IQWiG Reports – Commission No. A22-82

Glycopyrronium (severe primary axillary hyperhidrosis) –

Benefit assessment according to §35a Social Code Book V[1]

Extract

[1] Translation of Sections I 1 to I 5 of the dossier assessment *Glycopyrronium (schwere primäre axilläre Hyperhidrose) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 26 October 2022). Please note: This document was translated by an external translator and is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

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IQWiG thanks the medical and scientific advisor for his contribution to the dossier assessment. However, the advisor was not involved in the actual preparation of the dossier assessment. The responsibility for the contents of the dossier assessment lies solely with IQWiG.

Patient and family involvement

No feedback was received in the framework of the present dossier assessment.

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Part I: Benefit assessment

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[2] Table numbers start with “2” as numbering follows that of the full dossier assessment.

I List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
HDSS	Hyperhidrosis Disease Severity Scale
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
RCT	randomized controlled trial
SGB	Sozialgesetzbuch (Social Code Book)

I 1 Executive summary of the benefit assessment

Background

In accordance with § 35a Social Code Book (SGB) V, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to assess the benefit of the drug glycopyrronium. The assessment is based on a dossier compiled by the pharmaceutical company (hereinafter referred to as the "company"). The dossier was sent to IQWiG on 1 August 2022.

Research question

The aim of the present report is to assess the added benefit of glycopyrronium in comparison with an aluminium-containing formulation (at least 15%) or tap water iontophoresis as the appropriate comparator therapy (ACT) in patients with severe primary axillary hyperhidrosis.

The research question presented in Table 2 is derived from the ACT specified by the G-BA.

Table 2: Research question of the benefit assessment of glycopyrronium

Therapeutic indication	**ACT**[a]
Adult patients with severe primary axillary hyperhidrosis	An aluminium chloride-containing formulation [b] (at least 15%) or tap water iontophoresis
a. Presented is the ACT specified by the G-BA. Local injection with *Clostridium botulinum* toxin type A is approved for the treatment of primary axillary hyperhidrosis which cannot be adequately controlled with topical treatment. According to its marketing authorization, *Clostridium botulinum* toxin type A is therefore to be used only after failed topical therapy and, consequently, does not represent an adequate comparator for topical glycopyrronium treatment. b. The German New Prescription Formulary includes aluminium chloride-containing formulations for the symptomatic treatment of excessive sweating (hyperhidrosis). ACT: appropriate comparator therapy; G-BA: Federal Joint Committee	

The company partially departs from the ACT specified by the G-BA by listing, as the 2nd option, injection of botulinum toxin A rather than tap water iontophoresis. The company's deviation remains without consequence for the present benefit assessment because the data presented by the company's dossier are unsuitable for a comparison versus both of the ACTs, i.e. the one specified by the G-BA and the one specified by the company. The present assessment is implemented in comparison with the ACT specified by the G-BA.

The assessment is conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. Randomized controlled trials (RCTs) with a minimum duration of 24 weeks were used for the derivation of added benefit.

Results

The check of completeness of the study pool did not reveal any relevant RCTs offering a direct comparison with the ACT specified by the G-BA (aluminium chloride-containing formulations [at least 15%] or tap water iontophoresis).

The company likewise found no RCTs suitable for a direct comparison with an aluminium chloride-containing formulation (at least 15%) and no RCTs for a direct comparison versus botulinum toxin A, which it identified as the 2nd comparator therapy option instead of tap water iontophoresis. The company did not search for an RCT for a comparison with tap water iontophoresis.

Evidence provided by the company

Because the company did not identify any RCTs for a direct comparison with its defined ACT, the company's Module 4 A used the 1st part of the Hyp1-18/2016 study for deriving added benefit. As supplementary information, the company presented the results of the 2nd part of the study as well as those of the Hyp-02/2015 study.

The Hyp1-18/2016 study is a randomized, double-blind, placebo-controlled study which enrolled adults aged 18 to 65 years with severe primary axillary hyperhidrosis. The Hyp-02/2015 study is a randomized, double-blind, placebo-controlled trial applying glycopyrronium at 3 different doses. The enrolled patients were aged between 18 and 65 years and suffered from moderate to severe primary axillary hyperhidrosis.

Studies unsuitable for the benefit assessment

Since the Hyp1-18/2016 and Hyp-02/2015 studies compared glycopyrronium versus placebo, comparator arm participants did not receive active therapy as specified in the ACT. Therefore, the available evidence is unsuitable for deriving any conclusions on the added benefit of glycopyrronium in comparison with the ACT specified by the G-BA.

Results on added benefit

Since no relevant study is available for the benefit assessment, there is no hint of an added benefit of glycopyrronium in comparison with the ACT; an added benefit is therefore not proven.

Probability and extent of added benefit, patient groups with therapeutically important added benefit[3]

Table 3 summarizes the probability and extent of added benefit of glycopyrronium.

[3] On the basis of the scientific data analysed, IQWiG draws conclusions on the (added) benefit or harm of an intervention for each patient-relevant outcome. Depending on the number of studies analysed, the certainty of their results, and the direction and statistical significance of treatment effects, conclusions on the probability of (added) benefit or harm are graded into 4 categories: (1) "proof", (2) "indication", (3) "hint", or (4) none of the first 3 categories applies (i.e., no data available or conclusions 1 to 3 cannot be drawn from the available data). The extent of added benefit or harm is graded into 3 categories: (1) major, (2) considerable, (3) minor (in addition, 3 further categories may apply: non-quantifiable extent of added benefit, added benefit not proven, or less benefit). For further details see [1,2].

Table 3: Glycopyrronium – probability and extent of added benefit

Therapeutic indication	**ACT[a]**	**Probability and extent of added benefit**
Adult patients with severe primary axillary hyperhidrosis	An aluminium chloride-containing formulation [b] (at least 15%) or tap water iontophoresis	Added benefit not proven

a. Presented is the ACT specified by the G-BA. Local injection with *Clostridium botulinum* toxin type A is approved for the treatment of primary axillary hyperhidrosis which cannot be adequately controlled with topical treatment. According to its marketing authorization, *Clostridium botulinum* toxin type A is therefore to be used only after failed topical therapy and, consequently, does not represent an adequate comparator for topical glycopyrronium treatment.
b. The German New Prescription Formulary includes aluminium chloride-containing formulations for the symptomatic treatment of excessive sweating (hyperhidrosis).

ACT: appropriate comparator therapy; G-BA: Federal Joint Committee

The G-BA decides on the added benefit.

I 2 Research question

The aim of the present report is to assess the added benefit of glycopyrronium in comparison with an aluminium-containing formulation (at least 15%) or tap water iontophoresis as the ACT in patients with severe primary axillary hyperhidrosis.

The research question presented in Table 4 is derived from the ACT specified by the G-BA.

Table 4: Research question of the benefit assessment of glycopyrronium

Therapeutic indication	**ACT**[a]
Adult patients with severe primary axillary hyperhidrosis	An aluminium chloride-containing formulation [b] (at least 15%) or tap water iontophoresis

a. Presented is the ACT specified by the G-BA. Local injection with *Clostridium botulinum* toxin type A is approved for the treatment of primary axillary hyperhidrosis which cannot be adequately controlled with topical treatment. According to its marketing authorization, *Clostridium botulinum* toxin type A is therefore to be used only after the failure of topical therapy and consequently does not represent an adequate comparator for topical glycopyrronium treatment.
b. The German New Prescription Formulary includes aluminium chloride-containing formulations for the symptomatic treatment of excessive sweating (hyperhidrosis).

ACT: appropriate comparator therapy; G-BA: Federal Joint Committee

The company partially departs from the ACT specified by the G-BA by listing, as the 2nd option, injection of botulinum toxin A rather than tap water iontophoresis. The company justifies this by evidence regarding the use of tap water iontophoresis in axillary hyperhidrosis being, in its view, inadequate.

The company's deviation remains without consequence for the present benefit assessment because the data presented by the company's dossier are unsuitable for a comparison versus both of the ACTs, i.e. the one specified by the G-BA and the one specified by the company. The present assessment is implemented in comparison with the ACT specified by the G-BA.

The assessment is conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. RCTs with a minimum duration of 24 weeks were used for the derivation of added benefit. This deviates from the company's inclusion criteria, which did not specify a minimum study duration.

I 3 Information retrieval and study pool

The study pool of the assessment was compiled on the basis of the following information:

Sources of the company in the dossier:

- study list on glycopyrrolate (status: 1 June 2022)
- bibliographical literature search on glycopyrrolate (last search on 1 June 2022)
- search in trial registries / trial results databases for studies on glycopyrrolate (last search on 27 May 2022)
- search on the G-BA website for glycopyrrolate (last search on 27 May 2022)

To check the completeness of the study pool:

- search in trial registries for studies on glycopyrrolate (last search on 23 August 2022); for search strategies, see I Appendix A of the full dossier assessment

The check of completeness did not find any relevant RCTs for a direct comparison with the ACT specified by the G-BA (aluminium chloride-containing formulation (at least 15%) or tap water iontophoresis). This concurs with the company's evaluation in that the company likewise did not find any RCTs for a direct comparison with an aluminium chloride-containing formulation (at least 15%). However, the company did not search for RCTs for a direct comparison with tap water iontophoresis, because the company believes that this treatment option is not covered under the chosen ACT (see Section I 2). Instead, the company searched for RCTs allowing a direct comparison with botulinum toxin A, which the company identified as the 2nd comparator therapy option instead of tap water iontophoresis, but it likewise found no relevant study for this comparison.

Evidence provided by the company

Not having found any RCTs for a direct comparison with the company's specified ACT, the company's Module 4 A used the 1st part of the Hyp1-18/2016 study [3] for deriving added benefit. As supplementary information, the company presented the results of the 2nd part of the study [4] as well as the results of the Hyp-02/2015 study [5]. The studies presented by the company are unsuitable for deriving any added benefit of glycopyrronium because they do not allow a comparison with the ACT specified by the G-BA. A justification is provided hereinbelow.

Hyp1-18/2016 study

The Hyp1-18/2016 study is a randomized, double-blind, placebo-controlled study which enrolled adults aged 18 to 65 years with severe primary axillary hyperhidrosis, operationalized as a Hyperhidrosis Disease Severity Scale (HDSS) score of 3 or 4. The study included 171 patients, randomly allocated in a 1:1 ratio to the treatment arms (glycopyrronium N = 87; placebo N = 84). The duration of the randomized treatment phase with glycopyrronium or

placebo was 4 weeks (1st part of the study). Afterwards, participants were eligible to participate in an open-label, single-arm extension study (2nd part of the study). The planned additional treatment duration of 68 weeks in the extension study was followed by a 4-week follow-up observation phase. The extension study additionally included newly recruited patients who were likewise treated for 72 weeks and subsequently underwent 4 weeks of follow-up observation. The primary outcome was absolute change in sweat production.

Hyp-02/2015 study presented as supplementary information by the company

The Hyp-02/2015 study is a randomized, double-blind, placebo-controlled trial using glycopyrronium at 3 different doses (0.5%, 1%, and 2%). The enrolled patients were aged between 18 and 65 years. Alongside patients with severe primary axillary hyperhidrosis, those with moderate severity of disease, operationalized as an HDSS score of 2 to 4, were eligible for inclusion. Treatment duration was 14 days, with subsequent 1-week follow-up observation.

Evidence unsuitable for assessing added benefit

The Hyp1-18/2016 and Hyp-02/2015 studies compared glycopyrronium versus placebo. Hence, active therapy as specified in the ACT has not been implemented for participants in the Hyp1-18/2016 and Hyp-02/2015 studies' comparator arms. Therefore, the available evidence is unsuitable for deriving any conclusions on the added benefit of glycopyrronium in comparison with the ACT specified by the G-BA.

In addition to not offering a comparison with the ACT, both studies exhibit a randomized treatment duration insufficient for deriving an added benefit in the present therapeutic indication – at 4 weeks (Hyp1-18/2016) and 2 weeks (Hyp-02/2015).

I 4 Results on added benefit

No suitable data are available for assessing the added benefit of glycopyrronium in comparison with the ACT in patients with severe primary axillary hyperhidrosis. This results in no hint of an added benefit of glycopyrronium comparison with the ACT; an added benefit is therefore not proven.

I 5 Probability and extent of added benefit

Table 5 summarizes the result of the assessment of added benefit of glycopyrronium in comparison with the ACT.

Table 5: Glycopyrronium – probability and extent of added benefit

Therapeutic indication	**ACT**[a]	**Probability and extent of added benefit**
Adult patients with severe primary axillary hyperhidrosis	An aluminium chloride-containing formulation [b] (at least 15%) or tap water iontophoresis	Added benefit not proven

a. Presented is the ACT specified by the G-BA. Local injection with *Clostridium botulinum* toxin type A is approved for the treatment of primary axillary hyperhidrosis which cannot be adequately controlled with topical treatment. According to its marketing authorization, *Clostridium botulinum* toxin type A is therefore to be used only after failed topical therapy and, consequently, does not represent an adequate comparator for topical glycopyrronium treatment.
b. The German New Prescription Formulary includes aluminium chloride-containing formulations for the symptomatic treatment of excessive sweating (hyperhidrosis).

ACT: appropriate comparator therapy; G-BA: Federal Joint Committee

The above assessment deviates from the company's, which derived an indication of at least minor added benefit of glycopyrronium for the present research question.

The G-BA decides on the added benefit.

References for English extract

Please see full dossier assessment for full reference list.

The reference list contains citations provided by the company in which bibliographical information may be missing.

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The full report (German version) is published under https://www.iqwig.de/en/projects/a22-82.html.