Gemeinsamer Bundesausschuss

Justification

of the Resolution of the Federal Joint Committee (G-BA) on an Amendment of the Pharmaceuticals Directive: Annex XII – Benefit Assessment of Medicinal Products with New Active Ingredients according to Section 35a SGB V Glycopyrronium (severe primary axillary hyperhidrosis)

of 19 January 2023

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1. Legal basis

According to Section 35a paragraph 1 German Social Code, Book Five (SGB V), the Federal Joint Committee (G-BA) assesses the benefit of reimbursable medicinal products with new active ingredients. This includes in particular the assessment of the additional benefit and its therapeutic significance. The benefit assessment is carried out on the basis of evidence provided by the pharmaceutical company, which must be submitted to the G-BA electronically, including all clinical trials the pharmaceutical company has conducted or commissioned, at the latest at the time of the first placing on the market as well as the marketing authorisation of new therapeutic indications of the medicinal product, and which must contain the following information in particular:

1. approved therapeutic indications,
2. medical benefit,
3. additional medical benefit in relation to the appropriate comparator therapy,
4. number of patients and patient groups for whom there is a therapeutically significant additional benefit,
5. treatment costs for the statutory health insurance funds,
6. requirements for a quality-assured application.

The G-BA may commission the Institute for Quality and Efficiency in Health Care (IQWiG) to carry out the benefit assessment. According to Section 35a, paragraph 2 SGB V, the assessment must be completed within three months of the relevant date for submission of the evidence and published on the internet.

According to Section 35a paragraph 3 SGB V, the G-BA decides on the benefit assessment within three months of its publication. The resolution is to be published on the internet and forms part of the Pharmaceuticals Directive.

2. Key points of the resolution

The medicinal product Axhidrox, containing the active ingredient glycopyrronium, was first placed on the market on 1 August 2022. Relevant date according to Chapter 5, Section 8, paragraph 1, number 7 of the Rules of Procedure of the G-BA (VerfO) for the start of the evaluation procedure for the active ingredient glycopyrronium is within three months of the request by the G-BA. If the medicinal product has not yet been placed on the market at that time, the procedure shall start on the date on which it is first placed on the market.

At its session on 2 April 2020, the Federal Joint Committee (G-BA) decided to initiate a benefit assessment for the active ingredient glycopyrronium in the indication "axillary hyperhidrosis" according to Section 35a, paragraph 6 SGB V in conjunction with Chapter 5, Section 16, paragraph 1 VerfO.

The final dossier was submitted to the G-BA in due time on 29 July 2022. On 1 August 2022, the assessment procedure started.

The G-BA commissioned the IQWiG to carry out the assessment of the dossier. The benefit assessment was published on 1 November 2022 on the G-BA website (www.g-ba.de), thus initiating the written statement procedure. In addition, an oral hearing was held.

The G-BA came to a resolution on whether an additional benefit of glycopyrronium compared with the appropriate comparator therapy could be determined on the basis of the dossier of the pharmaceutical company, the dossier assessment prepared by the IQWiG, the statements submitted in the written statement and oral hearing procedure, and the addenda to the benefit assessment prepared by the IQWiG. In order to determine the extent of the additional benefit, the G-BA has evaluated the data justifying the finding of an additional benefit on the basis of their therapeutic relevance (qualitative), in accordance with the criteria laid down in Chapter 5, Section 5, paragraph 7 VerfO. The methodology proposed by the IQWiG in accordance with the General Methods [1] was not used in the benefit assessment of glycopyrronium.

In the light of the above, and taking into account the statements received and the oral hearing, the G-BA has come to the following assessment:

2.1 Additional benefit of the medicinal product in relation to the appropriate comparator therapy

2.1.1 Approved therapeutic indication of Glycopyrronium (Axhidrox) in accordance with the product information

Axhidrox is used for topical treatment of severe primary axillary hyperhidrosis in adults.

Therapeutic indication of the resolution (resolution of 19.01.2023):

see the approved therapeutic indication

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

Adults with severe primary axillary hyperhidrosis

Appropriate comparator therapy for glycopyrronium (topical therapy):

- a formulation containing aluminium chloride (min. 15 %) or tap water iontophoresis

Criteria according to Chapter 5, Section 6 of the Rules of Procedure of the G-BA:

The appropriate comparator therapy must be an appropriate therapy in the therapeutic indication in accordance with the generally recognised state of medical knowledge (Section 12 SGB V), preferably a therapy for which endpoint studies are available and which has proven

1 General Methods, version 6.1 from 24.01.2022. Institute for Quality and Efficiency in Health Care (IQWiG), Cologne.

its worth in practical application unless contradicted by the guidelines under Section 92, paragraph 1 SGB V or the principle of economic efficiency.

In determining the appropriate comparator therapy, the following criteria, in particular, must be taken into account as specified in Chapter 5, Section 6, paragraph 3 VerfO:

1. To be considered as a comparator therapy, the medicinal product must, principally, have a marketing authorisation for the therapeutic indication.
2. If a non-medicinal treatment is considered as a comparator therapy, this must be available within the framework of the SHI system.
3. As comparator therapy, medicinal products or non-medicinal treatments for which the patient-relevant benefit has already been determined by the G-BA shall be preferred.
4. According to the generally recognised state of medical knowledge, the comparator therapy should be part of the appropriate therapy in the therapeutic indication.

Justification based on the criteria set out in Chapter 5, Section 6, paragraph 3 VerfO:

on 1. In addition to glycopyrronium, the following active ingredients are generally approved for the treatment of hyperhidrosis: Clostridium botulinum toxin type A, bornaprine hydrochloride, methanthelinium bromide, methenamine, phenol methanal urea polycondensate sodium salt and sage leaves.

on 2. As a non-medicinal treatment, tap water iontophoresis (pulsed current) can be considered for the treatment of hyperhidrosis.

on 3. For the therapeutic indication of (axillary) hyperhidrosis, there are no resolutions on the benefit assessment of medicinal products with new active ingredients according to Section 35a SGB V.

on 4. The generally recognised state of medical knowledge was illustrated by a systematic search for guidelines as well as systematic reviews of clinical studies in the present therapeutic indication.

The German S1 guideline of the German Dermatological Society recommends a stepwise approach for the treatment of primary axillary hyperhidrosis - regardless of the severity grade: Topical therapy with antiperspirants is recommended as the first therapeutic option. The best evidence here is for aluminium chloride-containing topical preparations; moreover, these are the most commonly used topical therapeutics in care. The NRF (Neue Rezeptur-Formularium) contains, for example, aluminium chloride-containing formulations for the symptomatic treatment of excessive perspiration (hyperhidrosis). The second option recommended is tap water iontophoresis. A third option mentioned in the guideline is injection therapy with botulinum toxin A. Local injection with Clostridium botulinum toxin type A is approved for the treatment of severe, persistent primary axillary hyperhidrosis that has disruptive effects on activities of daily living and cannot be adequately controlled with topical treatment. According to the marketing authorisation, an injection with Clostridium botulinum toxin type A is therefore only considered after failure of a topical therapy and consequently does not represent an adequate comparator for a topical therapy with glycopyrronium.

Taking into account the available evidence, aluminium chloride-containing formulations (at least 15 %) and tap water iontophoresis are thus determined to be equally appropriate treatment options for the severe form of primary axillary hyperhidrosis in the context of topical therapy.

The findings in Annex XII do not restrict the scope of treatment required to fulfil the medical treatment order.

A change in the appropriate comparator therapy requires a resolution by the G-BA linked to the prior review of the criteria according to Chapter 5, Section 6, paragraph 3 Rules of Procedure.

2.1.3 Extent and probability of the additional benefit

In summary, the additional benefit of glycopyrronium is assessed as follows:

An additional benefit is not proven.

Justification:

For the assessment of the additional benefit of glycopyrronium, the pharmaceutical company submits the 1st part of the study *Hyp1-18/2016*. In addition, they present the results of the 2nd part of this study and the results of the *Hyp-02/2015* study.

Hyp1-18/2016 study

The *Hyp1-18/2016* study is a randomised, double-blind, placebo-controlled study that enrolled adults aged 18 to 65 years with severe primary axillary hyperhidrosis, according to a Hyperhidrosis Disease Severity Scale(HDSS) score of 3 or 4. A total of 171 patients were included and randomised in a 1:1 ratio to the treatment arms (glycopyrronium N = 87, placebo N = 84). The duration of the randomised treatment phase with glycopyrronium or placebo was 4 weeks (1st part of the study). Subsequently, the patients could participate in an open 1-arm extension study (2nd part of the study). The additional treatment duration of 68 weeks planned in the extension study was followed by a follow-up phase of 4 weeks. The extension study also included additional, newly recruited patients who were also treated for 72 weeks and then followed up for 4 weeks. The primary endpoint was the absolute change in sweat production.

Study Hyp-02/2015 (presented additionally)

The *Hyp-02/2015* study is a randomised, double-blind, placebo-controlled study in which glycopyrronium was used at 3 different doses (0.5%, 1% and 2%). The patients included were aged between 18 and 65 years. In addition to patients with severe primary axillary hyperhidrosis, those with moderate disease severity could also be included, according to an HDSS score of 2 to 4. The treatment period was 2 weeks, followed by 1 week of follow-up.

The studies presented *(Hyp1-18/2016* and *Hyp-02/2015*) each compared glycopyrronium to placebo. Thus, no conclusions on the additional benefit of glycopyrronium compared to an active intervention of the appropriate comparator therapy can be derived from these data. In addition, the randomised treatment duration of 4 weeks *(Hyp1 18/2016*) and 2 weeks *(Hyp-02/2015*) in both studies is too short to derive an additional benefit in the present indication.

Data for an indirect comparison of glycopyrronium versus an intervention of the appropriate comparator therapy were not submitted by the pharmaceutical entrepreneur.

In the overall assessment, no data suitable for the benefit assessment are available. The additional benefit of glycopyrronium compared to the appropriate comparator therapy is therefore not proven in the indication "for the topical treatment of adults with severe primary axillary hyperhidrosis".

2.1.4 Summary of the assessment

The present assessment concerns the benefit assessment of the new medicinal product Axhidrox with the active ingredient glycopyrronium.

Glycopyrronium is approved for the topical treatment of severe primary axillary hyperhidrosis in adults.

The G-BA determined an aluminium chloride-containing formulation (at least 15 %) or tap water iontophoresis as an appropriate comparator therapy.

For the target population to be considered, the pharmaceutical company submits data from the placebo-controlled studies *Hyp1-18/2016* and *Hyp-02/2015* respectively. Due to the lack of comparison with an active intervention of the appropriate comparator therapy, no statements on the additional benefit of glycopyrronium can be derived from these data. In addition, the randomised treatment duration of 4 weeks *(Hyp1 18/2016*) and 2 weeks *(Hyp-02/2015*) of the studies is too short to derive an additional benefit.

In the overall assessment, the additional benefit of glycopyrronium compared to the appropriate comparator therapy is not proven.

2.2 Number of patients or demarcation of patient groups eligible for treatment

The information on the number of patients is based on the target population in statutory health insurance (SHI).

The information provided by the pharmaceutical company in the dossier is subject to uncertainty due to methodological weaknesses in the studies used. Taking into account an adjusted range of the prevalence rate (own calculations), this results in a number of 73,000 to 704,000 patients with severe primary axillary hyperhidrosis in the SHI target population.

2.3 Requirements for a quality-assured application

The requirements in the product information are to be taken into account.

2.4 Treatment costs

The treatment costs are based on the contents of the product information and the information listed in the LAUER-TAXE® (last revised: 1 January 2023).

Unlike approved proprietary medicinal products, prescription medicinal products in the outpatient sector are subject to the regulation of Section 135 SGB V. Prescriptions containing aluminium chloride for the treatment of hyperhidrosis were already established in health care before 1 January 1989, which is why they can in principle be provided at the expense of the SHI system even without carrying out an assessment procedure according to Section 135 SGB V. The ingredients of the aluminium chloride prescriptions are not subject to prescription according to the Pharmaceutical Price Ordinance (AMVV), which is why these prescriptions are subject to the legal prescription exclusion according to Section 31 paragraph 1 sentence 1, and Section 34 paragraph 1 sentence 1 SGB V.

The appropriate comparator therapy comprises pharmacy-only, non-prescription medicinal products (aluminium chloride-containing formulation). These are excluded from care according to Section 31 SGB V. An exceptional circumstance according to Section 34 paragraph 1 sentence 2 SGB V does not exist. Thus, the prescription of these medicinal products is not allowed at the expense of the statutory health insurance. Therefore, the cost illustration for these preparations is omitted in the resolution according to Section 35a paragraph 3 SGB V.

An iontophoresis device is required to perform tap water iontophoresis. This is a tool. In the SHI list of medical aids, tap water iontophoresis devices are listed in product group 9 (monophasic ionto-phoresis device ionto+ (Pos. no. 09.30.01.1001))[2].
No uniform reimbursement amount can be quantified for tap water iontophoresis, since the actual costs incurred are regulated differently according to Section 127 paragraph 1 SGB V.

Treatment period:

If no maximum treatment duration is specified in the product information, the treatment duration is assumed to be one year (365 days), even if the actual treatment duration varies from patient to patient and/or is shorter on average. The time unit "days" is used to calculate the "number of treatments/ patient/ year", time intervals between individual treatments and the maximum treatment duration, if specified in the product information.

The costs for the first year of treatment are shown for the cost representation in the resolution.

In general, initial induction regimens are not taken into account for the cost representation, since the present indication is a chronic disease with a continuous need for therapy and, as a rule, no new titration or dose adjustment is required after initial titration.

2 https://hilfsmittel.gkv-spitzenverband.de/home/verzeichnis/f4548503-5618-4e6f-abe4-b72e0564f0ac

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Medicinal product to be assessed				
Glycopyrronium	Continuously, 2 x every 7 days Continuously, 1 x daily	104.3 - 365.0	1	104.3 - 365.0
Appropriate comparator therapy				
Tap water iontophoresis	Different from patient to patient			

Consumption:

For the cost representation, only the dosages of the general case are considered. Patient-individual dose adjustments, e.g., because of side effects or comorbidities, are not taken into account when calculating the annual treatment costs.

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Medicinal product to be assessed					
Glycopyrronium	4.4 mg	8.8 mg	4 x 2.2 mg	104.3 - 365.0	417.2 pump actuations each 2.2 mg 1,460.0 pump actuations each 2.2 mg
Appropriate comparator therapy					
Tap water iontophoresis	Different from patient to patient				

Costs:

In order to improve comparability, the costs of the medicinal products were approximated both on the basis of the pharmacy sales price level and also deducting the statutory rebates in accordance with Section 130 and Section 130a SGB V. To calculate the annual treatment costs, the required number of packs of a particular potency was first determined on the basis of consumption. Having determined the number of packs of a particular potency, the costs of the medicinal products were then calculated on the basis of the costs per pack after deduction of the statutory rebates.

Costs of the medicinal products:

Designation of the therapy	Packaging size	Costs (pharmacy sales price)	Rebate Section 130 SGB V	Rebate Section 130a SGB V	Costs after deduction of statutory rebates
Medicinal product to be assessed					
Glycopyrronium 50 g	1 CRE (124 pump actuations)	€ 67.16	€ 1.77	€ 5.30	€ 60.09
Appropriate comparator therapy					
Tap water iontophoresis	incalculable				
Abbreviations: CRE = Cream					

LAUER-TAXE® last revised: 1 January 2023

Costs for additionally required SHI services:

Only costs directly related to the use of the medicinal product are taken into account. If there are regular differences in the necessary use of medical treatment or in the prescription of other services in the use of the medicinal product to be evaluated and the appropriate comparator therapy in accordance with the product information, the costs incurred for this must be taken into account as costs for additionally required SHI services.

Medical treatment costs, medical fee services, and costs incurred for routine examinations (e.g., regular laboratory services such as blood count tests) that do not exceed the standard expenditure in the course of the treatment are not shown.

Because there are no regular differences in the necessary use of medical treatment or in the prescription of other services in the use of the medicinal product to be evaluated and the appropriate comparator therapy in accordance with the product information, no costs for additionally required SHI services had to be taken into account.

2.5 Medicinal products with new active ingredients according to Section 35a, paragraph 3, sentence 4 SGB V that can be used in a combination therapy with Glycopyrronium

According to Section 35a, paragraph 3, sentence 4, the Federal Joint Committee shall designate all medicinal products with new active ingredients that can be used in a combination

therapy with the assessed medicinal product for the therapeutic indication to be assessed on the basis of the marketing authorisation under Medicinal Products Act.

In accordance with Section 2, paragraph 1, sentence 1 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV), only medicinal products containing active ingredients whose effects are not generally known in medical science at the time of initial marketing authorisation are to be considered within the framework of the designation of medicinal products with new active ingredients that can be used in a combination therapy. According to Section 2, paragraph 1, sentence 2 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV), a medicinal product with a new active ingredient is considered to be a medicinal product with a new active ingredient for as long as there is dossier protection for the medicinal product with the active ingredient that was authorised for the first time.

The designation of the combination therapies is based solely on the specifications according to Section 35a, paragraph 3, sentence 4. The G-BA does not conduct a substantive review based on the generally recognised state of medical knowledge. Thus, the designation is not associated with a statement as to the extent to which a therapy with the designated medicinal product with new active ingredient in combination with the medicinal product to be assessed corresponds to the generally recognised state of medical knowledge.

3. Bureaucratic costs calculation

The proposed resolution does not create any new or amended information obligations for care providers within the meaning of Annex II to Chapter 1 VerfO and, accordingly, no bureaucratic costs.

4. Process sequence

At its session on 10 May 2022, the Subcommittee on Medicinal Products determined the appropriate comparator therapy.

On 29 July 2022, the pharmaceutical company submitted a dossier for the benefit assessment of glycopyrronium to the G-BA in due time in accordance with Chapter 5, Section 8, paragraph 1, number 7 VerfO.

By letter dated 1 August 2022 in conjunction with the resolution of the G-BA of 1 August 2011 concerning the commissioning of the IQWiG to assess the benefit of medicinal products with new active ingredients in accordance with Section 35a SGB V, the G-BA commissioned the IQWiG to assess the dossier concerning the active ingredient glycopyrronium.

The dossier assessment by the IQWiG was submitted to the G-BA on 26 October 2022, and the written statement procedure was initiated with publication on the G-BA website on 1 November 2022. The deadline for submitting written statements was 22 November 2022.

The oral hearing was held on 5 December 2022.

In order to prepare a recommendation for a resolution, the Subcommittee on Medicinal Products commissioned a working group (Section 35a) consisting of the members nominated by the leading organisations of the care providers, the members nominated by the SHI umbrella organisation, and representatives of the patient organisations. Representatives of the IQWiG also participate in the sessions.

The evaluation of the written statements received and the oral hearing was discussed at the session of the subcommittee on 10 January 2023, and the proposed resolution was approved.

At its session on 19 January 2023, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal product	10 May 2022	Determination of the appropriate comparator therapy
Working group Section 35a	30 November 2022	Information on written statements received; preparation of the oral hearing
Subcommittee Medicinal product	5 December 2022	Conduct of the oral hearing
Working group Section 35a	14 December 2022; 4 January 2023	Consultation on the dossier assessment by the IQWiG, assessment of the written statement procedure
Subcommittee Medicinal product	10 January 2023	Concluding discussion of the draft resolution
Plenum	19 January 2023	Adoption of the resolution on the amendment of Annex XII AM-RL

Berlin, 19 January 2023

Federal Joint Committee (G-BA)
in accordance with Section 91 SGB V
The Chair

Prof. Hecken