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)
Olopatadine/ mometasone (allergic rhinitis, ≥ 12 years)

of 1 June 2023

Contents

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 is part of the Pharmaceuticals Directive.

2. Key points of the resolution

The relevant date for the start of the benefit assessment procedure was the first placing on the (German) market of the combination of active ingredients olopatadine/ mometasone on 1 December 2022 in accordance with Chapter 5, Section 8, paragraph 1, number 1, sentence 2 of the Rules of Procedure (VerfO) of the G-BA. The pharmaceutical company submitted the final dossier to the G-BA in accordance with Section 4, paragraph 3, number 1 of the Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with Chapter 5, Section 8, paragraph 1, number 1 VerfO on 28 November 2022.

The G-BA commissioned the IQWiG to carry out the assessment of the dossier. The benefit assessment was published on 1 March 2023 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 olopatadine/ mometasone 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 addendum to the benefit assessment (patient numbers) prepared by 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 olopatadine/ mometasone.

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 Olopatadine/ mometasone (Ryaltris) according to the product information

Ryaltris is indicated in adults and adolescents 12 years of age and older for the treatment of moderate to severe nasal symptoms associated with allergic rhinitis.

Therapeutic indication of the resolution (resolution of 01.06.2023):

see the approved therapeutic indication

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

Adults and adolescents aged 12 years and older with moderate to severe nasal symptoms associated with allergic rhinitis

Appropriate comparator therapy:

- Intranasal glucocorticoids (inGCS) in combination with intranasal antihistamine (INAH)

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 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.

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

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. Medicinal products with the following product classes are approved for the present therapeutic indication:

- Intranasal glucocorticoids (inGCS)
- Intranasal antihistamines (INAH)
- Oral antihistamines

on 2. In the present therapeutic indication, no non-medicinal treatments can be considered.

on 3. In the therapeutic indication under consideration here, the following resolutions of the G-BA are available:

- Resolution on an Amendment of the Pharmaceuticals Directive (AM-RL): Annex I - OTC overview (antihistamines and nasal glucocorticoids)

on 4. The generally recognised state of medical knowledge was illustrated by a systematic search for guidelines as well as reviews of clinical studies in the present indication and is presented in the "Research and synopsis of the evidence to determine the appropriate comparator therapy according to Section 35a SGB V".

The scientific-medical societies and the Drugs Commission of the German Medical Association (AkdÄ) were also involved in writing on questions relating to the comparator therapy in the present indication according to Section 35a, paragraph 7 SGB V (see "Information on Appropriate Comparator Therapy").

According to the available evidence intranasal glucocorticoids, non-sedating oral antihistamines or intranasal antihistamines are recommended as first-line therapy for nasal symptoms associated with allergic rhinitis. For moderate to severe symptoms, a combination of an intranasal corticosteroid and an intranasal antihistamine may be considered as first-line therapy.

Thus, the combination of an intranasal glucocorticoid and an intranasal antihistamine is determined to be the appropriate comparator therapy for olopatadine in combination with mometasone. The appropriate comparator therapy comprises pharmacy-only, non-prescription medicinal products. These are categorically excluded from care according to Section 31, paragraph 1, sentence 1 in conjunction with Section 34, paragraph 1, sentence 1 SGB V. Exceptions according to Section 34, paragraph 1, sentence 2 et seqq. are regulated in Annex I to the AM-RL. Prescribing these medicinal products at the expense of the statutory health insurance is therefore only permissible in exceptional cases in accordance with the regulations in Annex I to the AM-RL.

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

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 olopatadine/ mometasone is assessed as follows:

An additional benefit is not proven for the treatment of adults and adolescents aged 12 years and older with moderate to severe nasal symptoms associated with allergic rhinitis.

Justification:

For the assessment of the additional benefit of olopatadine/ mometasone in the present indication, the pharmaceutical company therefore submits the GSP301-PoC study.

The GSP301-PoC study is a single-centre, double-blind, 5-arm randomised controlled trial (RCT). Adults between 18 and 65 years of age with seasonal allergic rhinitis for at least 2 years, a positive skin prick test for ragweed pollen and at least moderately pronounced nasal symptoms at the time of screening in the environmental exposure chamber were enrolled. A total of 180 patients who were randomised to the treatment arms in a 1:1:1:1:1 ratio were enrolled in the study. For the benefit assessment, the pharmaceutical company submits the results of the intervention arm (n = 36) with the fixed combination of olopatadine/ mometasone and the control arm (n = 36) with the fixed combination of azelastine/ fluticasone. The GSP301-PoC study consisted of a screening phase, a 14-day treatment phase and a final visit on day 15. The allergic symptoms were triggered by exposure to ragweed allergens in an environmental exposure chamber. The total of 4 sessions in the chamber took place the day before the start of treatment, on the treatment day and on days 14 and 15 after the start of treatment. The primary endpoint of the study was the mean change in Total Nasal Symptoms Score (TNSS) from day 1 (prior to the start of treatment) to the final visit on day 15.
The GSP301-PoC study is unsuitable for the assessment of the additional benefit of olopatadine/ mometasone over the appropriate comparator therapy.
In the GSP301-PoC study, symptoms of seasonal allergic rhinitis were artificially induced with ragweed allergens in an environmental exposure chamber. However, exposure in an environmental exposure chamber does not represent an everyday situation with natural pollen exposure characterised by high variability. Neither the allergen concentration used in the study nor the duration and frequency of exposure are comparable to natural exposure. Furthermore, it is unclear whether the moderate to severe symptoms observed at the start of the study after artificial exposure are equivalent to the symptom severity after natural exposure. Overall, it is thus unclear whether the results from a study with such artificial exposure can be transferred to the situation of natural allergen exposure and thus, to everyday care in Germany.
In addition, the treatment duration of the GSP301-PoC study was only 14 days. The final visit took place on day 15, and follow-up beyond this period was not planned. Treatment with olopatadine/ mometasone is for the treatment of a chronic disease. A study duration of only 14 days is not sufficient for the assessment of the additional benefit in the therapeutic indication "treatment of moderate to severe nasal symptoms associated with allergic rhinitis". A minimum duration of 24 weeks is generally considered necessary for the early benefit assessment for chronic diseases. A study duration of 2 weeks is too short to assess effects of olopatadine/ mometasone on patient-relevant endpoints such as symptom relief and its sustainability or the occurrence of adverse events. Furthermore, the GSP301-PoC study has limitations as it only includes patients with seasonal allergic rhinitis and exposure to ragweed

allergens. No data are available for other allergens or for patients with persistent allergic rhinitis.

Overall assessment/ conclusion

In summary, the study submitted by the pharmaceutical company is unsuitable to derive an additional benefit of olopatadine/ mometasone over the appropriate comparator therapy "intranasal glucocorticoid (inGCS) in combination with intranasal antihistamine (INAH)". The study duration of only 14 days is considered too short in the randomised comparative phase of the study for the early benefit assessment for a chronic disease. In addition, the transferability of results obtained under artificial induction to the medical treatment situation under natural exposure is unclear. An additional benefit is not proven.

2.1.4 Summary of the assessment

The present assessment concerns the benefit assessment of the new medicinal product Ryaltris with the combination of active ingredients olopatadine/ mometasone.

Olopatadine/ mometasone is approved for the treatment of adults and adolescents aged 12 years and older with moderate to severe nasal symptoms associated with allergic rhinitis. The G-BA determined "intranasal glucocorticoid (inGCS) in combination with intranasal antihistamine (INAH)" as the appropriate comparator therapy.

Along with the dossier for the assessment of additional benefit, the pharmaceutical company submits the results of the single-centre, double-blind, 5-arm RCT GSP301-PoC for the intervention arm (n = 36) with the fixed combination of olopatadine/ mometasone and for the control arm (n = 36) with the fixed combination of azelastine/ fluticasone. The GSP301-PoC study is unsuitable for deriving an additional benefit of olopatadine/ mometasone over the appropriate comparator therapy. The study duration of only 14 days is considered too short in the randomised comparative phase of the study for the early benefit assessment for a chronic disease. In addition, the transferability of results obtained under artificial induction to the medical treatment situation under natural exposure is unclear.

Overall, the additional benefit of olopatadine/ mometasone over the appropriate comparator therapy is not proven for adults and adolescents aged 12 years and older with moderate to severe nasal symptoms associated with allergic rhinitis.

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.

The G-BA bases its resolution on the calculation of the patient numbers submitted by IQWiG in the addendum. The range includes patients 12 years and older with moderate to severe nasal symptoms associated with allergic rhinitis. The lower limit is formed by patients who have been diagnosed with allergic rhinitis. For the upper limit, it is assumed that the prevalence estimate refers to the general population (i.e. without restriction to those in medical treatment). The sources used to calculate the percentage values are subject to various uncertainties.

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: 15 May 2023).

According to Annex I of the Pharmaceuticals Directive, non-prescription antihistamines in the present therapeutic indication are only prescribable at the expense of the statutory health insurance for the treatment of persistent allergic rhinitis associated with severe symptomatology for which topical nasal treatment with glucocorticoids is insufficient. Similarly, the prescribability of non-prescription glucocorticoids (topical nasal) is limited to the treatment of persistent allergic rhinitis associated with severe symptomatology (Annex I of the Pharmaceuticals Directive). Thus, the reimbursability of non-prescription antihistamines and glucocorticoids (topical nasal) is not given for a part of the patients in the therapeutic indication with moderately severe nasal and/or intermittent symptoms associated with allergic rhinitis. In contrast, prescription antihistamines and glucocorticoids can be prescribed without restriction within the scope of their marketing authorisation.

When deriving the costs for intranasal corticosteroids, budesonide from the reference price group "Glucocorticoids, inhaled nasal 1" is presented as an example.

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 for the maximum treatment duration, if specified in the product information.

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Medicinal product to be assessed				
Olopatadine mometasone furoate	Continuously, 2 x daily 4 SD	365	1	365
Appropriate comparator therapy				
Intranasal antihistamines (INAH)				
Azelastine	Continuously, 2 x daily 2 SD	365	1	365
Levocabastine[2]	Continuously, 2 x daily 4 SD	365	1	365

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Intranasal corticosteroids (INCS)				
Budesonide	Continuously, 2 x daily 2 SD	365	1	365
Fixed combination of intranasal antihistamine and intranasal corticosteroid				
Azelastine/ fluticasone	Continuously, 2 x daily 2 SD	365	1	365

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.
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.

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					
Olopatadine mometasone furoate	25 µg / 600 µg	200 µg / 4800 µg	8 x 25 µg/ 600 µg	365	2,920 x 25 µg/ 600 µg
Appropriate comparator therapy					
Intranasal antihistamines (INAH)					
Azelastine	140 µg	560 µg	4 x 140 µg	365	1,460 x 140 µg
Levocabastine	100 µg	400 µg	8 x 50 µg	365	2920 x 50 µg
Intranasal corticosteroids (INCS)					
Budesonide	100 µg	200 µg	4 x 50 µg	365	1,460 x 50 µg
Fixed combination of INAH + INCS					
Azelastine/ fluticasone	125 µg/ 50 µg	500 µg / 200 µg	4 x 125 µg/ 50 µg	365	1,460 x 125 µg / 50 µg

Costs:

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					
Olopatadine mometasone furoate 5 µg /600 µg	240 SD	€ 37.84	€ 2.00	€ 2.52	€ 33.32
Appropriate comparator therapy					
Azelastine 140 µg	120 SD	€ 26.99	€ 2.00	€ 2.05	€ 22.94
Levocabastine 50 µg[2]	50 SD	€ 8.58	€ 2.00	€ 0.71	€ 5.87
Budesonide 50 µg [3]	400 SD	€ 30.83	€ 2.00	€ 1.55	€ 27.28
Azelastine/ fluticasone 125 µg /50 µg	120 SD	€ 37.90	€ 2.00	€ 2.53	€ 33.37
Abbreviations: SD = single dose					

LAUER-TAXE® last revised: 15 May 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] OTC: According to Annex I of the Pharmaceuticals Directive in the present therapeutic indication, only prescribable at the expense of the statutory health insurance in cases of persistent allergic rhinitis associated with severe symptomatology for which topical nasal treatment with glucocorticoids is insufficient.
[3] Fixed reimbursement rate

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 Olopatadine/ mometasone

According to Section 35a, paragraph 3, sentence 4, the G-BA designates 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 11 May 2021, the Subcommittee on Medicinal Products determined the appropriate comparator therapy.

On 28 November 2022, the pharmaceutical company submitted a dossier for the benefit assessment of olopatadine/ mometasone to the G-BA in due time in accordance with Chapter 5 Section 8, paragraph 1, number 1, sentence 2 VerfO.

By letter dated 28 November 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 olopatadine/ mometasone.

The dossier assessment by the IQWiG was submitted to the G-BA on 27 February 2023, and the written statement procedure was initiated with publication on the G-BA website on 1 March 2023. The deadline for submitting statements was 22 March 2023.

The oral hearing was held on 12 April 2023.

By letter dated 27 April 2023, the IQWiG was commissioned with a supplementary assessment. The addendum (patient numbers) prepared by IQWiG was submitted to the G-BA on 12 May 2023.

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 23 May 2023, and the proposed resolution was approved.

At its session on 1 June 2023, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal products	11 May 2021	Determination of the appropriate comparator therapy
Working group Section 35a	5 April 2023	Information on written statements received; preparation of the oral hearing
Subcommittee Medicinal products	12 April 2023	Conduct of the oral hearing
Subcommittee Medicinal products	3 May 2023	Commissioning of the IQWiG with the supplementary assessment of documents (patient numbers)
Working group Section 35a	26 April 2023 10 May 2023 17 May 2023	Consultation on the dossier assessment by the IQWiG, assessment of the written statement procedure
Subcommittee Medicinal products	23 May 2023	Concluding discussion of the draft resolution
Plenum	1 June 2023	Adoption of the resolution on the amendment of Annex XII AM-RL

Berlin, 1 June 2023

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

Prof. Hecken