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
Delgocitinib (moderate to severe chronic hand eczema)

of 3 April 2025

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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 all 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 active ingredient delgocitinib on 15 October 2024 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 14 October 2024.

The G-BA commissioned the IQWiG to carry out the assessment of the dossier. The benefit assessment was published on 15 January 2025 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 delgocitinib 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, and the statements submitted in the written statement and oral hearing procedure, as well of the addendum drawn up by the IQWiG on the benefit assessment. 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 delgocitinib.

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 Delgocitinib (Anzupgo) in accordance with the product information

Anzupgo is indicated for the treatment of moderate to severe chronic hand eczema (CHE) in adults for whom topical corticosteroids are inadequate or inappropriate.

Therapeutic indication of the resolution (resolution of 03.04.2025):

see the approved therapeutic indication

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

Adults with moderate to severe chronic hand eczema for whom topical corticosteroids are inadequate or inappropriate

Appropriate comparator therapy for delgocitinib:

- Individualised therapy consisting of topical and systemic therapy

Criteria according to Chapter 5 Section 6 of the Rules of Procedure of the G-BA and Section 6 paragraph 2 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV):

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] General Methods, version 7.0 from 19.09.2023. Institute for Quality and Efficiency in Health Care (IQWiG), Cologne.

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.

According to Section 6, paragraph 2, sentence 2 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV), the determination of the appropriate comparator therapy must be based on the actual medical treatment situation as it would be without the medicinal product to be assessed. According to Section 6, paragraph 2, sentence 3 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV), the G-BA may exceptionally determine the off-label use of medicinal products as an appropriate comparator therapy or as part of the appropriate comparator therapy if it determines by resolution on the benefit assessment according to Section 7, paragraph 4 that, according to the generally recognised state of medical knowledge, this is considered a therapy standard in the therapeutic indication to be assessed or as part of the therapy standard in the medical treatment situation to be taken into account according to sentence 2, and

1. for the first time, a medicinal product approved in the therapeutic indication is available with the medicinal product to be assessed,
2. according to the generally recognised state of medical knowledge, the off-label use is generally preferable to the medicinal products previously approved in the therapeutic indication, or
3. according to the generally recognised state of medical knowledge, the off-label use for relevant patient groups or indication areas is generally preferable to the medicinal products previously approved in the therapeutic indication.

An appropriate comparator therapy may also be non-medicinal therapy, the best possible add-on therapy including symptomatic or palliative treatment, or monitoring wait-and-see approach.

<u>Justification based on the criteria set out in Chapter 5 Section 6, paragraph 3 VerfO and Section 6, paragraph 2 AM-NutzenV:</u>

On 1. In addition to delgocitinib, only the active ingredient alitretinoin is explicitly approved for the treatment of adult patients with chronic hand eczema in this therapeutic indication: "Indicated in adults with severe chronic hand eczema that does not respond to treatment with potent topical corticosteroids."

On 2. UV treatments (UVA/NB-UVB) are eligible as non-medicinal treatment, but UVA1 is ineligible as it is not a reimbursable treatment.

On 3. In the therapeutic indication under consideration here, no resolutions of the G-BA are available.

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 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 therapeutic indication according to Section 35a, paragraph 7 SGB V.

Only the active ingredient alitretinoin is explicitly approved for the treatment of chronic hand eczema. However, this is only approved for the treatment of severe chronic hand eczema that does not respond to treatment with potent topical corticosteroids (TCS). No active ingredients are explicitly approved in Germany for the treatment of the moderately severe form of chronic hand eczema.

Chronic hand eczema can be divided into several aetiological (irritant contact eczema, allergic contact dermatitis, atopic hand eczema, protein contact dermatitis) and clinical (hyperkeratotic hand eczema, acute recurrent vesicular hand eczema, nummular hand eczema, pulpitis) subentities.

Current guidelines indicate that, in addition to alitretinoin, class II to IV TCS, phototherapy and systemic glucocorticoids can be considered for the treatment of all subentities of chronic hand eczema as part of patient-individual therapy.

The subentity "atopic hand eczema" is to be assigned to the indication of atopic dermatitis, so that in addition to the therapy options mentioned, the topical calcineurin inhibitors (tacrolimus, pimecrolimus) and dupilumab are also an option for the treatment of atopic eczema. The active ingredients abrocitinib, baricitinib, lebrikizumab, tralokinumab and upadacitinib are new therapy options for the treatment of moderate-to-severe atopic dermatitis, the significance of which cannot yet be conclusively assessed, particularly with regard to the treatment of chronic hand eczema. Therefore, based on the generally recognised state of medical knowledge, abrocitinib, baricitinib, lebrikizumab, tralokinumab and upadacitinib are not determined as appropriate comparator therapy for patients with atopic hand eczema for the present resolution. If therapy with a TCS (if applicable in higher potency) is an option, this can also be considered as part of the therapy. Keeping the inadequate (prior) therapy unchanged does not correspond to the appropriate comparator therapy. Systemic glucocorticoids should only be used in the short term as part of flare therapy.

Taking into account the available evidence and the recommendations, an individualised therapy consisting of topical and systemic therapy is determined as the appropriate comparator therapy, depending on the manifestation of the disease, subentity and taking into account the previous therapy. The respective authorisation status of the medicinal products must be taken into account.

Editorial note: The term "individualised therapy" is used instead of previously used terms such as "patient-individual therapy" or "therapy according to doctor's instructions". This harmonises the terms used in the European assessment procedures (EU-HTA).

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 delgocitinib is assessed as follows:

Based on the DELTA FORCE study submitted by the pharmaceutical company for the benefit assessment, a separate assessment is conducted for patients for whom alitretinoin as monotherapy is the appropriate patient-individual therapy and patients for whom a therapy other than alitretinoin as monotherapy is the appropriate patient-individual therapy.

The additional benefit is not proven for adults with severe chronic hand eczema for whom alitretinoin as monotherapy is the appropriate patient-individual therapy option, or for adults for whom alitretinoin as monotherapy is not the appropriate patient-individual therapy option.

Justification:

For the proof of additional benefit of delgocitinib, the pharmaceutical company presented the DELTA FORCE study, which is a completed, partially blinded, multicentre RCT comparing delgocitinib with alitretinoin.

The continuation of the previous non-medicinal basic skin care (e.g. with emollients) was permitted as a concomitant therapy to delgocitinib or alitretinoin.

The efficacy endpoints (Investigator's Global Assessment for Chronic Hand Eczema [IGA-CHE] and Hand Eczema Severity Index [HECSI]) were assessed by a blinded principal investigator, all other endpoints by non-blinded principal investigators. The patients were not blinded to the assigned treatment. The treatment phase was up to 24 weeks.

Adult patients with severe chronic hand eczema who had a documented inadequate response to treatment with TCS within the last 12 months or for whom TCS were not medically indicated (e.g. due to side effects) were enrolled.

Patients in the intervention arm were largely treated in accordance with the product information. According to the product information, treatment with delgocitinib should be continued until the skin is completely or almost symptom-free. Treatment should be discontinued should there be no improvement after 12 weeks of continuous treatment. However, in the DELTA FORCE study, delgocitinib was administered until week 16, regardless of the response. At week 16, treatment could be discontinued in patients with a clinical response (IGA-CHE value of 0 or 1) or without a clinical response (IGA-CHE 4). The IGA-CHE data show that at week 12 in the intervention arm, only a very small percentage of patients (2.6%) showed no response, in the sense of an IGA-CHE value of 4, and should therefore have discontinued treatment according to the product information. However, 29% of patients could possibly have discontinued treatment before week 16, as they were already symptom-free at week 12 after an IGA-CHE score of 0 (9.4%) or almost symptom-free after an IGA-CHE score of 1 (19.6%). It remains unclear whether further treatment until potential absence of symptoms was indicated for patients who were almost symptom-free. Accordingly, an approximate percentage of patients continued to be treated with an unchanged treatment regimen until week 16 although they were completely or almost symptom-free. The treatment in the control arm was carried out according to the requirements in the product information of alitretinoin.

On the implementation of the appropriate comparator therapy

The appropriate comparator therapy for delgocitinib was determined as an individualised therapy consisting of topical and systemic therapy. In addition to alitretinoin, class II to IV topical glucocorticoids, phototherapy and systemic glucocorticoids for short-term flare therapy can be an option for the treatment of all subentities of chronic hand eczema as part of individualised therapy. The subentity of atopic hand eczema is to be assigned here to the indication of atopic dermatitis, so that in addition to the therapy options mentioned, calcineurin inhibitors (tacrolimus, pimecrolimus) and dupilumab are also generally an option for the treatment of atopic eczema.

The DELTA FORCE study did not provide for a patient-individual decision as to which therapy would have been optimal for the specific patient at the time of enrolment in the study. However, in the DELTA FORCE study, the principal investigator only had alitretinoin as monotherapy in the control arm. Topical or systemic corticosteroids for short-term flare therapy should not be used outside of rescue therapy. The use of phototherapy was also prohibited. The therapy recommendations in the S2k-LL Diagnosis, prevention and treatment of hand eczema[2] provide for a stepwise or escalating therapy regimen. The higher levels here include all therapy options of the previous levels. Active ingredients specifically approved for atopic dermatitis were also not available. However, the study excluded patients whose atopic eczema required medical treatment in skin areas other than the hands and feet. Against this background, the therapy options for the treatment of atopic dermatitis appear less relevant for the patients enrolled in the study.

Despite the therapy concept designed as a step therapy for treating chronic hand eczema, the scientific-medical societies explained in the written statement procedure that it may be appropriate to discontinue the other therapies used up to that point (for the time being) when treating with alitretinoin. This is justified in particular by the side effects of long-term therapy with TCS. Alitretinoin is also a particularly relevant therapy option for severe chronic hand eczema.

Despite the significance of alitretinoin within the individualised therapy for chronic hand eczema, it cannot be conclusively assessed on the basis of the available information whether alitretinoin as monotherapy is the appropriate patient-individual therapy for all patients enrolled in the study or whether all therapeutic alternatives to alitretinoin (as monotherapy) have already been exhausted or were unsuitable. However, the G-BA considers the DELTA FORCE study to be a suitable body of evidence, subject to limitations, for the assessment of delgocitinib with regard to the sub-population of patients for whom alitretinoin as monotherapy is the appropriate patient-individual therapy, particularly taking into account the statements of the scientific-medical societies.

Consequently, a separate assessment is made for patients for whom alitretinoin as monotherapy is the appropriate patient-individual therapy (patient group a)) and patients for whom a therapy other than alitretinoin as monotherapy is the appropriate patient-individual therapy (patient group b)).

[2]German Dermatological Society. Diagnosis, prevention and therapy of hand eczema [online]. 2023 https://register.awmf.org/assets/guidelines/013-053l_S2k_Diagnostik-Praevention-Therapie-Handekzem_2023-05.pdf

a) Adults with severe chronic hand eczema for whom alitretinoin as monotherapy is the appropriate patient-individual therapy option

Extent and probability of the additional benefit

Mortality

There were no deaths in the DELTA study.

Morbidity

Symptomatology (HECSI-90)

The HECSI is a valid instrument for the assessment of the severity of hand eczema by the attending physician. The HECSI score ranges from 0 to 360 and results from the severity of 6 clinical symptoms (erythema, infiltration/papule formation, cysts, fissures, scaling and oedema) and their extent (area) on each hand area (fingertips, fingers, palm, back of hand and wrists). Higher values mean a more severe manifestation of symptoms. According to the S2k guideline[2], the severity is divided into the following categories based on the HECSI score: healed (HECSI score 0); almost healed (HECSI score 17 - 37); severe (HECSI score 38 - 116); very severe (HECSI score ≥ 117).

The pharmaceutical company presented analyses of the pre-defined HECSI-90 and HECSI-75 (defined as a reduction in the HECSI score compared to the baseline value by at least 90% and 75% respectively) both in their dossier and in the subsequently submitted data. Analyses of HECSI-100, i.e. complete healing, are not available, in spite of being requested in the dossier assessment A24-107. However, complete healing is a pursued and potentially achievable goal in this therapeutic indication.

In the present therapeutic indication, which relates to the entire affected skin area on the hands and is therefore in the visible range, a 90% reduction in the HECSI score (as almost complete freedom from symptoms and due to the predefinition) is also considered relevant.

For the endpoint of symptomatology assessed using the HECSI-90, there was no statistically significant difference between the treatment groups at week 24.

Symptomatology (HESD)

The HESD is a questionnaire developed and validated by the pharmaceutical company to assess the symptoms of chronic hand eczema. A total of 6 questions investigate the most severe manifestation of the symptoms of itching, pain, cracking, redness, dryness and scaling respectively in the last 24 hours. The patient should indicate the worst degree of severity for each symptom on a rating scale from 0 (no symptom) to 10 (severe symptom). The total score (HESD total score) is calculated from the average of these 6 items and ranges from 0 to 10. In addition, a HESD pain score and a HESD itching score, which only consist of the two individual items for these symptoms, are shown. The pharmaceutical company presented responder analyses with an improvement by 4 points for the HESD total score and for the individual items on pain and itching at week 24. The response threshold of 4 points is based on the validation study and was also pre-specified in the study protocol. The response criterion presented by the pharmaceutical company thus fulfils the requirements of the benefit assessment.

For the endpoint of symptomatology assessed using the HESD, there was no statistically significant difference between the treatment groups at week 24.

Health status (EQ-5D-VAS)

Health status assessed using the VAS of the EQ-5D: The pharmaceutical company submitted responder analyses for improvement of the health status by ≥ 15 points at week 24. According to the information provided by the pharmaceutical company, patients with a baseline value ≥ 1.5 points were included in the analysis. This limit is not comprehensible. It is assumed that the analysis includes patients who can achieve an improvement, i.e. with a baseline value ≤ 85.

For the EQ-5D VAS endpoint, there was no statistically significant difference between the treatment groups at week 24.

Quality of life

HEIS

The HEIS is a questionnaire developed and validated by the pharmaceutical company to measure health-related quality of life in patients with chronic hand eczema. The HEIS comprises a total of 9 questions, which are summarised into 6 domains: on daily activities (everyday competence), shame due to the appearance of the hands, frustration about the CHE, sleep, work and physical functioning in the last 7 days. Each question is rated by the patient on a scale from 0 (not at all) to 4 (extreme). The total score is the average of the 9 questions and represents a range of values from 0 to 4. The pharmaceutical company submitted responder analyses on a reduction in the HEIS total score by ≥ 1.5 points at week 24. The response threshold ≥ 1.5 points was not pre-specified and does not correspond to the response threshold from the validation study. The response threshold of ≥ 1.5 points also does not correspond to the 15% criterion according to the module templates. The corresponding results of the responder analyses are therefore not presented. Instead, the results of the change in the HEIS total score at week 24 compared to baseline are presented.

For health-related quality of life, assessed using the HEIS, there was no statistically significant difference between the treatment groups at week 24 compared to baseline.

Side effects

SAEs

For the endpoint of SAEs, there was no statistically significant difference between the treatment groups.

Therapy discontinuation due to AEs

For the endpoint of therapy discontinuation due to AEs, there was a statistically significant difference between the treatment groups to the advantage of delgocitinib.

Gastrointestinal disorders (SOC, AE) and headache (PT, AE)

For the endpoints of gastrointestinal disorders (SOC, AE) and headache (PT, AE), there was a statistically significant difference between the treatment groups to the advantage of delgocitinib.

Overall assessment

For adults with severe chronic hand eczema, for whom alitretinoin as monotherapy is the appropriate patient-individual therapy option, results are available from the partially blinded, multicentre RCT DELTA FORCE study comparing delgocitinib with alitretinoin. Data on the

endpoints in the categories of mortality, morbidity, health-related quality of life and side effects are available.

With regard to the patient-relevant endpoints in the categories of mortality, morbidity and health-related quality of life, there were neither advantages nor disadvantages of delgocitinib compared to alitretinoin.

In the endpoint category of side effects, the overall rate of the SAEs did not show any statistically significant difference between the treatment arms. On the contrary, there was a statistically significant advantage of delgocitinib compared to alitretinoin for the endpoint of therapy discontinuation due to AEs. In detail, there were also statistically significant advantages of delgocitinib in the endpoints of gastrointestinal disorders and headache.

Taking into account the fact that there was no statistically significant difference in the overall rate of SAEs between the treatment arms and that no relevant differences for the benefit assessment were shown between the treatment groups in the endpoints of morbidity and quality of life, the positive effect in the endpoint of therapy discontinuation due to AEs is inadequate here to justify the derivation of an additional benefit of delgocitinib compared with alitretinoin as monotherapy.

Uncertainties in the assessment of the results also arise against the background that it cannot be conclusively assessed whether alitretinoin as monotherapy was the appropriate patient-individual therapy for all patients enrolled in the study and the fact that a high risk of bias must be assumed due to the partially blinded study design.

Thus, irrespective of the question of whether the appropriate comparator therapy was adequately implemented in the DELTA FORCE study, no additional benefit of delgocitinib can be derived, taking into account the results presented.

b) <u>Adults with moderate to severe chronic hand eczema for whom alitretinoin as monotherapy is not the appropriate patient-individual therapy option</u>

For adults with severe chronic hand eczema, for whom alitretinoin as monotherapy is not the appropriate patient-individual therapy option, the additional benefit is not proven.

Justification:

The pharmaceutical company did not provide any data for this endpoint. In the DELTA FORCE study, no direct comparator data were collected for adults with moderate to severe chronic hand eczema for whom alitretinoin as monotherapy is not the appropriate patient-individual therapy option. The transfer of the results of the DELTA FORCE study to patients with moderate chronic hand eczema as intended by the pharmaceutical company is inappropriate, as alitretinoin is not approved for this sub-population.

2.1.4 Summary of the assessment

The present assessment concerns the benefit assessment of the new medicinal product Anzupgo with the active ingredient delgocitinib.

Delgocitinib is approved for the treatment of moderate to severe chronic hand eczema (CHE) in adults for whom topical corticosteroids are inadequate or inappropriate.

The G-BA determined the appropriate comparator therapy to be an individualised therapy consisting of topical and systemic therapy, depending on the manifestation of the disease, subentity and taking into account the previous therapy.

Based on the data submitted, a distinction was made between two patient groups in the therapeutic indication to be considered:

a) Adults with severe chronic hand eczema for whom alitretinoin as monotherapy is the appropriate patient-individual therapy option

For adults with severe chronic hand eczema, for whom alitretinoin as monotherapy is the appropriate patient-individual therapy option, results are available from the partially blinded, multicentre RCT DELTA FORCE study comparing delgocitinib with alitretinoin. Data on the endpoints in the categories of mortality, morbidity, health-related quality of life and side effects are available.

With regard to the patient-relevant endpoints in the categories of mortality, morbidity and health-related quality of life, there were neither advantages nor disadvantages of delgocitinib compared to alitretinoin.

In the endpoint category of side effects, the overall rate of the SAEs did not show any statistically significant difference between the treatment arms. On the contrary, there was a statistically significant advantage of delgocitinib compared to alitretinoin for the endpoint of therapy discontinuation due to AEs. In detail, there were also statistically significant advantages of delgocitinib in the endpoints of gastrointestinal disorders and headache.

Taking into account the fact that there was no statistically significant difference in the overall rate of SAEs between the treatment arms and that no relevant differences for the benefit assessment were shown between the treatment groups in the endpoints of morbidity and quality of life, the positive effect in the endpoint of therapy discontinuation due to AEs is inadequate here to justify the derivation of an additional benefit of delgocitinib compared with alitretinoin as monotherapy.

Uncertainties in the assessment of the results also arise against the background that it cannot be conclusively assessed whether alitretinoin as monotherapy was the appropriate patient-individual therapy for all patients enrolled in the study and the fact that a high risk of bias must be assumed due to the partially blinded study design.

Thus, irrespective of the question of whether the appropriate comparator therapy was adequately implemented in the DELTA FORCE study, no additional benefit of delgocitinib can be derived, taking into account the results presented.

b) Adults with moderate to severe chronic hand eczema for whom alitretinoin as monotherapy is not the appropriate patient-individual therapy option

The pharmaceutical company did not provide any data for this endpoint. In the DELTA FORCE study, no direct comparator data were collected for adults with moderate to severe chronic hand eczema for whom alitretinoin as monotherapy is not the appropriate patient-individual therapy option.

For adults with severe chronic hand eczema, for whom alitretinoin as monotherapy is not the appropriate patient-individual therapy option, the additional benefit is not proven. The transfer of the results of the DELTA FORCE study to patients with moderate chronic hand eczema as intended by the pharmaceutical company is inappropriate, as alitretinoin is not approved for this sub-population.

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 resolution is based on the information from the dossier assessment of the IQWiG (mandate A24-107).

The derivation of the patient numbers in the pharmaceutical company's dossier is subject to uncertainties. The procedure of the pharmaceutical company is mathematically comprehensible. However, the methodological approach is inadequate in all calculation steps. The representativeness of the CHECK and RWEAL studies used by the pharmaceutical company for the calculation is unclear. For some of the patients surveyed in the CHECK study, information on the severity of the disease is missing. A further uncertainty exists due to inconsistency in the reporting of criteria for failure of topical corticosteroids within the RWEAL study.

2.3 Requirements for a quality-assured application

The requirements in the product information are to be taken into account. The European Medicines Agency (EMA) provides the contents of the product information (summary of product characteristics, SmPC) for Anzupgo (active ingredient: delgocitinib) at the following publicly accessible link (last access: 3 February 2025):

https://www.ema.europa.eu/en/documents/product-information/anzupgo-epar-product-information_en.pdf

Treatment with delgocitinib should only be initiated and monitored by doctors experienced in the therapy of chronic hand eczema.

2.4 Treatment costs

The treatment costs are based on the requirements in the product information and the information listed in the LAUER-TAXE® (last revised: 15 March 2025).

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

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.

Adults with moderate to severe chronic hand eczema for whom topical corticosteroids are inadequate or inappropriate

Treatment period:

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Medicinal product to be assessed				
Delgocitinib	Continuously, 2 x daily	84.0 – 365.0	1	84.0 – 365.0
Appropriate comparator therapy				
Individualised therapy consisting of topical and systemic therapy				
- topical therapies: Class II - IV glucocorticoids, calcineurin inhibitors				
Hydrocortisone butyrate	1-2 x daily for 7-14 days		Different from patient to patient	
Methylprednisolone aceponate	1 x daily for maximum 42 days		Different from patient to patient	
Clobetasol propionate	1 x daily for maximum 14 days		Different from patient to patient	
Tacrolimus	Flare: 1-2 x daily for maximum 42 days Maintenance: 2 x weekly		Different from patient to patient	
Pimecrolimus	2 x daily for maximum 42 days		Different from patient to patient	
- systemic therapies				
Alitretinoin	1st cycle[3] 1 x daily	84.0 – 168.0	1	84.0 – 168.0
Dupilumab	1 x every 14 days	26.1	1	26.1
Methylprednisolone	1 x daily for up to 28 days		Different from patient to patient	

Consumption:

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					
Delgocitinib	2 x daily for up to 168 days		Different from patient to patient		
Appropriate comparator therapy					
Individualised therapy consisting of topical and systemic therapy					

[3]Patients can benefit from further treatment cycles in the event of a relapse.

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
- topical therapies: Class II - IV glucocorticoids, calcineurin inhibitors					
Hydrocortisone butyrate	1-2 x daily for 7-14 days		Different from patient to patient		
Methylprednisolone aceponate	1 x daily for maximum 42 days		Different from patient to patient		
Clobetasol propionate	1 x daily for maximum 14 days		Different from patient to patient		
Tacrolimus	Flare: 1-2 x daily for maximum 42 days Maintenance: 1 x daily on 2 out of 7 days for maximum 12 months		Different from patient to patient		
Pimecrolimus	2 x daily for maximum 42 days		Different from patient to patient		
- systemic therapies					
Alitretinoin	10 mg – 30 mg	10 mg – 30 mg	1 x 10 mg – 1 x 30 mg	84.0 – 168.0	84.0 x 10 mg – 168.0 x 30 mg
Dupilumab	300 mg	300 mg	1 x 300 mg	26.1	26.1 x 300 mg
Methylprednisolone	Initially: 1 x daily, 80 mg – 160 mg with rapid dose reduction		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 Sections 130 and 130 a 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. Any reference prices shown in the cost representation may not represent the cheapest available alternative.

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					
Delgocitinib 20 mg/g (topical)	60 CRE	€ 953.25	€ 1.77	€ 52.15	€ 899.33
Appropriate comparator therapy					
Alitretinoin 10 mg	30 SC	€ 511.87	€ 1.77	€ 23.75	€ 486.35
Alitretinoin 30 mg	30 SC	€ 575.58	€ 1.77	€ 26.78	€ 547.03
Clobetasol propionate 0.5 mg[4]	30 CRE	€ 16.64	€ 1.77	€ 0.42	€ 14.45
Dupilumab 300 mg	6 SFI	€ 3,908.39	€ 1.77	€ 219.92	€ 3,686.70
Hydrocortisone 17-butyrate 1 mg[4]	100 CRE	€ 27.01	€ 1.77	€ 1.24	€ 24.00
Methylprednisolone 4 mg[4]	100 TAB	€ 29.35	€ 1.77	€ 1.43	€ 26.15
Methylprednisolone 8 mg[4]	100 TAB	€ 45.04	€ 1.77	€ 2.67	€ 40.60
Methylprednisolone 40 mg[4]	100 TAB	€ 127.02	€ 1.77	€ 9.15	€ 116.10
Methylprednisolone aceponate 1 mg[4]	100 CRE	€ 27.01	€ 1.77	€ 1.24	€ 24.00
Pimecrolimus 10 mg	100 CRE	€ 153.95	€ 1.77	€ 7.90	€ 144.28
Tacrolimus 0.31 mg	60 UNG	€ 99.32	€ 1.77	€ 4.87	€ 92.68
Tacrolimus 1 mg	60 UNG	€ 65.85	€ 1.77	€ 2.59	€ 61.49
Abbreviations: CRE = cream; SFI = solution for injection; TAB = tablets; UNG = ointment; SC = soft capsules					

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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 need to be taken into account.

[4]Fixed reimbursement rate

2.5 Designation of 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 the assessed medicinal product

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.

Basic principles of the assessed medicinal product

A designation in accordance with Section 35a, paragraph 3, sentence 4 SGB V requires that it is examined based on the product information for the assessed medicinal product whether it can be used in a combination therapy with other medicinal products in the assessed therapeutic indication. In the first step, the examination is carried out on the basis of all sections of the currently valid product information for the assessed medicinal product.

If the assessed medicinal product contains an active ingredient or a fixed combination of active ingredients in the therapeutic indication of the resolution (assessed therapeutic indication) and is approved exclusively for use in monotherapy, a combination therapy is not considered due to the marketing authorisation under Medicinal Products Act, which is why no designation is made.

A designation is also not considered if the G-BA has decided on an exemption as a reserve antibiotic for the assessed medicinal product in accordance with Section 35a, paragraph 1c, sentence 1 SGB V. The additional benefit is deemed to be proven if the G-BA has decided on an exemption for a reserve antibiotic in accordance with Section 35a, paragraph 1c, sentence 1 SGB V; the extent of the additional benefit and its therapeutic significance are not to be assessed by the G-BA. Due to the lack of an assessment mandate by the G-BA following the resolution on an exemption according to Section 35a, paragraph 1c, sentence 1 SGB V with regard to the extent of the additional benefit and the therapeutic significance of the reserve antibiotic to be assessed, there is a limitation due to the procedural privileging of the pharmaceutical companies to the effect that neither the proof of an existing nor an expected at least considerable additional benefit is possible for exempted reserve antibiotics in the procedures according to Section 35a paragraph 1 or 6 SGB V and Section 35a paragraph 1d SGB V. The procedural privileging of the reserve antibiotics exempted according to Section 35a, paragraph 1c, sentence 1 SGB V must therefore also be taken into account at the level of designation according to Section 35a, paragraph 3, sentence 4 SGB V in order to avoid valuation contradictions.

With regard to the further examination steps, a differentiation is made between a "determined" or "undetermined" combination, which may also be the basis for a designation.

A "determined combination" exists if one or more individual active ingredients which can be used in combination with the assessed medicinal product in the assessed therapeutic indication are specifically named.

An "undetermined combination" exists if there is information on a combination therapy, but no specific active ingredients are named. An undetermined combination may be present if the information on a combination therapy:

- names a product class or group from which some active ingredients not specified in detail can be used in combination therapy with the assessed medicinal product, or

- does not name any active ingredients, product classes or groups, but the assessed medicinal product is used in addition to a therapeutic indication described in more detail in the relevant product information, which, however, does not include information on active ingredients within the scope of this therapeutic indication.

Concomitant active ingredient

The concomitant active ingredient is a medicinal product with new active ingredients that can be used in combination therapy with the assessed medicinal product for the therapeutic indication to be assessed.

For a medicinal product to be considered as a concomitant active ingredient, it must be classified as a medicinal product with new active ingredients according to Section 2 paragraph 1 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with the corresponding regulations in Chapter 5 of the Rules of Procedure of the G-BA as of the date of the present resolution. In addition, the medicinal product must be approved in the assessed therapeutic indication, whereby a marketing authorisation is sufficient only for a sub-area of the assessed therapeutic indication.

Based on an "undetermined combination", the concomitant active ingredient must be attributable to the information on the product class or group or the therapeutic indication according to the product information of the assessed medicinal product in the assessed therapeutic indication, whereby the definition of a product class or group is based on the corresponding requirements in the product information of the assessed medicinal product.

In addition, there must be no reasons for exclusion of the concomitant active ingredient from a combination therapy with the assessed medicinal product, in particular no exclusive marketing authorisation as monotherapy.

In addition, all sections of the currently valid product information of the eligible concomitant active ingredient are checked to see whether there is any information that excludes its use in combination therapy with the assessed medicinal product in the assessed therapeutic indication under marketing authorisation regulations. Corresponding information can be, for example, dosage information or warnings. In the event that the medicinal product is used as part of a determined or undetermined combination which does not include the assessed medicinal product, a combination with the assessed medicinal product shall be excluded.

Furthermore, the product information of the assessed medicinal product must not contain any specific information that excludes its use in combination therapy with the eligible concomitant active ingredient in the assessed therapeutic indication under marketing authorisation regulations.

Medicinal products with new active ingredients for which the G-BA has decided on an exemption as a reserve antibiotic in accordance with Section 35a, paragraph 1c, sentence 1 SGB V are ineligible as concomitant active ingredients. The procedural privileging of the reserve antibiotics exempted according to Section 35a, paragraph 1c, sentence 1 SGB V also applies accordingly to the medicinal product eligible as a concomitant active ingredient.

Designation

The medicinal products which have been determined as concomitant active ingredients in accordance with the above points of examination are named by indicating the relevant active ingredient and the invented name. The designation may include several active ingredients, provided that several medicinal products with new active ingredients may be used in the same

combination therapy with the assessed medicinal product or different combinations with different medicinal products with new active ingredients form the basis of the designation.

If the present resolution on the assessed medicinal product in the assessed therapeutic indication contains several patient groups, the designation of concomitant active ingredients shall be made separately for each of the patient groups.

Exception to the designation

The designation excludes combination therapies for which - patient group-related - a considerable or major additional benefit has been determined by resolution according to Section 35a, paragraph 3, sentence 1 SGB V or it has been determined according to Section 35a, paragraph 1d, sentence 1 SGB V that at least considerable additional benefit of the combination can be expected. In this context, the combination therapy that is excluded from the designation must, as a rule, be identical to the combination therapy on which the preceding findings were based.

In the case of designations based on undetermined combinations, only those concomitant active ingredients - based on a resolution according to Section 35a, paragraph 3, sentence 1 SGB V on the assessed medicinal product in which a considerable or major additional benefit had been determined - which were approved at the time of this resolution are excluded from the designation.

Legal effects of the designation

The designation of combinations is carried out in accordance with the legal requirements according to Section 35a, paragraph 3, sentence 4 and is used exclusively to implement the combination discount according to Section 130e SGB V between health insurance funds and pharmaceutical companies. The designation is not associated with a statement as to the extent to which a therapy with the assessed medicinal products in combination with the designated medicinal products corresponds to the generally recognised state of medical knowledge. The examination was carried out exclusively on the basis of the possibility under Medicinal Products Act to use the medicinal products in combination therapy in the assessed therapeutic indication based on the product information; the generally recognised state of medical knowledge or the use of the medicinal products in the reality of care were not the subject of the examination due to the lack of an assessment mandate of the G-BA within the framework of Section 35a, paragraph 3, sentence 4 SGB V.

The findings made neither restrict the scope of treatment required to fulfil the medical treatment mandate, nor do they make statements about expediency or economic feasibility.

Justification for the findings on designation in the present resolution:

Adults with moderate to severe chronic hand eczema for whom topical corticosteroids are inadequate or inappropriate

No medicinal product with new active ingredients that can be used in a combination therapy and fulfils the requirements of Section 35a, paragraph 3, sentence 4 SGB V.

References:
Product information for delgocitinib (Anzupgo); Anzupgo 20 mg/g cream;
last revised: September 2024

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 their session on 29 August 2023, the Subcommittee on Medicinal Products determined the appropriate comparator therapy.

On 14 October 2024, the pharmaceutical company submitted a dossier for the benefit assessment of delgocitinib to the G-BA in due time in accordance with Chapter 5 Section 8, paragraph 1, number 1, sentence 2 VerfO.

By letter dated 15 October 2024 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 delgocitinib.

The dossier assessment by the IQWiG was submitted to the G-BA on 13 January 2025, and the written statement procedure was initiated with publication on the G-BA website on 15 January 2025. The deadline for submitting statements was 5 February 2025.

The oral hearing was held on 24 February 2025.

By letter dated 25 February 2025, the IQWiG was commissioned with a supplementary assessment. The addendum prepared by IQWiG was submitted to the G-BA on 14 March 2025.

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 25 March 2025, and the proposed draft resolution was approved.

At their session on 3 April 2025, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation

Subcommittee on Medicinal Products	29 August 2023	Determination of the appropriate comparator therapy
Working group Section 35a	18 February 2025	Information on written statements received; preparation of the oral hearing
Subcommittee on Medicinal Products	25 March 2025	Conduct of the oral hearing, commissioning of the IQWiG with the supplementary assessment of documents
Working group Section 35a	5 March 2025 19 March 2025	Consultation on the dossier evaluation by the IQWiG and evaluation of the written statement procedure
Subcommittee on Medicinal Products	25 March 2025	Concluding discussion of the draft resolution
Plenum	3 April 2025	Adoption of the resolution on the amendment of the Pharmaceuticals Directive

Berlin, 3 April 2025

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

Prof. Hecken