Olopatadine/mometasone (allergic rhinitis)

Benefit assessment according to §35a SGB V[1]

EXTRACT

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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
EAACI	European Academy of Allergy and Clinical Immunology
EMA	European Medicines Agency
FDA	Food and Drug Administration
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
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)
SPC	Summary of Product Characteristics
TNSS	total nasal symptom score

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 combination olopatadine/mometasone furoate. 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 29 November 2022.

Research question

The aim of the present report is to assess the added benefit of olopatadine/mometasone furoate in comparison with an intranasal glucocorticoid in combination with an intranasal antihistamine as appropriate comparator therapy (ACT) in adults and adolescents 12 years of age and older for the treatment of moderate to severe nasal symptoms associated with allergic rhinitis.

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

Table 2: Research question of the benefit assessment of olopatadine/mometasone furoate

Therapeutic indication	**ACT**[a]
Adults and adolescents 12 years of age and older for the treatment of moderate to severe nasal symptoms associated with allergic rhinitis[b]	Intranasal glucocorticoid (INCS) in combination with intranasal antihistamine (INAH)
a. Presented is the ACT specified by the G-BA. b. It is assumed that the nasal symptoms associated with allergic rhinitis in patients in the present therapeutic indication could not be adequately treated with an INCS and therefore require combination therapy. ACT: appropriate comparator therapy G-BA: Federal Joint Committee; INAH: intranasal antihistamine; INCS: intranasal glucocorticoid	

The company followed the G-BA's specification of the ACT.

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 are used for the derivation of added benefit.

Results

The check of completeness of the study pool did not reveal any relevant study for assessing the added benefit of olopatadine/mometasone furoate in comparison with the ACT.

The company used the RCT GSP301-PoC for its assessment. In addition, the company presented the results of the RCT GSP301-306 as supplementary information.

The data presented by the company are unsuitable to draw conclusions on the added benefit of olopatadine/mometasone furoate in comparison with the ACT.

Evidence presented by the company – study GSP301-PoC

The GSP301-PoC study is a single-centre, double-blind, 5-arm RCT on the comparison of olopatadine/mometasone furoate with azelastine/fluticasone propionate, which was conducted using an environmental exposure chamber.

The study included adults aged 18 to 65 years with a history of seasonal allergic rhinitis for at least 2 years who had a positive skin prick test result for ragweed pollen, and at least moderate nasal symptoms in the environmental exposure chamber at screening.

A total of 180 patients participated in the study, who were randomized to the treatment arms in a 1:1:1:1:1 ratio. For the benefit assessment, the company used the intervention arm (n = 36) with the fixed combination of olopatadine/mometasone furoate in the dosage in accordance with the Summary of Product Characteristics (SPC), and the control arm (n = 36) with the fixed combination of azelastine/fluticasone propionate. The GSP301-PoC study consisted of a screening phase, a 14-day treatment phase and an end-of-study 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 treatment initiation, the day of treatment initiation, and on days 14 and 15 after treatment initiation.

The primary outcome of the study was the mean change in total nasal symptom score (TNSS) from day 1 (before treatment initiation) to the end-of-study visit on day 15.

GSP301-PoC study is unsuitable for the benefit assessment

Transferability of results from an environmental exposure chamber is unclear

In the GSP301-PoC study, symptoms of seasonal allergic rhinitis were artificially induced in an environmental exposure chamber with ragweed allergens.

The exposure in an environmental exposure chamber does not represent an everyday situation with natural pollen exposure, which is characterized by high variability. While standardized conditions exist in the chamber, natural exposure is individual for each patient and cannot be sufficiently quantified. Therefore, 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 – corresponding to the therapeutic indication to be assessed – the moderate to severe symptoms after artificial exposure observed at baseline can be equated 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 health care in Germany.

As the allergic symptoms in the GSP301-PoC study in patients with seasonal allergic rhinitis were exclusively caused by allergen exposure in an environmental exposure chamber, no conclusions on the added benefit of olopatadine/mometasone furoate in comparison with the ACT are possible on the basis of this study.

Duration of the GSP301-PoC study is not sufficient

The treatment duration in the GSP301-PoC study was only 14 days. The end-of-study visit took place on day 15, and follow-up beyond this period was not planned.

Treatment with olopatadine/mometasone furoate is for the treatment of a chronic condition. As a rule, RCTs with a minimum duration of 24 weeks are used for the benefit assessment in this case. Although shorter studies are conceivable in the present therapeutic indication, e.g. for short-term use in seasonal allergic rhinitis, a study duration of 2 weeks is nevertheless too short to be able to assess effects of olopatadine/mometasone furoate on patient-relevant outcomes of both symptom relief and the occurrence of adverse events.

No information on the patients' pretreatment

The research question of the benefit assessment includes patients who could not be adequately treated with an intranasal glucocorticoid in the present therapeutic indication and therefore require combination therapy. However, inadequate response to intranasal glucocorticoid monotherapy was not an inclusion criterion for the GSP301-PoC study. It is therefore not possible to assess whether all patients in the GSP301-PoC study had received sufficient pretreatment and thus correspond to the research question of the benefit assessment.

Study GSP301-306 used by the company as supporting evidence is unsuitable

The company presented the results of the multi-centre, open-label, randomized, parallel GSP301-306 study as supplementary information. In the study, 278 adults with seasonal allergic rhinitis were randomized to treatment with olopatadine/mometasone furoate or a fixed combination of azelastine (intranasal antihistamine) and mometasone furoate (intranasal glucocorticoid). The treatment duration was 14 days. As the fixed combination of azelastine/mometasone furoate is not approved in Germany, the company did not use the study to assess the added benefit in comparison with the ACT. The company's approach is appropriate.

Results on added benefit

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

Probability and extent of added benefit[3]

Table 3 shows a summary of probability and extent of the added benefit of olopatadine/mometasone furoate.

Table 3: Olopatadine/mometasone furoate – probability and extent of added benefit

Therapeutic indication	ACT[a]	Probability and extent of added benefit
Adults and adolescents 12 years of age and older for the treatment of moderate to severe nasal symptoms associated with allergic rhinitis[b]	Intranasal glucocorticoid (INCS) in combination with intranasal antihistamine (INAH)	Added benefit not proven

a. Presented is the ACT specified by the G-BA.
b. It is assumed that the nasal symptoms associated with allergic rhinitis in patients in the present therapeutic indication could not be adequately treated with an INCS and therefore require combination therapy.

ACT: appropriate comparator therapy G-BA: Federal Joint Committee; INAH: intranasal antihistamine; INCS: intranasal glucocorticoid

The G-BA decides on the added benefit.

[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].

I 2 Research question

The aim of the present report is to assess the added benefit of olopatadine/mometasone furoate in comparison with an intranasal glucocorticoid in combination with an intranasal antihistamine as ACT in adults and adolescents 12 years of age and older for the treatment of moderate to severe nasal symptoms associated with allergic rhinitis.

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

Table 4: Research question of the benefit assessment of olopatadine/mometasone furoate

Therapeutic indication	**ACT**[a]
Adults and adolescents 12 years of age and older for the treatment of moderate to severe nasal symptoms associated with allergic rhinitis[b]	Intranasal glucocorticoid (INCS) in combination with intranasal antihistamine (INAH)
a. Presented is the ACT specified by the G-BA. b. It is assumed that the nasal symptoms associated with allergic rhinitis in patients in the present therapeutic indication could not be adequately treated with an INCS and therefore require combination therapy. ACT: appropriate comparator therapy G-BA: Federal Joint Committee; INAH: intranasal antihistamine; INCS: intranasal glucocorticoid	

The company followed the G-BA's specification of the ACT.

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 are used for the derivation of added benefit (see also Chapter I 3). This departs from the inclusion criteria used by the company, which applied no restrictions regarding minimum 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 olopatadine/mometasone furoate (status: 19 October 2022)
- bibliographical literature search on olopatadine/mometasone furoate (last search on 19 October 2022)
- search in trial registries/trial results databases for studies on olopatadine/mometasone furoate (last search on 19 October 2022)
- search on the G-BA website for olopatadine/mometasone furoate (last search on 20 October 2022)

To check the completeness of the study pool:

- search in trial registries for studies on olopatadine/mometasone furoate (last search on 12 December 2022); for search strategies, see I Appendix A of the full dossier assessment

No relevant study was identified from the check.

In contrast, the company identified the RCT GSP301-PoC [3] and used it to assess the added benefit of olopatadine/mometasone furoate. In addition, the company presented the results of the RCT GSP301-306 [4,5] as supplementary information, but did not use them to derive the added benefit.

The data presented by the company are unsuitable to draw conclusions on the added benefit of olopatadine/mometasone furoate in comparison with the ACT. This is justified below.

Evidence provided by the company

Study GSP301-PoC

The GSP301-PoC study is a single-centre, double-blind, 5-arm RCT on the comparison of olopatadine/mometasone furoate with azelastine/fluticasone propionate, which was conducted using an environmental exposure chamber.

The study included adults aged 18 to 65 years with a history of seasonal allergic rhinitis for at least 2 years who had a positive skin prick test result for ragweed pollen, and at least moderate nasal symptoms in the environmental exposure chamber at screening.

A total of 180 patients participated in the study, who were randomized in a 1:1:1:1:1 ratio to the following treatments: fixed combination of olopatadine/mometasone furoate (2 arms with different dosages), fixed combination of azelastine/fluticasone propionate, olopatadine monotherapy, and placebo. For the benefit assessment, the company used the olopatadine/mometasone furoate intervention arm (n = 36) with the dosage in compliance with the SPC [6], and the azelastine/fluticasone propionate control arm (n = 36) [7].

The GSP301-PoC study consisted of a screening phase, a 14-day treatment phase and an end-of-study visit on day 15. The study was conducted outside the pollen season. Instead, the allergic symptoms were triggered by exposure to ragweed allergens in an environmental exposure chamber. A total of 4 sessions were held in the chamber: The first session took place the day before treatment initiation and served to identify those patients who developed moderate to severe nasal symptoms as a result of allergen exposure and to induce sensitization of the mucous membranes to the allergen (priming). The second session took place on the day of treatment initiation. The last 2 sessions took place on days 14 (post-dosing priming) and 15 after treatment initiation to examine the symptoms after the 14-day treatment. The sessions lasted 6 hours each, 10 hours on the day of treatment initiation.

Before and during the allergen exposure in the chamber, the patients recorded their nasal and ocular symptoms at regular intervals and answered a questionnaire to assess their quality of life.

The primary outcome of the study was the mean change in TNSS from day 1 (before treatment initiation) to the end-of-study visit on day 15.

GSP301-PoC study presented by the company is unsuitable for the benefit assessment

Transferability of results from an environmental exposure chamber is unclear

In the GSP301-PoC study, symptoms of seasonal allergic rhinitis were artificially induced in an environmental exposure chamber. Ragweed allergens with an average concentration of 3500 ± 500 particles/m^3 were used for this purpose. Patients in the study were exposed to allergens at the beginning and at the end of the 14-day treatment phase, in each case on 2 consecutive days for a period of at least 6 hours. No exposure took place on the further 12 treatment days between the sessions in the chamber.

The exposure in an environmental exposure chamber does not represent an everyday situation with natural pollen exposure, which is characterized by high variability. While standardized conditions exist in the chamber, natural exposure is individual for each patient and cannot be sufficiently quantified [8]. Therefore, 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 – corresponding to the therapeutic indication to be assessed – the moderate to severe symptoms after artificial exposure observed at baseline

can be equated 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 health care in Germany. The company did not comment on the transferability of the results or on the comparability of the exposure in the chamber to that in a natural environment.

The guidelines issued by the European Medicines Agency (EMA) and the Food and Drug Administration (FDA) also provide for environmental exposure chamber-only studies only for pharmacodynamic studies [9,10]. Similarly, the European Academy of Allergy and Clinical Immunology (EAACI) critically discusses the comparability of the observed treatment effects in an environmental exposure chamber to the effects under natural conditions, suggesting a hybrid study design, for example [8].

As the allergic symptoms in the GSP301-PoC study in patients with seasonal allergic rhinitis were exclusively caused by allergen exposure in an environmental exposure chamber, no conclusions on the added benefit of olopatadine/mometasone furoate in comparison with the ACT are possible on the basis of this study.

Duration of the GSP301-PoC study is not sufficient

The treatment duration in the GSP301-PoC study was only 14 days. The end-of-study visit took place on day 15, and follow-up beyond this period was not planned.

Treatment with olopatadine/mometasone furoate is for the treatment of a chronic condition. As a rule, RCTs with a minimum duration of 24 weeks are used for the benefit assessment in this case [1,11]. The therapeutic indication of olopatadine/mometasone furoate comprises both intermittent (seasonal) and persistent forms of allergic rhinitis, whereby even in the intermittent form there is usually repeated use within a longer period of time [9]. The SPC does not contain any limitation of the duration of use. Shorter studies are conceivable for short-term use, e.g. in seasonal allergic rhinitis. However, a study duration of 2 weeks is nevertheless too short to be able to assess effects of olopatadine/mometasone furoate on patient-relevant outcomes of both symptom relief and the occurrence of adverse events.

No information on the patients' pretreatment

The research question of the benefit assessment includes patients who could not be adequately treated with an intranasal glucocorticoid in the present therapeutic indication and therefore require combination therapy. The approval of the comparator azelastine/fluticasone propionate used in the GSP301-PoC study is also restricted to patients with the corresponding pretreatment. However, inadequate response to intranasal glucocorticoid monotherapy was not an inclusion criterion for the GSP301-PoC study. An inclusion criterion in this regard was only a history of seasonal allergic rhinitis for at least 2 years and at least moderate nasal symptoms at screening. Furthermore, the presented study

documents do not contain any information on the previous medication of the patients. It is therefore not possible to assess whether all patients in the GSP301-PoC study had received sufficient pretreatment and thus correspond to the research question of the benefit assessment.

Study GSP301-306 used by the company as supporting evidence

The company presented the results of the multi-centre, open-label, randomized, parallel GSP301-306 study as supplementary information. In the study, 278 adults with seasonal allergic rhinitis were randomized to treatment with olopatadine/mometasone furoate or a fixed combination of azelastine (intranasal antihistamine) and mometasone furoate (intranasal glucocorticoid). The treatment duration was 14 days. As the fixed combination of azelastine/mometasone furoate is not approved in Germany, the company did not use the study to assess the added benefit in comparison with the ACT. The company's approach is appropriate.

Summary

All things considered, no data suitable for answering the research question of this benefit assessment are available.

For the GSP301-PoC RCT presented by the company, which exclusively investigated patients with seasonal rhinitis after exposure to ragweed pollen, on the one hand, this is due to the artificial allergen exposure, which took place in an environmental exposure chamber. On the other hand, the study duration is too short for the benefit assessment. Furthermore, no information is available on whether all patients correspond to the research question of the benefit assessment with regard to pretreatment. The company itself did not derive any added benefit of olopatadine/mometasone furoate on the basis of the results of the GSP301-PoC study.

No data are available for other allergens or for persistent allergic rhinitis, which is also covered by the present research question.

I 4 Results on added benefit

No suitable data are available for assessing the added benefit of olopatadine/mometasone furoate in comparison with the ACT in adults and adolescents 12 years of age and older for the treatment of moderate to severe nasal symptoms associated with allergic rhinitis. There is no hint of an added benefit of olopatadine/mometasone furoate in 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 olopatadine/mometasone furoate in comparison with the ACT.

Table 5: Olopatadine/mometasone furoate – probability and extent of added benefit

Therapeutic indication	**ACT[a]**	**Probability and extent of added benefit**
Adults and adolescents 12 years of age and older for the treatment of moderate to severe nasal symptoms associated with allergic rhinitis[b]	Intranasal glucocorticoid (INCS) in combination with intranasal antihistamine (INAH)	Added benefit not proven
a. Presented is the ACT specified by the G-BA. b. It is assumed that the nasal symptoms associated with allergic rhinitis in patients in the present therapeutic indication could not be adequately treated with an INCS and therefore require combination therapy. ACT: appropriate comparator therapy G-BA: Federal Joint Committee; INAH: intranasal antihistamine; INCS: intranasal glucocorticoid		

The assessment described above concurs with that of the company.

The G-BA decides on the added benefit.

I 6 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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