indicated some additional resource, either pharmacist or GP time (5/10) or further resource use including additional secondary care appointments (2/10).

**Table 17: Qualitative information from clinician survey on the management of adverse events in patients with primary axillary hyperhidrosis**

| Respondent | In your experience, do patients experiencing mild or moderate adverse events, particularly with oral antimuscarinics, typically require additional resource use beyond the scheduled monitoring? If so, can you describe this resource use? | Even if these mild or moderate adverse events are managed within the routine monitoring schedule, would they trigger any additional resource use e.g., a new or amended prescription, or any other form of healthcare contact? |
|---|---|---|

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| | | | |
|---|---|---|---|
| | #1 | The side effects rarely trigger heavy resource use. Pharmacists often field the dry mouth/constipation troubleshooting, saving the system from unnecessary appointments. | Only when symptoms mimic something more sinister. If tolerability is poor, they may bounce back to dermatology slightly sooner than planned. Not a massive resource sink, usually a single appointment or virtual review. |
| | #2 | No. Routine monitoring is often enough. | Yes, a switch of treatment may often generate a new prescription or contact, but this is relatively uncommon and is manageable. |
| | #3 | No they don't | No further appointments ever needed in addition to the routine monitoring schedule in my experience but often dosage is changed or switched to an alternative agent but within routine monitoring schedule. |
| | #4 | Additional clinician time in terms of virtual reviews, telephone calls, arranging blood tests, writing correspondence to patients and GPs when patients contact with issues | Additional healthcare contact as outlined above |
| | #5 | No, they don't require anything beyond scheduled monitoring. They are counselled about possible side effects prior to starting treatment and if the side effects become intolerable, they stop the treatment and wait for their next scheduled appointments. | Yes, they would trigger a new treatment plan, which may include a new prescription. |
| | #6 | More appointments needed for dose adjustment (every 6-8 weeks) | Yes, there will be a need for more appointments for prescriptions |

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| | | | |
|---|---|---|---|
| | #7 | Patients with hyperhidrosis would not be getting monitored that frequently. Nurse led services would typically be 6 monthly at best, often running very late | Due to delays or restrictions in access to treatments, patients sometimes top up their NHS treatments with additional options in the private sector |
| | #8 | No. Adverse events are usually not significant. | New or amended prescription can be advised through GPs. |
| | #9 | Yes, patients may the onset of side-effects often require a telephone or f2f review or at least written advice on how to manage their side-effects, these interactions are typically 1-3 per patient | As above regarding healthcare contact. Some of these side-effects may require an additional prescription (e.g. laxatives) or advice for OTC products such as eye drops |
| | #10 | No | No |
| 8 | We are concerned that the committee is underestimating the impact of GPB 1% cream on patient QoL. The committee concluded that GPB 1% cream may improve QoL but that the magnitude of benefit is uncertain. We believe this conclusion does not take account of the evidence from the PIII studies of GPB 1% cream.<br><br>Across the PIII studies, three QoL tools were used. HDSS, HidroQoL, and DLQI. In the PIIIa study the key pre-specified secondary endpoints were the percentage of responders assessed by the HDSS scale (≥2-point improvement from baseline) and the absolute change in the HidroQoL from baseline to Day 29. The same outcomes at day 15 and absolute change in HDSS and DLQI at days 15 and day 29 were also pre-specified secondary outcomes.<br><br>Every single one of the outcomes above was statistically significant in favour of GPB 1% cream vs. placebo with the exception of the proportion of responders assessed by HDSS scale (≥2-point improvement from baseline) at day 29 which was just shy of statistical significance:[23,29]<br>▪ Absolute change in the HDSS from Baseline to Day 29 by treatment group and in the 1% GPB group compared with the placebo group; [p = 0.0138]<br>▪ Absolute change in the HDSS from Baseline to Day 15 by treatment group and in the 1% GPB group compared with the placebo group; [p = 0.0020] | | |

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| | |
|---|---|
| | ▪ Percentage of responders assessed by the HDSS (≥2-point improvement from Baseline) on Day 15 in the 1% GPB group compared with the placebo group; [p = 0.0542]<br>▪ Absolute change in the HidroQoL from Baseline to Day 15 by treatment group and in the 1% GPB group compared with the placebo group; [p = 0.0003]<br>▪ Absolute change in the HidroQoL from Baseline to Day 29 by treatment group; [p <0.0001]<br>▪ Absolute change in the dermatology life quality index (DLQI) from Baseline to Day 15 by treatment group and in the 1% GPB group compared with the placebo group; [p = 0.0016]<br>▪ Absolute change in the DLQI from Baseline to Day 29 by treatment group and in the 1% GPB group compared with the placebo group. [p = 0.0034]<br><br>The responder analysis is however not a measure of QoL as HDSS can be considered more appropriately as a tool to measure disease severity and to assess treatment effects over time. The choice a 2-point improvement in HDSS representing a 'response' is arbitrary and based only on precedent from previous HH studies (Wade et al 2017) as there is no minimal important difference established for HDSS. HDSS was originally developed by Allergan (the then makers of BTX) to provide a clinical endpoint that would be more readily interpretable than measurement of axillary sweat production.[9] Treatment success was defined as the ability to achieve at least a 2-point improvement in score after two consecutive treatment sessions, including those who respond after one session. An increase in HDSS score was used to determine when a patient became eligible for retreatment with BTX.<br><br>The evidence available on QoL from the PIIIa study demonstrated that GPB 1% cream has a significant and meaningful impact on patient QoL compared to placebo, as determined by three validated PROMs. Further validation of this impact on QoL was provided by the results from the same three PROMs in the PIIIb open label study where all these assessments showed an improvement over time, irrespective of the potential reduction in application frequency after Week 4 (with a median of 7 applications per week at Week 4 and 3 to 5 applications per week at later timepoints up to Week 72).<br><br>We believe the data for GPB 1% cream clearly demonstrates a significant benefit on patient QoL. |
| 9 | Since the original submission, updated NHS Reference Costs for the 2024/25 cost year have been released,[30] replacing the 2023/24 figures used previously. Additionally, during the preparation of our submission, the NHS Reference Costs website was temporarily unavailable, so one key cost (the cost of the BTX procedure) was taken from Wade et al. |

(2017);[5] this study reflected the NHS Reference costs in 2014/15. All costs in the submission have now been reviewed and updated to ensure the most current sources are used. A small number of updates were required based on the latest information from the BNF, eMIT, and the 2024/25 NHS Reference Costs. Note: the PSSRU 2024 remains the most current source for health and social care costs.

Table 18 compares the costs from the EAG's base case and the updated Company base case. Note the EAG's base case was selected as some costs have already been updated throughout this submission.

**Table 18: Updates to costs in the updated Company base case**[30–33]

| | Original value | Source | Updated value | Source |
|---|---|---|---|---|
| Modified release oxybutynin 5mg | £28.16 | EAG's report | £13.95 | BNF, accessed December 2025[31] |
| Glycopyrronium bromide 2mg tablets / pack size 30 | £71.35 | EAG's report, eMIT | £32.28 | eMIT, June 2025[32] |
| BTX 125U | £134.82 | BNF | £126.99 | BNF, accessed December 2025[31] |
| Secondary care | £168.00 | NHS Reference Costs 2023/24 | £172.82 | NHS Reference Costs 2024/25[30] |
| BTX procedure | £156.00 | Wade et al. (2017) | £263.82 | NHS Reference Costs 2024/25[30] |
| Unlicensed GPB | £129.70 | April 2025 NHS Drugs Tariff | £166.00 | December 2025 NHS Drugs Tariff[33] |

Abbreviations: BNF, British National Formulary; BTX, botulinum toxin type A; EAG, External Assessment Group; eMIT, electronic market information tool.

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## Updated Company base case

Table 19 summarises all revisions made to the updated Company base case relative to the EAG and Committee's base case, which formed our starting point. It also indicates whether each comment described in the sections above resulted in a change and how it is explored through scenario analyses. Further detail on each comment is provided in the corresponding sections above. Each of these changes is described and can be implemented from the "ACM1" sheet in the primary and secondary care models. Note: The Company's response is based on the EAG's version of the model, incorporating the NICE Committee's preferred base case settings, which served as the starting point for all updates presented here.

**Table 19: Summary of updates to the updated Company base case**

| Comment | Change in base case? | EAG and Committee's preferred base case | Updated Company base case |
|---|---|---|---|
| **1. Relative efficacy of oral antimuscarinics** | **Yes** | Assume relative efficacy based on the Bucher ITCs using Schollhammer et al. (2105) for oxybutynin. | Assume oral antimuscarinics have the same HDSS responder rate as GPB 1% cream. Scenario analyses test alternative efficacy assumptions. |
| **2. Relative efficacy of BTX** | **No** | Assume relative efficacy based on the Bucher ITCs using Lowe et al. (2007) for BTX. | No change to assumed HDSS responder rate vs GPB 1% cream. Scenario analyses explore alternative efficacy assumptions. |
| **3. Waning effect of BTX** | **Yes** | Assume peak efficacy at 16 weeks, followed by waning. | Assume peak efficacy at 8 weeks, followed by waning. |
| **4. Distribution of subsequent therapies** | **Yes** | Based on feedback from EAG's clinical expert.<br>In the primary care model, no treatment and private treatment were excluded.<br>In the secondary care model, patients receiving no treatment were assumed to revert to baseline | Updated using new UK real-world evidence from a clinician survey (10 dermatologists). Private-sector patients assumed to revert to baseline HDSS. Scenarios explore private patients accruing average |

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| Comment | Change in base case? | EAG and Committee's preferred base case | Updated Company base case |
|---|---|---|---|
| | | HDSS and patients receiving private treatment were assumed to continue to accrue treatment benefit at no additional cost. | treatment benefit and EAG base-case approach. |
| **5. Time horizon** | **Yes** | 2-year time horizon | Updated to 5-year time horizon. |
| **6. Treatment discontinuation** | **Yes** | Assumed a constant rate of discontinuation for GPB 1% cream derived from the Phase IIIb trial. Assumed 1/3 of patients discontinued antimuscarinics in the first month, followed by a constant probability of discontinuation. Assumed discontinuations aligned with the formal discontinuations reported in Lowe et al. (2007). | Updated using clinician survey data on % discontinuing at 1, 2, and 5 years for oral antimuscarinics and BTX. Long-term GPB discontinuation assumed equivalent to antimuscarinics. |
| **7. AE costs** | **Yes** | Assumed no costs. | Updated using new UK real-world evidence from a clinician survey (10 dermatologists). Pharmacy cost now applied to all AEs. |
| **8. HRQoL** | **No** | Assumes utilities of 0.90, 0.74, 0.70, and 0.57 for HDSS 1, 2, 3, and 4. | Aligned with EAG and Committee's preferred base case. |
| **9. Costs** | **Yes** | Used the costs from the original submission. | Updated to latest cost year. Ensures all costing reflects current NHS pricing. |

Abbreviations: AE, adverse event; BTX, botulinum toxin type A; EAG, External Assessment Group; GPB, glycopyrronium bromide; HDSS, Hyperhidrosis Disease Severity Scale; ITC, indirect treatment comparison.

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**Primary care setting**

Table 20 presents the stepwise changes from the EAG's and Committee's base case to the updated Company base case for GPB 1% cream vs. propantheline bromide in the primary care setting. These changes show the NMB moving from [redacted] in the EAG's and NICE's base case to [redacted] in the updated Company base case at a WTP threshold of £20,000 for GPB 1% cream vs. propantheline bromide.

**Table 20: Step changes from EAG's and NICE Committee's base case following the first ACM to updated Company base case | Primary care setting**

| | GPB cream vs. propantheline bromide | |
|---|---|---|
| | ICER (£/QALY) | NMB |
| EAG's base case | [redacted] | [redacted] |
| Corrections to application of treatment discontinuation for antimuscarinics (CQ B19) | [redacted] | [redacted] |
| Comment 1: Relative efficacy of oral antimuscarinics vs. GPB 1% cream | [redacted] | [redacted] |
| Comment 3: Botox treatment waning | [redacted] | [redacted] |
| Comment 4a: Subsequent therapy distribution | [redacted] | [redacted] |
| Comment 4b: Benefits accrued to private treatment | [redacted] | [redacted] |
| Comment 5: Time horizon | [redacted] | [redacted] |
| Comment 6a: Treatment discontinuation antimuscarinics | [redacted] | [redacted] |
| Comment 6b: Treatment discontinuation Botox | [redacted] | [redacted] |
| Comment 7: AE costs | [redacted] | [redacted] |
| Comment 9: Updated costs | [redacted] | [redacted] |

Abbreviations: ACM, Appraisal Committee meeting; AE, adverse event; CQ, clarification question; ICER, incremental cost-effectiveness ratio; GPB, glycopyrronium bromide; NICE, National Institute for Health and Care Excellence; NMB, net monetary benefit; QALY, quality adjusted life year.

Table 21 presents the updated base case pairwise results vs. GPB 1% cream. In the updated analysis, GPB 1% cream generates [redacted] additional QALYs at a reduced cost of [redacted] compared to propantheline bromide. As it delivers greater health benefits at a lower overall cost, GPB 1% cream is considered dominant relative to propantheline bromide. The NHB is [redacted] at a WTP threshold of £20,000, and [redacted] at a threshold of £30,000. Corresponding NMBs are [redacted] and [redacted], respectively.

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**Table 21: Updated Company base case | Primary care setting**

| Technologies | Total costs (£) | Total QALYs | Inc costs (£) | Inc QALYs | ICER (£/QALY) | NMB (WTP £20,000) |
|---|---|---|---|---|---|---|
| GPB 1% cream | [redacted] | [redacted] | | | | |
| Propantheline bromide | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |

Abbreviations: GPB, glycopyrronium bromide; ICER, incremental cost-effectiveness ratio; LYG, life years gained; NMB, net monetary benefit; QALYs, quality-adjusted life years; WTP, willingness-to-pay.

Key scenario analyses are presented for the following comments (aligning with the comments on the Draft Guidance outlined above):

- **Comment 1: Relative efficacy of propantheline bromide.** Scenarios apply a range of alternative odds ratios (ORs), including those derived from Müller et al. (2013) and Wade et al. (2017) within the Bucher ITC framework, fixed ORs of 3 and 4, and the ORs from Schollhammer et al. (2015), which reflect the EAG's and Committee's preferred base case as well as the original Company submission. Except for the Schollhammer et al. (2015) scenario, all analyses assume the same OR for both ≥2-point and ≥1-point HDSS improvement.
- **Comment 2: Relative efficacy of BTX.** Scenarios examine ORs derived from the Wade et al. (2017) ITC and fixed ORs of 1, 2, and 3. As above, all scenarios apply the same OR for both ≥2-point and ≥1-point HDSS improvement.
- **Comment 4: Distribution of subsequent therapies and benefits for private therapies.** Scenarios explore alternative assumptions regarding private treatment benefit, including assuming that patients receiving private therapies accrue benefits equal to the average of all therapies, as well as the EAG's original approach to modelling private therapy outcomes.

The scenario analyses exploring assumptions about the relative efficacy of propantheline bromide versus GPB 1% cream are summarised in Table 22. These scenarios show that when propantheline bromide is assumed to be more effective (in terms of HDSS responder rate) than GPB 1% cream, the results move into the south-west quadrant of the cost-effectiveness plane i.e., GPB 1% cream becomes cheaper but less effective.

As detailed in the response to Comment 1, the evidence underpinning the ITCs between GPB 1% cream and propantheline bromide is extremely limited and the methods are not robust. The available data, whether from

Schollhammer et al. (2015) or from the simulated responder estimates based on Müller et al. (2013), are characterised by very wide confidence intervals. Schollhammer et al. (2015) has a non-comparable patient population, an inconsistent outcome measure, and a misaligned assessment timepoint. The responder estimates from Müller et al. (2013) are based on a simulation assuming a unimodal distribution across response rates, an assumption which has not been tested. The Company believe that the resulting estimates are too flawed and uncertain to support the base case.

Furthermore, the response to Comment 1 outlines that there is no biological or clinical rationale to expect that a topically applied antimuscarinic acting directly at the axillae would be less effective than systemic oral antimuscarinics. GPB 1% cream delivers targeted antimuscarinic activity at the site of sweating with minimal systemic exposure, and its sustained effect allows reduced application frequency after the initial treatment period. In contrast, oral antimuscarinics require multiple daily doses to maintain effect and are constrained by systemic tolerability.

Given (i) the high level of uncertainty associated with the ITCs, and (ii) the lack of any mechanistic rationale for assuming lower efficacy of GPB 1% cream, the updated Company base case adopts equal efficacy between GPB 1% cream and propantheline bromide. Scenarios applying ITC-derived values, such as the ORs estimated using the Müller et al. (2013) data, are included for completeness and sensitivity testing, but they should not be regarded as sufficiently robust or reliable to inform the base case.

**Table 22: Scenarios exploring the relative efficacy for propantheline bromide vs. GPB 1% cream | Primary care setting**

| | GPB cream vs. propantheline bromide | | |
|---|---|---|---|
| | **ICER (£/QALY)** | **NMB** | **Change in NMB vs. updated Company base case** |
| Updated Company base case | [redacted] | [redacted] | [redacted] |
| Relative efficacy based on Muller et al. (2013) and Wade et al. (2017) | [redacted] | [redacted] | [redacted] |
| Relative efficacy assuming OR=3 | [redacted] | [redacted] | [redacted] |
| Relative efficacy assuming OR=4 | [redacted] | [redacted] | [redacted] |
| Relative efficacy based on Schollhammer et al. (2015). | [redacted] | [redacted] | [redacted] |

Abbreviations: GPB, glycopyrronium bromide; ICER, incremental cost-effectiveness ratio; NA, not applicable; NMB, net monetary benefit; OR, odds ratio; QALYs, quality-adjusted life years.

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The scenario analyses exploring assumptions about the relative efficacy of BTX versus GPB 1% cream are summarised in Table 23. These scenarios show that varying the relative efficacy of BTX vs. GPB 1% cream has a limited impact in the primary care setting and GPB 1% cream remains dominant across all scenarios.

**Table 23: Scenarios exploring the relative efficacy for BTX vs. GPB 1% cream | Primary care setting**

| | GPB cream vs. propantheline bromide | | |
|---|---|---|---|
| | **ICER (£/QALY)** | **NMB** | **Change in NMB vs. updated Company base case** |
| Updated Company base case. | [redacted] | [redacted] | [redacted] |
| Relative efficacy based on Wade et al. (2017) | [redacted] | [redacted] | [redacted] |
| Relative efficacy assuming OR=1 | [redacted] | [redacted] | [redacted] |
| Relative efficacy assuming OR=2 | [redacted] | [redacted] | [redacted] |
| Relative efficacy assuming OR=3 | [redacted] | [redacted] | [redacted] |

Abbreviations: GPB, glycopyrronium bromide; ICER, incremental cost-effectiveness ratio; NA, not applicable; NMB, net monetary benefit; OR, odds ratio; QALYs, quality-adjusted life years.

The scenario analyses exploring assumptions about the benefits accrued to patients who receive private treatment are summarised in Table 24. In the updated Company base case, patients who move to private treatment are assumed to revert to their baseline HDSS values. To test the impact of this assumption, we explored two alternative scenarios:

1. Patients receiving private treatment accrue the average benefit of all therapies.
2. The EAG's approach, in which neither "no treatment" nor "private treatment" options are assigned a subsequent HDSS value.

When patients are assumed to accrue the average benefit of all therapies, the NMB decreases by 11%. In contrast, applying the EAG's approach results in an increase in NMB of 214%. It is important to note that, in the EAG's base case, "no treatment" and "private treatment" were excluded entirely. As a result, assumptions about benefits associated with these options had no influence on the EAG's results. This is not the case in the updated Company base case, where subsequent therapy distributions explicitly include these options, making their associated assumptions important to the model outputs.

As described in the response to Comment 4b, from an NHS perspective, it is neither appropriate nor equitable to assume that patients who discontinue NHS-provided treatments will obtain private treatment at zero cost while continuing to receive full clinical benefit. Private treatments fall outside the NHS commissioning pathway and should not be modelled as if they are freely available to all patients. For these reasons, the base case

should assume that patients who move to private treatment accrue no additional NHS costs and no additional benefits.

**Table 24: Scenarios exploring the benefits accrued to patients who receive private treatment | Primary care setting**

| | GPB cream vs. propantheline bromide | | |
|---|---|---|---|
| | **ICER (£/QALY)** | **NMB** | **Change in NMB vs. updated Company base case** |
| Updated Company base case | [redacted] | [redacted] | [redacted] |
| Assume private treatment accrues benefit equal to average of therapies | [redacted] | [redacted] | -11% |
| EAG's approach | [redacted] | [redacted] | 214% |

Abbreviations: EAG, External Assessment Group; GPB, glycopyrronium bromide; ICER, incremental cost-effectiveness ratio; NA, not applicable; NMB, net monetary benefit; QALYs, quality-adjusted life years.

**Secondary care setting**

Table 25 presents the stepwise changes from the EAG's and Committee's base case to the updated Company base case for GPB 1% cream vs. oxybutynin and BTX in the secondary care setting. These changes show the NMB moving from [redacted] in the EAG's and NICE's base case to [redacted] in the updated Company base case at a WTP threshold of £20,000 for GPB 1% cream vs. oxybutynin. Likewise, these changes show the NMB moving from [redacted] in the EAG's and NICE's base case to [redacted] in the updated Company base case at a WTP threshold of £20,000 for GPB 1% cream vs. BTX.

**Table 25: Step changes from EAG's and NICE Committee's base case following the first ACM to updated Company base case | Secondary care setting**

| | GPB cream vs. oxybutynin | | GPB cream vs. BTX | |
|---|---|---|---|---|
| | **ICER (£/QALY)** | **NMB** | **ICER (£/QALY)** | **NMB** |
| EAG's base case | [redacted] | [redacted] | [redacted] | [redacted] |
| Corrections to application of treatment discontinuation for antimuscarinics (CQ B19) | [redacted] | [redacted] | [redacted] | [redacted] |
| Comment 1: Relative efficacy of oral antimuscarinics vs. GPB 1% cream | [redacted] | [redacted] | [redacted] | [redacted] |

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

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| | GPB cream vs. oxybutynin | | GPB cream vs. BTX | |
|---|---|---|---|---|
| | ICER (£/QALY) | NMB | ICER (£/QALY) | NMB |
| Comment 3: Botox treatment waning | [redacted] | [redacted] | [redacted] | [redacted] |
| Comment 4a: Subsequent therapy distribution | [redacted] | [redacted] | [redacted] | [redacted] |
| Comment 4b: Benefits accrued to private treatment | [redacted] | [redacted] | [redacted] | [redacted] |
| Comment 5: Time horizon | [redacted] | [redacted] | [redacted] | [redacted] |
| Comment 6a: Treatment discontinuation antimuscarinics | [redacted] | [redacted] | [redacted] | [redacted] |
| Comment 6b: Treatment discontinuation Botox | [redacted] | [redacted] | [redacted] | [redacted] |
| Comment 7: AE costs | [redacted] | [redacted] | [redacted] | [redacted] |
| Comment 9: Updated costs | [redacted] | [redacted] | [redacted] | [redacted] |

Abbreviations: ACM, Appraisal Committee meeting; AE, adverse event; CQ, clarification question; EAG, External Assessment Group; GPB, glycopyrronium bromide; ICER, incremental cost-effectiveness ratio; NICE, National Institute for Health and Care Excellence; NMB, net monetary benefit; QALY, quality adjusted life year.

Table 26 presents the updated base case pairwise results vs. GPB 1% cream. In the updated analysis, GPB 1% cream generates [redacted] additional QALYs at an additional cost of [redacted] compared to oxybutynin. The NHB is [redacted] at a WTP threshold of £20,000, and [redacted] at a threshold of £30,000. Corresponding NMBs are [redacted] and [redacted], respectively.

In the updated analysis, GPB 1% cream generates [redacted] additional QALYs at a reduced cost of [redacted] compared to BTX. The NHB is [redacted] at a WTP threshold of £20,000, and [redacted] at a threshold of £30,000. Corresponding NMBs are [redacted] and [redacted], respectively.

**Table 26: Updated Company base case | Secondary care setting**

| Technologies | Total costs (£) | Total QALYs | Inc costs (£) | Inc QALYs | ICER (£/QALY) | NMB (WTP £20,000) |
|---|---|---|---|---|---|---|
| GPB 1% cream | [redacted] | [redacted] | | | | |
| Oxybutynin | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| BTX | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |

Abbreviations: BTX, botulinum toxin type A; GPB, glycopyrronium bromide; ICER, incremental cost-effectiveness ratio; LYG, life years gained; NMB, net monetary benefit; QALYs, quality-adjusted life years; WTP, willingness-to-pay.

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Key scenario analyses are presented for the following comments (aligning with the comments on the Draft Guidance outlined above):

- **Comment 1: Relative efficacy of oxybutynin.** Scenarios apply a range of alternative ORs, including those derived from Müller et al. (2013) and Wade et al. (2017) within the Bucher ITC framework, fixed ORs of 3 and 4, and the ORs from Schollhammer et al. (2015), which reflect the EAG's and Committee's preferred base case as well as the original Company submission. Except for the Schollhammer et al. (2015) scenario, all analyses assume the same OR for both ≥2-point and ≥1-point HDSS improvement.
- **Comment 2: Relative efficacy of BTX.** Scenarios examine ORs derived from the Wade et al. (2017) ITC and fixed ORs of 1, 2, and 3. As above, all scenarios apply the same OR for both ≥2-point and ≥1-point HDSS improvement.
- **Comment 4: Distribution of subsequent therapies and benefits for private therapies.** Scenarios explore alternative assumptions regarding private treatment benefits, including assuming that patients receiving private therapies accrue benefits equal to the average of all therapies, as well as the EAG's original approach to modelling private therapy outcomes.

The scenario analyses exploring assumptions about the relative efficacy of oxybutynin versus GPB 1% cream are summarised in Table 27. These scenarios show that when oxybutynin is assumed to be more effective (in terms of HDSS responder rate) than GPB 1% cream, the results reduce in cost-effectiveness vs. oxybutynin and have a limited impact on the cost-effectiveness vs. BTX. Note: whilst the cost-effectiveness is shown to reduce vs. oxybutynin, all scenarios remain cost-effective for GPB 1% cream vs. oxybutynin.

Whilst the efficacy of oxybutynin is less of a key driver in the secondary care setting than the primary care setting, the same limitations explained in the primary care setting hold i.e., the evidence underpinning the ITCs between GPB 1% cream and propantheline bromide is extremely limited and the methods are not robust. The available data, whether from Schollhammer et al. (2015) or from the simulated responder estimates based on Müller et al. (2013), are characterised by very wide confidence intervals. Schollhammer et al. (2015) has a non-comparable patient population, an inconsistent outcome measure, and a misaligned assessment timepoint. The responder estimates from Müller et al. (2013) are based on a simulation assuming a unimodal distribution across response rates, an assumption which has not been tested. The Company believe that the resulting estimates are too flawed and uncertain to support the base case.

Furthermore, the response to Comment 1 outlines that there is no biological or clinical rationale to expect that a topically applied antimuscarinic acting directly at the axillae would be less effective than systemic oral antimuscarinics. GPB 1% cream delivers targeted antimuscarinic activity at the site of sweating with minimal

systemic exposure, and its sustained effect allows reduced application frequency after the initial treatment period. In contrast, oral antimuscarinics require multiple daily doses to maintain effect and are constrained by systemic tolerability.

Given (i) the high level of uncertainty associated with the ITCs, and (ii) the lack of any mechanistic rationale for assuming lower efficacy of GPB 1% cream, the updated Company base case adopts equal efficacy between GPB 1% cream and oxybutynin. Scenarios applying ITC-derived values, such as the ORs estimated using the Müller et al. (2013) data, are included for completeness and sensitivity testing, but they should not be regarded as sufficiently robust or reliable to inform the base case.

**Table 27: Scenarios exploring the relative efficacy for oxybutynin vs. GPB 1% cream | Secondary care setting**

| | GPB cream vs. oxybutynin | | | GPB cream vs. BTX | | |
|---|---|---|---|---|---|---|
| | ICER (£/QALY) | NMB | Change in NMB vs. updated Company base case | ICER (£/QALY) | NMB | Change in NMB vs. updated Company base case |
| Updated Company base case | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Relative efficacy based on Muller et al. (2013) and Wade et al. (2017) | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Relative efficacy assuming OR=3 | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Relative efficacy assuming OR=4 | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Relative efficacy based on Schollhammer et al. (2015). EAG and NICE Committee base case. | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |

Abbreviations: BTX, botulinum toxin type A; EAG, External Assessment Group; GPB, glycopyrronium bromide; ICER, incremental cost-effectiveness ratio; NA, not applicable; NICE, National Institute for Health and Care Excellence; NMB, net monetary benefit; OR, odds ratio; QALYs, quality-adjusted life years.

The scenario analyses exploring assumptions about the relative efficacy of BTX versus GPB 1% cream are summarised in Table 28. These scenarios show that varying the relative efficacy of BTX vs. GPB 1% cream

has a limited impact in the secondary care setting and GPB 1% cream remains cost-effective across all scenarios.

**Table 28: Scenarios exploring the relative efficacy for BTX vs. GPB 1% cream | Secondary care setting**

| | GPB cream vs. oxybutynin | | | GPB cream vs. BTX | | |
|---|---|---|---|---|---|---|
| | ICER (£/QALY) | NMB | Change in NMB vs. updated Company base case | ICER (£/QALY) | NMB | Change in NMB vs. updated Company base case |
| Updated Company base case. | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Relative efficacy based on Wade et al. (2017) | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Relative efficacy assuming OR=1 | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Relative efficacy assuming OR=2 | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Relative efficacy assuming OR=3 | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |

Abbreviations: BTX, botulinum toxin type A; GPB, glycopyrronium bromide; ICER, incremental cost-effectiveness ratio; NA, not applicable; NMB, net monetary benefit; OR, odds ratio; QALYs, quality-adjusted life years.

The scenario analyses exploring assumptions about the benefits accrued to patients who receive private treatment are summarised in Table 29. In the updated Company base case, patients who move to private treatment are assumed to revert to their baseline HDSS values. To test the impact of this assumption, we explored two alternative scenarios:

1. Patients receiving private treatment accrue the average benefit of all therapies.
2. The EAG's approach, in which neither "no treatment" nor "private treatment" options are assigned a subsequent HDSS value.

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When patients are assumed to accrue the average benefit of all therapies, the NMB decreases between 19% - 52%. Applying the EAG's approach results in a decrease in NMB between 17% - 51%. It is important to note that, in the EAG's base case, "no treatment" and "private treatment" were excluded entirely. As a result, assumptions about benefits associated with these options had no influence on the EAG's results. This is not the case in the updated Company base case, where subsequent therapy distributions explicitly include these options, making their associated assumptions important to the model outputs.

As described in the response to Comment 4b, from an NHS perspective, it is neither appropriate nor equitable to assume that patients who discontinue NHS-provided treatments will obtain private treatment at zero cost while continuing to receive full clinical benefit. Private treatments fall outside the NHS commissioning pathway and should not be modelled as if they are freely available to all patients. For these reasons, the base case should assume that patients who move to private treatment accrue no additional NHS costs and no additional benefits.

**Table 29: Scenarios exploring the benefits accrued to patients who receive private treatment | Secondary care setting**

| | GPB cream vs. oxybutynin | | | GPB cream vs. BTX | | |
|---|---|---|---|---|---|---|
| | **ICER (£/QALY)** | **NMB** | **Change in NMB vs. updated Company base case** | **ICER (£/QALY)** | **NMB** | **Change in NMB vs. updated Company base case** |
| Updated Company base case | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Assume private treatment accrues benefit equal to average of therapies | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| EAG's approach | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |

Abbreviations: BTX, botulinum toxin type A; EAG, External Assessment Group; GPB, glycopyrronium bromide; ICER, incremental cost-effectiveness ratio; NA, not applicable; NMB, net monetary benefit; QALYs, quality-adjusted life years.

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

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

**Draft guidance comments form**

**Consultation on the draft guidance document – deadline for comments** by the end of 5 December 2025. Please submit via NICE Docs.

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# NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

## Single Technology Appraisal

# Glycopyrronium bromide cream (Axhidrox®) for treating severe primary axillary hyperhidrosis [ID6487]

## Clarification questions

**10 December 2025**

| File name | Version | Contains confidential information | Date |
|---|---|---|---|
| ID6487_GPB 1% cream_PAHH_EAG clarification questions_DG [redacted] | V1.0 | No | 10th December 2025 |

## 1. Please provide probabilistic results for the updated company base case.

**Response:** As outlined in the Company's response to the Draft Guidance dated 8 December 2025, the base case has been updated to reflect feedback from the consultation period and newly available evidence.

Table 1 presents the updated base case pairwise results vs. GPB 1% cream in the primary care setting. In the updated analysis, GPB 1% cream generates [redacted] additional QALYs at a reduced cost of [redacted] compared to propantheline bromide. As it delivers greater health benefits at a lower overall cost, GPB 1% cream is considered dominant relative to propantheline bromide. The NHB is [redacted] at a WTP threshold of £20,000, and [redacted] at a threshold of £30,000. Corresponding NMBs are [redacted] and [redacted], respectively.

**Table 1: Updated Company base case | Primary care setting**

| Technologies | Total costs (£) | Total QALYs | Inc costs (£) | Inc QALYs | ICER (£/QALY) | NMB (WTP £20,000) |
|---|---|---|---|---|---|---|
| GPB 1% cream | [redacted] | [redacted] | | | | |
| Propantheline bromide | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |

Abbreviations: GPB, glycopyrronium bromide; ICER, incremental cost-effectiveness ratio; LYG, life years gained; NMB, net monetary benefit; QALYs, quality-adjusted life years; WTP, willingness-to-pay.

Table 2 presents the updated base case pairwise results vs. GPB 1% cream in the secondary care setting. In the updated analysis, GPB 1% cream generates [redacted] additional QALYs at an additional cost of [redacted] compared to oxybutynin. The NHB is [redacted] at a WTP threshold of £20,000, and [redacted] at a threshold of £30,000. Corresponding NMBs are [redacted] and [redacted], respectively. In the updated analysis, GPB 1% cream generates [redacted] additional QALYs at a reduced cost of [redacted] compared to BTX. The NHB is [redacted] at a WTP threshold of £20,000, and [redacted] at a threshold of £30,000. Corresponding NMBs are [redacted] and [redacted], respectively.

**Table 2: Updated Company base case | Secondary care setting**

| Technologies | Total costs (£) | Total QALYs | Inc costs (£) | Inc QALYs | ICER (£/QALY) | NMB (WTP £20,000) |
|---|---|---|---|---|---|---|
| GPB 1% cream | [redacted] | [redacted] | | | | |

| Technologies | Total costs (£) | Total QALYs | Inc costs (£) | Inc QALYs | ICER (£/QALY) | NMB (WTP £20,000) |
|---|---|---|---|---|---|---|
| Oxybutynin | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| BTX | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |

Abbreviations: BTX, botulinum toxin type A**;** GPB, glycopyrronium bromide; ICER, incremental cost-effectiveness ratio; LYG, life years gained; NMB, net monetary benefit; QALYs, quality-adjusted life years; WTP, willingness-to-pay.

In response to the EAG's question, PSAs with 1,000 iterations were conducted for the primary care setting base case and the secondary care setting base case. The results are presented using scatterplots of incremental costs versus incremental QALYs, alongside cost-effectiveness acceptability curves (CEACs) showing the probability that GPB 1% cream is cost-effective across a range of WTP thresholds. The economic models with the completed PSA runs have also been uploaded for NICE and the EAG, labelled with the suffix "_PSA".

In the primary care setting, the PSA results indicate an average incremental cost of [redacted] and an average incremental QALY gain of [redacted] for GPB 1% cream compared to propantheline bromide (Table 3). These results are consistent with the deterministic analysis, confirming that GPB 1% cream is dominant (i.e., more effective and less costly). This consistency is visually supported by the overlap of the deterministic and probabilistic base case markers in the cost-effectiveness plane (Figure 1).

The proportion of PSA iterations where GPB 1% cream is considered cost-effective is [redacted] at a £20,000/QALY threshold. The CEAC is shown in Figure 2.

**Table 3: Updated Company base case, probabilistic results | Primary care setting**

| Technologies | Total costs (£) | Total QALYs | Inc costs (£) | Inc QALYs | ICER (£/QALY) | NMB (WTP £20,000) |
|---|---|---|---|---|---|---|
| GPB 1% cream | [redacted] | [redacted] | | | | |
| Propantheline bromide | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |

Abbreviations: GPB, glycopyrronium bromide; ICER, incremental cost-effectiveness ratio; LYG, life years gained; NMB, net monetary benefit; QALYs, quality-adjusted life years; WTP, willingness-to-pay.

**Figure 1: Cost-effectiveness plane (1,000 iterations) | GPB 1% cream vs. propantheline bromide | Primary care setting**

Abbreviations: GPB, glycopyrronium bromide; QALY, quality adjusted life year; WTP, willingness-to-pay.

**Figure 2: CEAC | GPB 1% cream vs. propantheline bromide | Primary care setting**

Abbreviations: CEAC, cost-effectiveness acceptability curve; GPB, glycopyrronium bromide.

In the secondary care setting, the PSA results indicate an average incremental cost of [redacted] and an average incremental QALY gain of [redacted] for GPB 1% cream compared to oxybutynin (Table 4). These results indicate a probabilistic ICER of [redacted] and a probabilistic NMB of [redacted] which is consistent with the deterministic analysis ICER and NMB of [redacted] and [redacted],

respectively. Note: variations in the ICER are driven by the very small incremental costs and QALYs, which make the ratio highly sensitive. This consistency is visually supported by the overlap of the deterministic and probabilistic base case markers in the cost-effectiveness plane (Figure 3).

The PSA results indicate an average incremental cost of [redacted] and an average incremental QALY gain of [redacted] for GPB 1% cream compared to BTX (Table 4). These results are consistent with the deterministic analysis, confirming that GPB 1% cream is dominant (i.e., more effective and less costly). This consistency is visually supported by the overlap of the deterministic and probabilistic base case markers in the cost-effectiveness plane (Figure 4).

The proportion of PSA iterations where GPB 1% cream is considered cost-effective is [redacted] at a £20,000/QALY threshold. The CEAC is shown in Figure 5.

**Table 4: Updated Company base case, probabilistic results | Secondary care setting**

| Technologies | Total costs (£) | Total QALYs | Inc costs (£) | Inc QALYs | ICER (£/QALY) | NMB (WTP £20,000) |
|---|---|---|---|---|---|---|
| GPB 1% cream | [redacted] | [redacted] | | | | |
| Oxybutynin | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| BTX | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |

Abbreviations: BTX, botulinum toxin A; GPB, glycopyrronium bromide; ICER, incremental cost-effectiveness ratio; LYG, life years gained; NMB, net monetary benefit; QALYs, quality-adjusted life years; WTP, willingness-to-pay.

**Figure 3: Cost-effectiveness plane (1,000 iterations) | GPB 1% cream vs. oxybutynin | Secondary care setting**

Abbreviations: GPB, glycopyrronium bromide; QALY, quality adjusted life year; WTP, willingness-to-pay.

**Figure 4: Cost-effectiveness plane (1,000 iterations) | GPB 1% cream vs. BTX | Secondary care setting**

Abbreviations: BTX, botulinum toxin A; GPB, glycopyrronium bromide; QALY, quality adjusted life year; WTP, willingness-to-pay.

**Figure 5: CEAC | GPB 1% cream vs. oxybutynin and BTX | Secondary care setting**

Abbreviations: BTX, botulinum toxin A; CEAC, cost-effectiveness acceptability curve; GPB, glycopyrronium bromide.

2. **The company has corrected an error in the B19 scenario. However, in the company clarification response dated the 4th of July, the B19 scenario was corrected for an error that was picked up by the EAG. The company hasn't explained what the error is that has been picked up for the DG response and having looked in the model, the EAG is unclear what the error was in the last model update and how the company has corrected it. Please provide more explanation on this issue.**

**Response:** As outlined in the Company's response to the Draft Guidance dated 8 December 2025, two errors were identified in the model regarding the application of the EAG's preferred discontinuation rates in response to Clarification Question B19. These have now been corrected in both the primary and secondary care models. The errors related to the timing of when one-third of patients discontinue antimuscarinics and the calculation of the instantaneous discontinuation rate thereafter. Within the models, these two errors can be corrected separately on the "ACM1" sheet. More detail is provided below.

The first issue concerns the timing of when one-third of patients discontinue antimuscarinics. Before correction, the EAG's scenario - intended to assume one-third of patients discontinue by week 4 - was only applying the discontinuation at week 2, meaning fewer than one-third of patients stopped treatment within the initial 4-week period.

This was due to the formula in the "Trace_AMSC" sheet using "<" instead of "<=" for the cutoff. For example, the original formula (e.g., cell J13 in "Trace_AMSC") was:

IF(B13=0,1,IF(C13<AMSC_Disc_Cutoff,J12*(1-G13)*(1-AMSC_Disc),J12*(1-G13)*(1-AMSC_Disc_LT)))

The corrected formula is:

IF(B13=0,1,IF(C13<=AMSC_Disc_Cutoff,J12*(1-G13)*(1-AMSC_Disc),J12*(1-G13)*(1-AMSC_Disc_LT)))

After implementing this change, selecting the "EAG's base case" for the discontinuation of antimuscarinics on the "ACM1" sheet now correctly shows that one-third of patients discontinue antimuscarinics by week 4.

The second issue concerns the formula used to calculate the probability of discontinuation per 2-week cycle over the remainder of the time horizon on the "TxDuration" sheet. According to the EAG's description, 10% of the remaining patients were expected to discontinue treatment across the original two year time horizon. However, the original formula did not account for the fact that one-third of patients had already discontinued, meaning the denominator should be the remaining two-thirds, not the full cohort.

The original formula in D70 on the "TxDuration" sheet was:

1-EXP((LN(1-0.1)/(((((365.25/7)*2)-4)-4)/2)))

The corrected formula is:

1 - (1 - (0.1 / (1 - D67)))^(1/(((365.25/7*2)-4)/2))

After applying both corrections and selecting the "EAG's base case" for antimuscarinic discontinuation on the "ACM1" sheet, column K on the "Trace_AMSC" sheet (prior to mortality and half-cycle adjustments) now correctly shows that one-third of patients have discontinued by week 4, and 43.3% have discontinued by 2 years i.e., the initial one-third plus an additional 10%. Note: these corrections do not impact the Company's updated base case.

3. **The drop down in the model to remove the correction and revert the previous implementation of oral antimuscarinic discontinuation doesn't seem to work. Please check and ensure that using the drop down allows the user to go back to the previous approach**

**Response:** As noted above, these corrections do not affect the Company's updated base case, as the Company relies on clinician survey data at 1, 2, and 5 years to estimate antimuscarinic discontinuation rates over time. The option to remove the corrections functions

as intended when the “EAG’s base case” is selected for antimuscarinic discontinuation, which can be found in row 95 of the “ACM1” sheet.

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

**Draft guidance comments form**

**Consultation on the draft guidance document – deadline for comments** by the end of 5 December 2025. Please submit via NICE Docs.

| | |
|---|---|
| | Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly.<br><br>The Appraisal Committee is interested in receiving comments on the following:<br>• has all of the relevant evidence been taken into account?<br>• are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?<br>• are the provisional recommendations sound and a suitable basis for guidance to the NHS?<br><br>NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations:<br>• could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology;<br>• could have any adverse impact on people with a particular disability or disabilities.<br><br>Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced**.** |
| **Organisation name – Stakeholder or respondent** (if you are responding as an individual rather than a registered stakeholder please leave blank): | British Association of Dermatologists (BAD) |

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| | |
|---|---|
| **Disclosure**<br>Please disclose any funding received from the company bringing the treatment to NICE for evaluation or from any of the comparator treatment companies in the last 12 months. [Relevant companies are listed in the appraisal stakeholder list.]<br>Please state:<br>• the name of the company<br>• the amount<br>• the purpose of funding including whether it related to a product mentioned in the stakeholder list<br>• whether it is ongoing or has ceased. | None. |
| Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry. | None. |
| **Name of commentator person completing form:** | [Insert name] |

| **Comment number** | **Comments**<br><br>Insert each comment in a new row.<br>Do not paste other tables into this table, because your comments could get lost – type directly into this table. |
|---|---|
| Example 1 | We are concerned that this recommendation may imply that …….. |
| 1 | The treatment improved HDSS scores in just over 20% of patients which was not statistically significant to the placebo arm. This would be in keeping with anecdotal clinical experience of topical glycopyrrolate preparations which can certainly help patients with hyperhidrosis in 10-20% |

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| | |
|---|---|
| | of cases and appears to be more effective for facial sweating than sweating at other sites. The decision to not recommend is disappointing, as patients with hyperhidrosis have very few options for treatment and this could have potentially helped a proportion of those patients who otherwise have no option to any treatments for this condition. |
| 2 | Not having access to GPB cream will perpetuate the inequality of access to treatment for severe primary axillary hyperhidrosis (PAHH).<br>Botulinum toxin injections and oral modified release oxybutynin or glycopyrronium bromide are not available in all hospitals / regions of the UK.<br>GPB cream could have potentially be available in primary care (and secondary care) so this would have been more widely accessible. |
| 3 | |
| 4 | |
| 5 | |
| 6 | |

Insert extra rows as needed

**Checklist for submitting comments**

- Use this comment form and submit it as a Word document (not a PDF).
- Complete the disclosure about funding from the company and links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into one response. We cannot accept more than one set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
- In line with the NICE Health Technology Evaluation Manual (sections 5.4.4 to 5.4.21), if a comment contains confidential information, it is the responsibility of the responder to provide two versions, one complete and one with the confidential information removed (to be published on NICE's website), together with a checklist of the confidential information. Please underline all confidential information, and separately highlight information that is submitted as 'confidential [CON]' in turquoise, and all information submitted as 'depersonalised data [DPD]' in pink. If confidential information is submitted, please submit a second version of your comments form with that information replaced with asterixis and highlighted in black.
- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations.
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
- If you have received agreement from NICE to submit additional evidence with your comments on the draft guidance document, please submit these separately.

**Note:** We reserve the right to summarise and edit comments received during consultations, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

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

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| | |
|---|---|
| | Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly.<br><br>The Appraisal Committee is interested in receiving comments on the following:<br>• has all of the relevant evidence been taken into account?<br>• are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?<br>• are the provisional recommendations sound and a suitable basis for guidance to the NHS?<br><br>NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations:<br>• could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology;<br>• could have any adverse impact on people with a particular disability or disabilities.<br><br>Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced**.** |
| **Organisation name – Stakeholder or respondent** (if you are responding as an individual rather than a registered stakeholder please leave blank): | The Primary Care Dermatology Society<br><br>Comments from the executive committee collated and Submitted by [redacted] |

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|---|---|
| **Disclosure**<br>Please disclose any funding received from the company bringing the treatment to NICE for evaluation or from any of the comparator treatment companies in the last 12 months. [Relevant companies are listed in the appraisal stakeholder list.]<br>Please state:<br>• the name of the company<br>• the amount<br>• the purpose of funding including whether it related to a product mentioned in the stakeholder list<br>• whether it is ongoing or has ceased. | The PCDS has no funding relationships or affiliations with Leith Healthcare, nor any links with companies involved in the development of glycopyrronium bromide.<br><br>The PCDS is a registered charity dedicated to supporting education and training in primary care dermatology. We provide teaching across the breadth of dermatology, including dermoscopy, and maintain an extensive educational website and guidance resources for the primary care community. Our organisation represents more than 11,000 primary care clinicians with an interest in dermatology.<br><br>To support this educational mission, the PCDS receives sponsorship from a range of pharmaceutical and medical-device companies. These sponsorships are unrestricted and solely support our educational activities; sponsors have no influence on content, outputs, or policy positions.<br><br>As is standard practice for UK medical charities and professional societies, the PCDS receives unrestricted educational sponsorship from multiple pharmaceutical and device companies across dermatology. These funds support the delivery of educational events, digital learning resources, and workforce development initiatives. Sponsorship agreements do not permit sponsors to influence educational content, clinical guidance, speaker selection, or organisational policy positions, and all activities are developed independently by the PCDS executive committee. |
| Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry. | The PCDS has no past or current links to the tobacco industry. |
| **Name of commentator person completing form:** | [redacted], |

| **Comment number** | **Comments**<br><br>Insert each comment in a new row.<br>Do not paste other tables into this table, because your comments could get lost – type directly into this table. |
|---|---|
| Example 1 | We are concerned that this recommendation may imply that …….. |
| 1 | 1.1: We disagree with the recommendation that glycopyrronium bromide (GPB) cream should not be used for the treatment of primary axillary hyperhidrosis in adults. We believe there is a role in patients intolerant of topical aluminium-based perspirants and/or oral anticholinergics, and the use |

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| | |
|---|---|
| | of GPB cream may reduce demand on botulinum toxin A, which has patchy availability and limited benefit. |
| 2 | 3.1: We agree with these statements. Hyperhidrosis can have substantial impacts on individuals, affecting mental health, personal relationships, educational attainment, work performance, and financial wellbeing. |
| 3 | 3.2: We disagree with this statement. Aluminium-based antiperspirants, although available over the counter and from specialist suppliers, are widely prescribed in primary care as first-line treatment for axillary hyperhidrosis. Whether patients are signposted to purchase products themselves varies according to local prescribing policies and restrictions. |
| 4 | 3.2: Botulinum toxin (BtA) provision is highly variable across Integrated Care Boards (ICBs). In some ICBs it is not commissioned at all; in others, only one or two treatment cycles are funded. Patients often seek referral to alternative providers in an attempt to access BtA, but in general it remains a non-commissioned service. Some secondary-care providers may offer more than two cycles when an individual funding request is approved. |
| 5 | 3.2: GPB cream is likely to be most appropriate for people who do not tolerate, or who have an inadequate response to, aluminium-based antiperspirants; as an adjunct to oral anticholinergic therapy where systemic side effects or absorption are of concern; or following BtA, given that individuals who benefit from BtA often do not pursue private treatment due to prohibitive cost. Nearly all patients referred to secondary care for axillary hyperhidrosis will have already tried and failed aluminium-based antiperspirants, representing a substantial cohort for whom GPB cream may be clinically appropriate. It may also be suitable for those who cannot tolerate the systemic effects of oral anticholinergics. |
| 6 | 3.3: This positioning does not accurately reflect current clinical practice. Primary care treatments typically include aluminium-based antiperspirants, propantheline (for which supply issues have persisted over the past year), standard-release oxybutynin, modified-release oxybutynin (also subject to ongoing shortages), and oral glycopyrronium bromide.<br>Oral glycopyrronium bromide is an unlicensed special, with monthly costs of up to £8,000 for doses of 1–8 mg daily. Glycopyrronium oral suspension is more cost-effective but still costly (up to approximately £1,500 per month) and also supplied as a special. All of these treatments can be prescribed in primary care and feature in PCDS guidance.<br>In many trusts, referral for BtA is not accepted until first-, second-, and third-line therapies have been tried and have failed. Oral glycopyrronium is rarely used in primary care due to high cost and limited formulary inclusion, particularly when its cost exceeds that of several biologic therapies for other dermatological conditions.<br>Topical compounded glycopyrronium (0.5–2% in an emollient base - cetomacrogol) is available in some trusts but also supplied as a special, with pricing dependent on local procurement. |
| 7 | 3.3: The most relevant comparators are **topical compounded glycopyrronium**, and BtA. BtA is not a curative option; it typically provides up to a 50% reduction in sweating for 3–6 months. After the standard two treatment cycles, ongoing therapy is usually required. Sympathectomy is not a suitable comparator given that it is not recommended due to the high risk of compensatory hyperhidrosis. |
| 8 | In all, it is not clear whether clinical failure or modelling distrust has led to the recommendation against GPB cream. **We strongly believe that safety, tolerability, and primary-care access appears to be ignored.** Modelling data in light of the above-mentioned comparators could be visited. There are flaws both in the data offered by the company and assumptions made by the appraisal committee. We would advise a representative from the PCDS or expert GPs with Extended Roles in Dermatology be part of the appraisal committee. |
| 9 | Given that compounded topical glycopyrronium (0.5-2%) is already available, albeit in limited supply, it remains an unlicensed special with inherent variability in formulation and clinical performance. Such products are typically costly for primary care, as high-street pharmacies do not routinely stock them and procurement through specials manufacturers is substantially more |

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| | |
|---|---|
| | expensive than secondary-care sourcing. In addition, prescribing is generally restricted to secondary-care clinicians.<br>In this context, the availability of a licensed topical GPB preparation for use in primary care would offer a more consistent, reliable, and ultimately more cost-effective option for both the NHS and patients. |
| | |

Insert extra rows as needed

**Checklist for submitting comments**

- Use this comment form and submit it as a Word document (not a PDF).
- Complete the disclosure about funding from the company and links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into one response. We cannot accept more than one set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
- In line with the NICE Health Technology Evaluation Manual (sections 5.4.4 to 5.4.21), if a comment contains confidential information, it is the responsibility of the responder to provide two versions, one complete and one with the confidential information removed (to be published on NICE's website), together with a checklist of the confidential information. Please underline all confidential information, and separately highlight information that is submitted as 'confidential [CON]' in turquoise, and all information submitted as 'depersonalised data [DPD]' in pink. If confidential information is submitted, please submit a second version of your comments form with that information replaced with asterixis and highlighted in black.
- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations.
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
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# Glycopyrronium bromide cream for treating severe primary axillary hyperhidrosis [ID6487]

Committee preferred base case

October 2025

**Source of funding**

This report was commissioned by the NIHR Evidence Synthesis Programme as project number 175751.

# 1 Summary

This document provides the results of the committee preferred assumptions, including the proposed list price of [redacted] per 50g tube provided for glycopyrronium bromide (GPB) 1% cream.

The committee preferred assumptions that are included in the committee preferred incremental cost-effectiveness ratio (ICER) are presented in Table 1.

Table 1. Committee preferences post-ACM2

| Parameter | Committee preferred assumptions | |
|---|---|---|
| | Primary care | Secondary care |
| Positioning of GPB | Alternative to propantheline bromide | Alternative to oxybutynin and botox |
| Time horizon | 2 years | |
| Source of relative effectiveness for oral antimuscarinics | Methantheline bromide (Muller et al. 2013) – note that the OR was for the ≥2 point improvement in HDSS and this has been assumed for the ≥1 improvement in HDSS as well. | Oxybutynin (Schollhammer et al. 2015) – no change from the committee preferred base case at ACM1, except it uses the EAG's corrected analysis using matched population. |
| ITC analysis | EAG's corrected analysis using matched population – analysis 18 from Table 4 of the EAG response to company DG comments. | EAG's corrected analysis using matched population – analysis 1 from Table 4 of the EAG response to company DG comments. |
| Treatment discontinuation for oral antimuscarinics and botox | Company's updated base case informed by survey of 10 UK dermatologists – for the base case, it is assumed that discontinuation for GPB cream is still informed by Hyp1-18 (removes the company assumption that GPB cream treatment discontinuation is equivalent to oral antimuscarinics). | |
| Treatment-effect waning of botox | From 16 weeks | |
| Distribution of subsequent treatments | Company's updated base case approach | |
| Modelling of subsequent treatment benefits and costs | Company's approach assuming people who move onto private healthcare revert to baseline HDSS and incur no costs | |
| Additional AE costs | Exclude | |
| ICER threshold | £25,000 | |

## 1.1 Primary care model

Table 2. Primary care model – committee preferred assumptions ACM2, GPB 1% cream versus propantheline bromide

| Interventions | Total Costs (£) | Total LY | Total QALYs | Incremental costs (£) | Incremental LYs | Incremental QALYs | ICER (£/QALY) |
|---|---|---|---|---|---|---|---|
| **Deterministic results** | | | | | | | |
| Propantheline bromide | [redacted] | [redacted] | [redacted] | - | - | - | - |
| GPB 1% cream | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| **Probabilistic results** | | | | | | | |
| Propantheline bromide | [redacted] | [redacted] | [redacted] | - | - | - | - |
| GPB 1% cream | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |

Abbreviations: GPB, glycopyrronium bromide; ICER, incremental cost-effectiveness ratio; LY, life year; QALY, quality-adjusted life-year; SW, south-west.

### *1.1.1 Scenarios around the primary care model base case*

Table 3. Committee requested scenario analysis

| Scenario | Incremental costs | Incremental QALYs | ICER (£/QALY) |
|---|---|---|---|
| Committee base case | [redacted] | [redacted] | [redacted] |
| Scenario 1: EAG's assumptions on people moving into private healthcare ([redacted]): benefits and costs borne by NHS | [redacted] | [redacted] | [redacted] |
| Scenario 2: Committee requested scenario in which the proportion of people who moved into private healthcare [redacted]) are redistributed across the remaining subsequent treatment category options including no further treatment | [redacted] | [redacted] | [redacted] |

Abbreviations: ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year; SW, south-west.

## 1.2 Secondary care model

Table 4. Secondary care model – committee preferred assumption, GPB 1% cream versus modified-release oxybutynin

| Interventions | Total Costs (£) | Total LY | Total QALYs | Incremental costs (£) | Incremental LYs | Incremental QALYs | ICER (£/QALY) |
|---|---|---|---|---|---|---|---|
| **Deterministic results** | | | | | | | |
| Modified-release oxybutynin | [redacted] | [redacted] | [redacted] | - | - | - | - |
| GPB 1% cream | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |

| Interventions | Total Costs (£) | Total LY | Total QALYs | Incremental costs (£) | Incremental LYs | Incremental QALYs | ICER (£/QALY) |
|---|---|---|---|---|---|---|---|
| **Deterministic results** | | | | | | | |
| **Probabilistic results** | | | | | | | |
| Modified-release oxybutynin | [redacted] | [redacted] | [redacted] | - | - | - | - |
| GPB 1% cream | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |

Abbreviations: GPB, glycopyrronium bromide; ICER, incremental cost-effectiveness ratio; LY, life year; QALY, quality-adjusted life-year; SW, south-west.

Table 5. Secondary care model – committee preferred assumptions, GPB 1% cream versus botulinum toxin A

| Interventions | Total Costs (£) | Total LY | Total QALYs | Incremental costs (£) | Incremental LYs | Incremental QALYs | ICER (£/QALY) |
|---|---|---|---|---|---|---|---|
| **Deterministic results** | | | | | | | |
| Botulinum toxin A | [redacted] | [redacted] | [redacted] | - | - | - | - |
| GPB 1% cream | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| **Probabilistic results** | | | | | | | |
| Botulinum toxin A | [redacted] | [redacted] | [redacted] | - | - | - | - |
| GPB 1% cream | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |

Abbreviations: GPB, glycopyrronium bromide; ICER, incremental cost-effectiveness ratio; LY, life year; QALY, quality-adjusted life-year; SW, south-west.

Table 6. Fully incremental analysis (based on PSA results) – Secondary care model, committee preferred assumptions

| Interventions | Total Costs (£) | Total LY | Total QALYs | Incremental costs (£) | Incremental LYs | Incremental QALYs | ICER (£/QALY) |
|---|---|---|---|---|---|---|---|
| Modified-release oxybutynin | [redacted] | [redacted] | [redacted] | - | - | - | - |
| GPB 1% cream | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Botulinum toxin A | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |

Abbreviations: GPB, glycopyrronium bromide; ICER, incremental cost-effectiveness ratio; LY, life year; QALY, quality-adjusted life-year; SW, south-west.

### 1.2.1 *Scenarios around the secondary care model*

Table 7. Committee requested scenario analysis

| Scenario | Oral antimuscarinics | | | Botulinum toxin A | | |
|---|---|---|---|---|---|---|
| | Incremental costs | Incremental QALYs | ICER (£/QALY) | Incremental costs | Incremental QALYs | ICER (£/QALY) |
| Committee base case | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Scenario 1: EAG's assumptions on people moving into private healthcare: benefits and costs borne by NHS | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Scenario 2: Committee requested scenario in which the proportion of people who moved into private healthcare are redistributed across the remaining subsequent treatment category options including no further treatment | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |

Abbreviations: ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year; SW, south-west.

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

EAG response to company draft guidance comments

December 2025

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# 1 Summary

This document provides the External Assessment Group's (EAG's) critique of the company's response to the draft guidance (DG) document produced by the National Institute for Health and Care Excellence (NICE) for the appraisal of glycopyrronium bromide (GPB) 1% cream for treating severe primary axillary hyperhidrosis.

The EAG has outlined the assumptions informing the committee's preferred incremental cost-effectiveness ratio (ICER) for the primary and secondary population in Table 1. In their response to the DG, the company updated their base case, accepting several but not all of the committee preferred assumptions. The assumptions informing the updated company base case are also presented in Table 1. The EAG notes that the price for GPB 1% cream remains the same as in the original submission.

The company corrected an error in both the primary and secondary care models with regard to how treatment discontinuation for oral antimuscarinics was applied in the EAG base case. The EAG investigated the company's correction and agrees with the changes made. The correction only affects the committee preferred base case and not the company updated base case, as different discontinuation assumptions are made by the company (discussed in Section 2).

In addition to the revisions to the company base case outlined in Table 1, the company also changed the treatment effectiveness assumption for oral antimuscarinics, to assume equal effectiveness with GPB 1% cream (company comment 1), and this is discussed further in Section 2.

Table 1. Committee preferred assumptions

| Assumption | Committee preference | Company base case post ACM1 |
|---|---|---|
| Time horizon | EAG base case - 2 years | 5 years |
| General population mortality | EAG base case | Committee preferred assumption |
| Comparators | EAG base case - propantheline bromide (primary care); botulinum toxin A and modified oxybutynin (secondary care) | Committee preferred assumption |
| Propantheline bromide price | Propantheline bromide price | Propantheline bromide price |
| Treatment monitoring | Anti-muscarinics – start of treatment monitored more closely but annual monitoring when on a stable dose - more aligned with the company base case. | Committee preferred assumption |

| | | |
|---|---|---|
| | The EAG notes for the committee preferred base case it has used the company's preferred assumption (quarterly in the first year, annually thereafter), but with the assumption monitoring takes place in primary care (applies to both primary and secondary care models). The EAG notes that the company preferred assumption also applies to GPB cream (quarterly in the first year, annually thereafter, all appointments taking place in primary care) | |
| | Botulinum toxin A – every 6-9 months.<br>For the committee preferred base case, the EAG has assumed that monitoring is included as part of the botulinum toxin A administration appointment which takes place every 6 months, aligned with the EAG base case.<br><br>Cost of administration and monitoring - cost for nurse time AND cost for intermediate skin procedure (in line with the company base case). | Committee preferred assumption |
| Botulinum toxin A treatment waning | EAG base case - treatment wanes after week 16 | Treatment wanes after 8 weeks |
| Botulinum toxin A Odds Ratio | EAG base case | Committee preferred assumption |
| Basket of subsequent treatments | No preference due the small impact on the ICER.<br>The EAG notes for the committee preferred base case, it has used the EAG preferred assumption because for the secondary care model, this assumption is linked to the subsequent treatment QALY benefit. | Updated based on evidence from the company's clinical expert elicitation (company comment 4). Also, the company's base case assumes that patients who seek private treatment revert back to baseline HDSS. |
| Adverse effects | AE disutility included, AE costs excluded. | AE cost and disutility included. AE costs updated to include the cost of pharmacist time for all AEs. |
| Discontinuation rates | EAG base case | Updated based on evidence from the company's clinical expert elicitation (company comment 6). |
| Utility values | EQ-5D-5L cross-walked to 3L | Committee preferred assumption |
| Subsequent treatment QALY benefit | Subsequent treatment QALY benefit | Committee preferred assumption |
| Administration costs for propantheline bromide | 90% primary care, 10% primary care + A&G services (1st appointment only). | Committee preferred assumption |

| | | |
|---|---|---|
| (primary care model only) | | |

Abbreviations: A&G, advice and guidance; ACM1, appraisal committee meeting 1; EAG, external assessment group; HDSS, Hyperhidrosis disease severity scale; QALY, quality-adjusted life-year;

Table 2 and Table 3 presents the committee base case and the company's base case post appraisal committee meeting 1 (ACM1) for the primary care and secondary care models, respectively. Please note that the EAG accepts the company's corrections to the model (and the updated costs). In addition, the EAG found an error in the company's original ITC for oral antimuscarinics versus GPB 1% cream used in the company's original base case and included in the committee's preferred base case. The error is discussed in Section 2.1 and the EAG notes that it does not affect the company's updated base case. The EAG's corrected ITC has been included as part of a corrected committee base case, summarised in Table 2 and Table 3 below, and also presented in Section 3.1.

Table 2. Cost-effectiveness results – primary care model

| Results per patient | GPB 1% cream | Propantheline bromide | Incremental value |
|---|---|---|---|
| **Corrected committee preferred base case - deterministic** | | | |
| Total costs (£) | [redacted] | [redacted] | [redacted] |
| QALYs | [redacted] | [redacted] | [redacted] |
| ICER (£/QALY) | - | - | [redacted] |
| **Corrected committee preferred base case - probabilistic** | | | |
| Total costs (£) | [redacted] | [redacted] | [redacted] |
| QALYs | [redacted] | [redacted] | [redacted] |
| ICER (£/QALY) | - | - | [redacted] |
| **Company base case post ACM1 – deterministic** | | | |
| Total costs (£) | [redacted] | [redacted] | [redacted] |
| QALYs | [redacted] | [redacted] | [redacted] |
| ICER (£/QALY) | - | - | [redacted] |
| **Company base case post ACM1 – probabilistic** | | | |
| Total costs (£) | [redacted] | [redacted] | [redacted] |
| QALYs | [redacted] | [redacted] | [redacted] |
| ICER (£/QALY) | - | - | [redacted] |

Abbreviations: ACM1, appraisal committee meeting 1; EAG, External Assessment Group; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year; SW, south-west.

Table 3. Cost-effectiveness results – secondary care model

| Results per patient | GPB 1% cream (1) | Modified-release oxybutynin (2) | Botulinum toxin A (3) | Incremental value (1-2) | Incremental value (1-3) |
|---|---|---|---|---|---|
| **Corrected committee preferred base case - deterministic** | | | | | |

| | | | | | |
|---|---|---|---|---|---|
| Total costs (£) | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| QALYs | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| ICER (£/QALY) | - | - | - | [redacted] | [redacted] |
| **Corrected committee preferred base case – probabilistic** | | | | | |
| Total costs (£) | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| QALYs | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| ICER (£/QALY) | - | - | - | [redacted] | [redacted] |
| **Company base case post ACM1 – deterministic** | | | | | |
| Total costs (£) | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| QALYs | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| ICER (£/QALY) | - | - | - | [redacted] | [redacted] |
| **Company base case post ACM1 – probabilistic** | | | | | |
| Total costs (£) | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| QALYs | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| ICER (£/QALY) | - | - | - | [redacted] | [redacted] |

Abbreviations: ACM1, appraisal committee meeting 1; EAG, External Assessment Group; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year; SW, south-west.

In addition to the committee preferences, the committee outlined three areas of uncertainty that required further exploration and analysis:

- Further validation of the discontinuation modelling, including additional scenario analyses exploring alternative discontinuation rates for oral anticholinergics and botulinum toxin to explore the impact on the cost-effectiveness estimates.
    - The company has attempted to address the committee's concerns in comment 6 of their DG comments, and this is discussed further in Section 2 of this report.
- If possible, utility values based on a mapping analysis of DLQI to EQ-5D-3L.
    - The company has not provided any comments on this in their DG response. No mapping analysis has been provided, nor any comment on the feasibility of the requested analysis.
- More detail from the Hyp-1-18 trials, specifically relating to the proportion of people in the trials who had previous treatment with topical aluminium-based antiperspirants.
    - No comment or data provided by the company.

The EAG's detailed response to the company's comments on DG is provided in Section 2. Section 3 presents the committee preferred base case results for the primary and secondary care models with

the company's correction and updated unit costs applied. Additionally, scenarios around the committee preferred base case are also presented in Section 3.

# 2 EAG critique of company comments

The company provided nine comments on the draft guidance for glycopyrronium bromide (GPB) 1% cream, and the EAG has provided detailed responses to comments one to seven in the subsections below. The company's comment eight related to its view that the committee is underestimating the impact of GPB 1% cream on patients' quality of life (QoL). The company discussed the different tools used in the Hyp-1-18 trials to assess patient QoL, but did not provide any new data or scenarios for the committee to consider. As such, the EAG considers that company comment eight does not warrant a detailed critique from the EAG. Additionally, company comment nine related to updated unit costs in the model to reflect the latest BNF prices and NHS reference costs for 2024-25. The EAG checked the company's updated unit costs in the model and considers that they are correct and appropriate.

Overall, the EAG considers that no compelling evidence has been put forward by the company that would warrant changes to the committee preferred base case. Instead, the EAG has performed scenarios around the committee preferred base case to assess the impact of changes for certain aspects of the model, where the company has provided evidence to address uncertainty, discussed in the remainder of this section. Scenarios around the committee preferred base case are presented in Section 3.1.1.

## 2.1 Company comment 1: Efficacy of GPB 1% cream compared to oral antimuscarinics

The company conducted a new Bucher indirect treatment comparison (ITC) to compare GPB 1% cream with methantheline bromide, and reported the results from this analysis in their response to the draft guidance. The External Assessment Group (EAG) notes that the company uses data for GPB 1% cream from the Hyp1-18/2016 Phase 3a study[1] and the methantheline bromide data were taken from the Muller *et al.* 2013 trial,[2] which was identified in the company's original systematic literature review (SLR). The EAG notes that the company has highlighted that methantheline bromide is not used in UK clinical practice, but the EAG also agrees with the company that it is plausible to expect methantheline bromide (the isopropyl analogue of propantheline) to be likely to be a closer clinical proxy for propantheline bromide than oxybutynin.

The Muller *et al.* study was conducted in Germany with limited baseline characteristics reported for the study and so the EAG considers it to be unclear how similar the population is to the expected UK

population likely to be eligible for GPB 1% cream. However, the EAG notes that the mean and median baseline axillary sweat production in the placebo arm of the Muller *et al.* trial (mean 161 milligrams [mg]; median 124 mg, [range 51 to 718]) [redacted] compared to the GPB 1% cream trial Hyp1-18/2016 Phase3a placebo arm ([redacted]).

The EAG also notes that Muller *et al.* did not report sufficient data on hyperhidrosis disease severity scale (HDSS) outcomes for direct use in the indirect treatment comparisons (ITCs) for the outcomes of interest required for the economic model. The data for Muller *et al.* that are used in the company's ITCs instead have been obtained from a review publication by Wade *et al.*,[3] which simulated ≥2-point HDSS response rates based on the available continuous HDSS data from Muller *et al*. The EAG is unclear how reliable the analysis by Wade *et al.* is, and the EAG is also concerned that the use of simulated data introduces further uncertainty into the results of the ITCs. In addition, the EAG notes that there are no data for HDSS improvement of 1, and instead for the scenario analysis, the company uses the HDSS improvement of ≥2 as a proxy.

During the validation of the company's new ITC, the EAG identified a potential error in the data used from the placebo arm of the Schollhammer *et al.* study in the company's original ITCs for antimuscarinics versus GPB 1% cream. The EAG notes that the full analysis set from the Phase A (FASa) population in the Hyp1-18/2016 Phase 3a study of GPB 1% cream used in the ITCs includes all patients randomised and treated at least once with the study intervention in the Phase 3a part of the study, with patients analysed in the group they were originally randomised. The EAG considers the FASa to comprise a modified intention-to-treat (mITT) population and that similar populations from the comparator studies should be used in the ITCs where possible. In addition, the EAG notes that the company had an ITC for antimuscarinics versus GPB 1% cream using the per-protocol set from Phase A (PPSa) for GPB 1% cream, and the EAG considers that a similar per-protocol population from Schollhammer *et al.* should also be used for this analysis. The EAG has therefore conducted its own analyses using the data from the Schollhammer *et al.* study to match as closely as possibly to the relevant mITT and PPS data used for GPB 1% cream in the Bucher ITCs, with results reported alongside the company's results in Table 4. The EAG is also concerned that the analysis population for the data used for methantheline bromide from Muller *et al.* does not align with the mITT FASa population used in the company's ITC, as the Muller *et al.* population does not include all randomised patients who received at least one dose of study intervention. The EAG has therefore conducted an additional analysis which includes the equivalent of an mITT population from Muller *et*

*al.* and makes the conservative assumption that missing patients are non-responders (analysis 18 in Table 4).

The EAG considers that the results of the company's ITC for ≥2-point HDSS improvement with methantheline bromide versus GPB 1% cream (odds ratio [OR] [redacted], 95% confidence interval [95% CI]: [redacted]) are not inconsistent with the findings from the company's previous ITC for antimuscarinics versus GPB 1% cream, which used data on oxybutynin from Schollhammer *et al.* 2015[4] for antimuscarinics (OR: [redacted]; 95% CI: [redacted]). The results from the EAG's analysis of methantheline bromide versus GPB 1% cream yields a mean OR [redacted] than the company's estimate [redacted] In addition, the EAG's analyses using the Schollhammer *et al.* data result in [redacted] than the company's analyses. All ITCs are associated with [redacted] (Table 4). The EAG also notes that the ORs are [redacted]

Table 4. Results from the company's Bucher ITCs[1-5] and EAG analyses (adapted from Table 17 of the CS)

| # | Treatment | Source of data | Timepoint | HDSS response endpoint | Company analysis OR (95% CI) | EAG analysis OR (95% CI) |
|---|---|---|---|---|---|---|
| **Antimuscarinics vs GPB 1% cream** | | | | | | |
| 1 | GPB 1% cream | FASa | Day 29 | ≥2 | [redacted] | [redacted] |
| | Antimuscarinics | Schollhammer *et al.* 2015 | 6 weeks | ≥2 | | |
| 2 | GPB 1% cream | PPSa | Day 29 | ≥2 | [redacted] | [redacted] |
| | Antimuscarinics | Schollhammer *et al.* 2015 | 6 weeks | ≥2 | | |
| 3 | GPB 1% cream | FASa | Day 29 | ≥1 | [redacted] | [redacted] |
| | Antimuscarinics | Schollhammer *et al.* 2015 | 6 weeks | ≥1 | | |
| 4 | GPB 1% cream | FASa | Day 29 | ≥2 | [redacted] | [redacted] |
| | Antimuscarinics | Wade *et al.* 2017 | 4 weeks | ≥2 | | |
| **Methantheline bromide vs GPB 1% cream** | | | | | | |
| 17 | GPB 1% cream | FASa | Day 29 | ≥2 | [redacted] | [redacted] |
| | Methantheline bromide | Muller *et al.* 2013 (using data from Wade *et al.* 2017) | Day 28 ± 1 | ≥2 | | |
| 18 | GPB 1% cream | FASa | Day 29 | ≥2 | [redacted] | [redacted] |
| | Methantheline bromide | Muller *et al.* 2013 (using data from | Day 28 ± 1 | ≥2 | | |

| | | | | | | |
|---|---|---|---|---|---|---|
| | | Wade *et al.* 2017) mITT | | | | |

* EAG analysis includes all patients who were randomised and received their allocated intervention in Schollhammer *et al.* (oxybutynin N=30, placebo N=30). Missing patients are assumed to be non-responders.

# EAG analysis excludes 2 patients (1 lost to follow-up and 1 discontinued intervention) from the placebo arm in Schollhammer *et al.* (oxybutynin N=30, placebo N=28).

+ EAG analysis includes all patients who were randomised and received their allocated intervention in Muller *et al.* (methantheline bromide N=171, placebo N=168). Missing patients are assumed to be non-responders.

Abbreviations: CI, confidence interval; FAS, full analysis set; GPB, glycopyrronium bromide; HDSS, Hyperhidrosis Disease Severity Scale; ITC, indirect treatment comparison; mITT, modified intention-to-treat; N, number; N/A, not applicable; OR, odds ratio; PPS, per-protocol set.

Given the limitations described regarding the methantheline bromide data, the EAG considers the ITC for antimuscarinics versus GPB 1% cream, using antimuscarinics data from Schollhammer *et al.* to comprise a more robust estimate than the new ITCs using data from Muller *et al*. In addition, the EAG considers it important to highlight that the EAG does not consider a lack of statistical significance in the results from the company's ITCs to be sufficient evidence to conclude clinical equivalence.

The assumption of equal treatment effectiveness of oral antimuscarinics and GPB 1% cream had the biggest impact on the ICER. The EAG considers that the equal treatment effectiveness assumption is not justified in light of all the evidence from the various ITCs, which estimates that oral antimuscarinics may be more effective than GPB 1% cream for improving HDSS score, albeit with a high degree of uncertainty. As such, the EAG considers that it is more appropriate to maintain the committee preferred base case assumptions to use the ORs from the company's original ITC in the model. Nonetheless, for completeness, the EAG has provided a scenario around the committee preferred base case using the company's OR for methantheline bromide versus GPB 1% cream in Section 3.1.1.

## 2.2 Company comment 2: Efficacy of GPB 1% cream compared to botulinum toxin

The company raised concerns regarding a potential difference in the criteria for defining HDSS responders in the GPB 1% cream Hyp1-18/2016 Phase 3a/3b studies[1] compared with the Lowe *et al.* study[5] of BOTOX used in the company's ITCs. However, the EAG is concerned that the company's argument is flawed given the treatment regimen for BOTOX in the Lowe *et al.* trial required patients to relapse prior to receiving further treatment with BOTOX, whereas GPB 1% cream is given continuously and does not require a reduction in response prior to the next treatment with GPB 1% cream. However, the EAG agrees with the company that the potential difference flagged by the company in the definition of a responder between the two trials is very unlikely to have impacted on

the outcomes of the trials at the 4-week outcome assessment timepoint used in the ITC, especially given the median duration of effect with BOTOX in Lowe *et al.* was approximately 200 days.

The EAG notes that the company has also identified data for BOTOX from a 52-week outcome assessment of the Lowe *et al.* study[5, 6] and that the company provided a naïve comparison of these with the Hyp1-18/2016 Phase 3b GPB 1% cream study data. The EAG recommends caution in drawing any conclusions from this naïve comparison as the Phase 3b GPB 1% cream data are open-label single-arm trial data, whereas the BOTOX trial was a double-blind, placebo-controlled RCT. In addition, the EAG considers it to be unclear how similar the outcome definitions are between the two trials as the company reported that the definition used for the GPB 1% cream trial Phase 3b data presented in the company response document was based on defining a HDSS response as a patient with a ≥2-point change at any time during the study who spent most of the study period (52 -72 weeks) with an HDSS score of 1 or 2.[7] The EAG is also concerned that this outcome appears to be from a *post hoc* analysis.

The company supplied additional scenarios exploring the impact of different OR assumptions (OR =1, 2 & 3, data from Wade *et al*. 2017) for botulinum toxin A versus GPB 1% cream in the model (Table 28 of the company's DG response). The scenarios were applied to the company's updated base case for the secondary care setting and showed minimal impact on the cost-effectiveness results. The EAG considers that the scenarios are not as robust as the committee's base case preference, which the company has maintained for their updated base case. As such, no further exploration of the scenarios was deemed necessary.

## 2.3 Company comment 3: Waning of botulinum toxin A

The committee preferred that treatment effect waning for botulinum toxin A was applied after week 16 in line with clinical expert feedback. In their updated base case, the company did not accept the committee's preference and instead applied treatment effect waning from week 8 onwards. In their DG response, the company explained that week 16 represents the upper limit of treatment effect waning based on the published literature. However, the EAG notes that many of the studies the company refers to in support of its argument are over 20 years old and so may not represent current clinical practice. In their clarification response, and in the DG response, the company presented data from a more recent study (Lee *et al*. 2022), used to inform the committee preferred base case, which shows that improvement in HDSS score slightly declined between week 12 (78.5%) and week 16

(73.0%). The EAG notes that no 95% confidence intervals or p-values are presented for the data, and considers it likely that the difference in the week 12 and week 16 data is not statistically significant.)

The company also presented data on mean sweat reduction for patients on botulinum toxin A from a study by Lowe *et al*. 2023 (Figure 2 of the company DG response), which shows an increase between week 12 and 16. However, in their clarification response the company found no strong correlation between HDSS score and mean sweat production, and therefore does not consider this evidence to be supportive of a treatment waning effect for the main outcome of the model, which is improvement in HDSS score.

The EAG agrees with the company that data in the published literature shows variability in peak efficacy for botulinum toxin treatment. However, due to different study designs, populations and formulations, it is hard to draw firm conclusions. The EAG highlights that its clinical experts and the clinical experts at the appraisal committee meeting were aligned with the assumption that treatment effect waning for botulinum toxin A should be applied from week 16 onwards, and considers that this assumption should be maintained for the committee preferred base case.

## 2.4 Company comment 4: Distribution of subsequent therapies (a) and benefits accrued to private treatments (b)

In the DG, the committee noted that the distribution of subsequent treatment had a small impact on the cost-effectiveness results. However, under the company's assumption of equal treatment effectiveness of oral antimuscarinics and GPB 1% cream (Section 2.1), changes to the subsequent treatment distribution improved the company's ICER estimates. As such, the company considered this aspect of the model to have greater importance than before and so provided additional evidence and updated their base case with a revised distribution of subsequent treatments post GPB 1% cream, oral antimuscarinics and botulinum toxin A.

The committee noted in Section 3.19 of the DG that some patients may have difficulty accessing botulinum toxin A treatment and the company agreed. For the DG response, the company performed a review of 42 NHS integrated care boards (ICBs) to understand access to botulinum toxin A treatment for patients with PAHH. The company stated that 55% of the population in England (not specifically patients with PAHH) across 24 ICBs do not have access to botulinum toxin A treatment. The company considered there were flaws with the reporting of access to botulinum toxin A and assumed a maximum coverage of 45% of PAHH patients having access to treatment. However, the

EAG notes that this does not provide a clear picture of the number of PAHH patients who are eligible for botulinum toxin A and that receive treatment.

The company also looked at hospital episode statistics (HES) data for the use of botulinum toxin A treatment and found that 1,047 treatments across 36 trusts/clinics were delivered in a 12-month period. However, the EAG notes that these data are not specific to treatment for PAHH and no data are presented on the number of patients the treatments relate to. Moreover, in their original submission, the company stated that the prevalence of hyperhidrosis is unknown. As such, the EAG considers the data to be too incomplete to draw any conclusions on access to treatment for patients with PAHH.

With regards to treatment with propantheline bromide, the company reviewed NHS prescription data on propantheline bromide and found that over 12 months, 3,435 patients were using this treatment on a repeat basis. Again, the data are not specific to patients with PAHH and along with an unknown prevalence, the EAG considers that no conclusions on access to treatment can be made.

The company consulted their clinical experts who provided alternative distributions of subsequent treatment for the primary and secondary care models (Tables 6 and Table 7 of the company's DG response). Together with the clinical expert feedback and their estimate that the upper limit to access for botulinum toxin treatment is 45%, the company updated their base case with revised distributions of subsequent treatments that are presented in Table 5 and Table 6 alongside the committee preferred distributions.

In addition to the revised subsequent treatment distributions, the company deemed the assumption that patients who exit NHS care to seek private treatment accrue the utility benefits of treatment without the costs is misaligned. The company considered that the assumption models a situation where it is beneficial for the NHS for patients to seek private treatment as this incurs no costs to the system but accrues the benefit. Instead, for their updated base case, the company preferred to assume that patients who seek private treatment (and therefore incur no further costs to the NHS) revert to their baseline HDSS score.

Table 5. Distribution of subsequent treatments for the primary care model – committee preference compared to the company updated base case.

| Subsequent treatment | Committee preferred distribution | | Updated company base case | |
|---|---|---|---|---|
| | GPB 1% cream | Oral antimuscarinics | GPB 1% cream | Oral antimuscarinics |
| Antimuscarinics (primary care) | 0.0% | 0.0% | 14.0% | 3.2% |
| Antimuscarinics (primary care and A&G) | 0.0% | 0.0% | 12.0% | 8.0% |
| Antimuscarinics (secondary care) | 20.0% | 10.0% | 26.6% | 22.3% |
| BTX (secondary care) | 80.0% | 90.0% | 33.9% | 45.4% |
| Unlicensed GPB (secondary care) | 0.0% | 0.0% | 1.9% | 4.2% |
| Private treatment | 0.0% | 0.0% | 5.1% | 7.3% |
| No further treatment | 0.0% | 0.0% | 6.5% | 9.6% |

Abbreviations: A&G, advice and guidance; BTX, botulinum toxin A; GPB, glycopyrronium bromide.

Table 6. Distribution of subsequent treatments for the secondary care model – committee preference compared to the company updated base case.

| Subsequent treatment | Committee preferred base case | | | Updated company base case | | |
|---|---|---|---|---|---|---|
| | GPB 1% cream | Oral antimuscarinics | Botulinum toxin A | GPB 1% cream | Oral antimuscarinics | Botulinum toxin A |
| Antimuscarinics (primary care) | 0.0% | 0.0% | 0.0% | 2.1% | 1.7% | 11.0% |
| Antimuscarinics (primary care and A&G) | 0.0% | 0.0% | 0.0% | 3.3% | 0.0% | 3.0% |
| Antimuscarinics (secondary care) | 10.0% | 10.0% | 25.0% | 31.0% | 9.3% | 18.5% |
| BTX (secondary care) | 80.0% | 63.0% | 0.0% | 45.4% | 45.4% | 0.0% |
| Unlicensed GPB (secondary care) | 0.0% | 2.0% | 25.0% | 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% |

Abbreviations: A&G, advice and guidance; BTX, botulinum toxin A; GPB, glycopyrronium bromide.

As mentioned previously, changes to the subsequent treatment distribution improved the company's ICER under the assumption that oral antimuscarinics and GPB 1% cream have the same treatment effectiveness. This improvement was driven by shifting patients away from botulinum toxin A treatment, which is more effective than GPB 1% cream. Instead, more patients are assumed to receive oral antimuscarinics, which under the company's new assumptions, are only as effective

as GPB 1% cream. In the committee's preferred base case, oral antimuscarinics were considered to be more effective. Additionally, in the company's updated base case, more patients are assumed to access private care, whereas under the company's new assumptions, patients revert to their baseline HDSS score. Therefore, a proportion of patients who received benefit in the committee's base case now have this benefit removed in the company's updated base case.

However, as previously mentioned, the EAG disagrees with the company's assumption of equal treatment effectiveness for GPB 1% cream and oral antimuscarinics, and so under the committee's preferred approach, the changes to the distribution of subsequent treatments still have a small impact on the ICER. While the EAG considers that costs and benefits should be accounted for as patients receive them (in terms of benefits but not costs being attributed to patients in private healthcare), the EAG has some sympathy for the company's position that this could be considered a perverse incentive to drive patients into private healthcare. The EAG provides a scenario that assumes that patients receive the benefit of treatment in private care, but that the model assumes that this is paid for by the NHS. While this is also a strong assumption, the EAG considers it to be preferable to the company's assumption that patients revert to their baseline health state.

The EAG ran two scenarios using the committee's and the company's preferred subsequent treatment distributions and assumed that patients who receive private treatment are accessing botulinum toxin A and assigned the costs of treatment. For the committee preferred subsequent treatment distribution, this scenario only affects the secondary care model, as no private treatment was assumed in the primary care model. The EAG's scenarios are presented in Section 3.1.1..

## 2.5 Company comment 5: Time horizon (2 years vs 5 years)

The company has updated its base case to use a time horizon of five years compared to the committee's preferred assumption of two years. In the DG, it was noted that the clinical experts in attendance at the committee meeting agreed with the EAG's clinical experts, that response to treatment is seen soon after treatment has commenced and then response is stable over time. Based on this, the committee stated that most of the differences in the costs and benefits of GPB 1% cream would be captured in the first two years of the model. The committee went further and explained that many of the company's assumptions were biased against the comparators, and the longer time horizon of the model compounded the effects of the assumptions.

The company's justification for a time horizon of five years is that there is still a proportion of patients who remain on treatment with GPB 1% cream, oral antimuscarinics and botulinum toxin A. As such, they considered five years as a reasonable compromise as it sufficiently captures the differences in costs and benefits, while still alleviating the committee's concerns regarding the influence of subsequent treatments for each arm of the model on the overall cost-effectiveness results.

The EAG considers that there is no strong reason for the committee to change its position on the time horizon, especially as one of the underlying issues is that observed data from the Hyp1-18/2016 Phase 3b are only available for 72 weeks, after which in the model no further transitions between health states are possible. However, should the committee want to consider a time horizon of five years, the EAG has supplied a scenario around the committee preferred base case using a time horizon of five years, presented in Section 3.1.1.

## 2.6 Company comment 6: Discontinuation rates for oral antimuscarinics (a) and BTX (b)

In the DG, the committee requested further validation of the treatment discontinuation for oral antimuscarinics and botulinum toxin A in the model. In response, the company consulted with its clinical experts who provided landmark estimates of treatment discontinuation at one, two and five years, presented in Table 7. The company implemented the data in Table 7 as part of their updated base case. The EAG notes that company's clinical expert feedback is broadly supportive of what was used for the committee preferred base case (also presented in Table 7). However, the EAG highlights that for the committee base case, 1/3 of patients discontinued oral antimuscarinics at week 4, after which the model assumed a slower rate of discontinuation at 0.2% every two weeks. Whereas in the company's updated base case, there is continuous discontinuation, with the two-week probability declining over time (presented in Table 8)

The company also stated that for their updated base case, after week 72 it is assumed that GPB 1% cream will have the same 2-week probability of discontinuation as oral antimuscarinics (presented in Table 8). However, the EAG notes that in the company's original base case and included in the committee preferred base case, the two-week probability of discontinuation GPB 1% cream was [redacted]%, which was based on the discontinuation data from Hyp1-18/2016 Phase 3b for 72 weeks. Therefore, under the company's updated assumptions, between week 72 and 104 discontinuations are [redacted] to 0.6%.

Table 7. Landmark treatment discontinuation rates – committee base case compared with company updated base case

| Time point | Committee base case treatment discontinuation | | Updated company base case treatment discontinuation | |
|---|---|---|---|---|
| | Oral antimuscarinics | Botulinum toxin A | Oral antimuscarinics | Botulinum toxin A |
| 1 year | 38% | 21% | 38% | 14% |
| 2 years | 43% | 37% | 52% | 30% |
| 5 years | 56% | 69% | 69% | 55% |
| Abbreviations: | | | | |

Table 8. Per-cycle probability of treatment discontinuation for oral antimuscarinics – company updated base case

| Time point | Oral antimuscarinics |
|---|---|
| 0-52 weeks | 1.8% |
| 52-104 weeks | 1.0% |
| 104-261 weeks | 0.6% |
| Abbreviations: | |

As mentioned in Section 2.1, the EAG does not agree with the assumption of equal treatment effectiveness for oral antimuscarinics and GPB 1% cream. Equally, the EAG does not agree that discontinuations would be the same for GPB 1% cream and oral antimuscarinics, as originally the data for GPB 1% cream was based on the trial, which the EAG considers to be appropriate. Additionally, reasons for discontinuation are likely to be different for a cream versus a systemic treatment, especially as the adverse event profiles are different.

The EAG considers that it is worth exploring the company's clinical expert feedback on treatment discontinuation for oral antimuscarinics and botulinum toxin A treatment, as even though the data are supportive of the committee's base case preferences, it is useful to assess the magnitude of impact on the ICER due to the small differences. However, in the scenarios that the EAG has run, it has maintained the original treatment discontinuation rate for GPB 1% cream used in the committee preferred base case. The scenarios are presented in Section 3.1.1 and demonstrate that the company's preferred base case assumption does not have a substantial impact on the ICER.

## 2.7 Company Comment 7: Cost of management of adverse events

In the DG, the committee heard from clinical experts that adverse events (AEs) would not be severe and would be managed by dose reductions and stopping treatment. The committee noted that GPB 1% cream would be expected to have fewer side effects as it is a topical treatment and that it was

important to capture both the costs and utility impact in the model. However, the committee considered that costs of AEs were already captured in the monitoring costs, so for its preferred base case, only disutilities associated with AEs were included.

For their DG response, the company sought input from 10 clinical experts on how AEs would be managed in clinical practice and concluded that additional resources, in the form of pharmacist time, would be needed to manage AEs over and above the resources for monitoring patients. For their updated base case, the company assumed the cost of 10 minutes of pharmacist time (£9.17, PSSRU)[8] for each AE in the model.

The EAG considered the feedback from the company's clinical experts, presented in Table 17 of the DG response, and concluded that the view of most of the clinical experts aligned with the EAG and committee clinical experts' view. Specifically, that most side effects are mild and are typically managed through routine appointments. As such, the EAG considers that the evidence presented by the company is not compelling enough to warrant the committee to deviate from its preferred assumption to exclude additional costs for AEs.

# 3 Cost-effectiveness results

## 3.1 Updated committee preferred base case

As mentioned in Section 1, the company made a correction to how treatment discontinuation for oral antimuscarinics is applied and updated several unit costs in the model, both of which the EAG agree are appropriate changes. Additionally, as discussed in Section 2, the EAG found an error in the company's original ITC for oral antimuscarinics versus GPB 1% cream used in the company's original base case and included in the committee's preferred base case. The EAG's corrected ITC has been included as part of a corrected committee base case. Table 9 presents the corrected committee preferred base case results for the primary care model. Table 10 – Table 12 presents the results for the secondary care model, including fully incremental analysis.

Table 9. Primary care model – committee preferred assumptions, GPB 1% cream versus propantheline bromide

| Interventions | Total Costs (£) | Total LY | Total QALYs | Incremental costs (£) | Incremental LYs | Incremental QALYs | ICER (£/QALY) |
|---|---|---|---|---|---|---|---|
| **Deterministic results** | | | | | | | |
| Propantheline bromide | [redacted] | [redacted] | [redacted] | - | - | - | - |
| GPB 1% cream | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| **Probabilistic results** | | | | | | | |
| Propantheline bromide | [redacted] | [redacted] | [redacted] | - | - | - | - |
| GPB 1% cream | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |

Abbreviations: GPB, glycopyrronium bromide; ICER, incremental cost-effectiveness ratio; LY, life year; QALY, quality-adjusted life-year; SW, south-west.

Table 10. Secondary care model – committee preferred assumption, GPB 1% cream versus modified-release oxybutynin

| Interventions | Total Costs (£) | Total LY | Total QALYs | Incremental costs (£) | Incremental LYs | Incremental QALYs | ICER (£/QALY) |
|---|---|---|---|---|---|---|---|
| **Deterministic results** | | | | | | | |
| Modified-release oxybutynin | [redacted] | [redacted] | [redacted] | - | - | - | - |
| GPB 1% cream | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |

| Interventions | Total Costs (£) | Total LY | Total QALYs | Incremental costs (£) | Incremental LYs | Incremental QALYs | ICER (£/QALY) |
|---|---|---|---|---|---|---|---|
| **Deterministic results** | | | | | | | |
| **Probabilistic results** | | | | | | | |
| Modified-release oxybutynin | [redacted] | [redacted] | [redacted] | - | - | - | - |
| GPB 1% cream | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |

Abbreviations: GPB, glycopyrronium bromide; ICER, incremental cost-effectiveness ratio; LY, life year; QALY, quality-adjusted life-year; SW, south-west.

Table 11. Secondary care model – committee preferred assumptions, GPB 1% cream versus botulinum toxin A

| Interventions | Total Costs (£) | Total LY | Total QALYs | Incremental costs (£) | Incremental LYs | Incremental QALYs | ICER (£/QALY) |
|---|---|---|---|---|---|---|---|
| **Deterministic results** | | | | | | | |
| Botulinum toxin A | [redacted] | [redacted] | [redacted] | - | - | - | - |
| GPB 1% cream | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| **Probabilistic results** | | | | | | | |
| Botulinum toxin A | [redacted] | [redacted] | [redacted] | - | - | - | - |
| GPB 1% cream | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |

Abbreviations: GPB, glycopyrronium bromide; ICER, incremental cost-effectiveness ratio; LY, life year; QALY, quality-adjusted life-year; SW, south-west.

Table 12. Fully incremental analysis (based on PSA results) – Secondary care model, committee preferred assumptions

| Interventions | Total Costs (£) | Total LY | Total QALYs | Incremental costs (£) | Incremental LYs | Incremental QALYs | ICER (£/QALY) |
|---|---|---|---|---|---|---|---|
| Modified-release oxybutynin | [redacted] | [redacted] | [redacted] | - | - | - | - |
| GPB 1% cream | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Botulinum toxin A | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |

Abbreviations: GPB, glycopyrronium bromide; ICER, incremental cost-effectiveness ratio; LY, life year; QALY, quality-adjusted life-year; SW, south-west.

### *3.1.1 Scenarios around the committee preferred base case*

The EAG has run the following scenarios around the corrected committee base case:

- OR based on company's ITC for methantheline bromide versus GPB 1% cream.
- Time horizon of five years.
- Botulinum toxin A costs applied to patients on private treatment – committee preferred subsequent treatment distribution (secondary care model only). This scenario represents the EAG's preferred assumption and considers this should be included as part of the committee's base case.
- Botulinum toxin A costs applied to patients on private treatment – company preferred subsequent treatment distribution.
- Company clinical expert feedback on treatment discontinuation for oral antimuscarinics and botulinum toxin A. Treatment discontinuation for GPB 1% cream as per the committee preferred base case.

Results for the scenario are presented in Table 13 and Table 14 for the primary and secondary care models, respectively.

Table 13. Results of EAG's deterministic exploratory analyses using corrected committee's base case – primary care model

| Exploratory analysis number | Scenario applied to committee's base case | Incremental costs (£) | Incremental QALYs | ICER (£/QALY) |
|---|---|---|---|---|
| **Corrected committee base case** | - | [redacted] | [redacted] | [redacted] |
| 1a | OR based on company's ITC for methantheline bromide versus GPB 1% cream. | [redacted] | [redacted] | [redacted] |
| 1b | OR based on EAG's ITC for methantheline bromide versus GPB 1% cream. | [redacted] | [redacted] | [redacted] |
| 2 | Time horizon of 5 years | [redacted] | [redacted] | [redacted] |
| 3 | Botulinum toxin A costs applied to patients on private treatment – company preferred subsequent treatment distribution | [redacted] | [redacted] | [redacted] |
| 4 | Company clinical expert feedback on treatment discontinuation for oral antimuscarinics and botulinum toxin A. | [redacted] | [redacted] | [redacted] |

Abbreviations: EAG, External Assessment Group; GPB, ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year; SW, south-west.

Table 14. Results of EAG's deterministic exploratory analyses using corrected committee's base case – secondary care model

| Exploratory analysis number | Scenario applied to committee's base case | Vs oral antimuscarinics | | | Vs botulinum toxin A | | |
|---|---|---|---|---|---|---|---|
| | | Δ Costs (£) | Δ QALYs | ICER (£/QALY) | Δ Costs (£) | Δ QALYs | ICER (£/QALY) |
| **Corrected committee base case** | - | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| 1a | OR based on company's ITC for methantheline bromide versus GPB 1% cream. | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| 1b | OR based on EAG's ITC for methantheline bromide versus GPB 1% cream. | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| 2 | Time horizon of 5 years | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| 3 | Botulinum toxin A costs applied to patients on private treatment – committee preferred subsequent treatment distribution | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| 4 | Botulinum toxin A costs applied to patients on private treatment – company preferred subsequent treatment distribution | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| 5 | Company clinical expert feedback on treatment discontinuation for oral antimuscarinics and botulinum toxin A. | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |

Abbreviations: EAG, External Assessment Group; GPB, ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year; SW, south-west.

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