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)
Spesolimab (Generalised Pustular Psoriasis, Acute Treatment)

of 20 July 2023

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1. Legal basis

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

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

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

According to Section 35a paragraph 3 SGB V, the G-BA decides on the benefit assessment within three months of its publication. The resolution is to be published on the internet and 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 spesolimab on 1 February 2023 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 20 January 2023.

The G-BA commissioned the IQWiG to carry out the dossier assessment. The benefit assessment was published on 1 May 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 spesolimab compared to 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. 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 spesolimab.

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 Spesolimab (Spevigo) in accordance with the product information

Spevigo is indicated for the treatment of flares in adult patients with generalised pustular psoriasis (GPP) as monotherapy.

Therapeutic indication of the resolution (resolution of 20.07.2023):

see the approved therapeutic indication

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

Adults with generalised pustular psoriasis with an acute flare

Appropriate comparator therapy for spesolimab as monotherapy:

Therapy according to doctor's instructions, taking into account systemic glucocorticoids and best supportive care

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.
2. If a non-medicinal treatment is considered as a comparator therapy, this must be available within the framework of the SHI system.

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

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 active ingredients are approved for use in pustular psoriasis:

- Systemic glucocorticoids
- Topical glucocorticoids
- Dapsone

on 2. In the therapeutic indication of an acute flare of generalised pustular psoriasis, no non-medicinal treatments are indicated.

on 3. In the mentioned therapeutic indication, there are no resolutions approved by the G-BA on the benefit assessment of medicinal products with new active ingredients according to Section 35a SGB V or of non-medicinal treatments.

on 4. The generally recognised state of medical knowledge, on which the G-BA's decision is based, 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").

There are no specific guidelines for the treatment of GPP. In the absence of significant studies, only very limited recommendations for GPP therapy have been made in general guidelines for psoriasis therapy. Overall, no established therapy standard can be derived for GPP.

In clinical practice, the focus in the treatment of the acute flare of GPP is usually on primarily intercepting the pronounced inflammatory reactions, which are often accompanied by fever and general malaise.

The drugs that are sometimes used to control GPP, such as ciclosporin, retinoids, dapsone and biologics are not approved for the treatment of GPP (except for dapsone). Systemic glucocorticoids have a broad marketing authorisation for the treatment of inflammatory skin disorders; the active ingredients prednisone and prednisolone also have an explicit marketing authorisation for pustular psoriasis and can be used for flare control.

In the overall assessment, the G-BA initially considered systemic glucocorticoids to be an appropriate comparator therapy for spesolimab for the treatment of an acute flare of GPP.

Change of the appropriate comparator therapy

The written and oral statement procedure makes it clear that a therapy with systemic glucocorticoids is only an option for some of the patients concerned, since the risk-benefit assessment has to be weighed up individually for each patient, among other things due to contraindications or rebound effects after discontinuation.

In addition to the approved systemic glucocorticoids, off-label therapy trials are used, from which, however, no general therapy standard can be derived. Furthermore, supportive therapy is available to treat the symptoms of the inflammatory reaction.

In the overall assessment of the evidence and clinical practice, the G-BA considers a therapy according to doctor's instructions, taking into account systemic glucocorticoids and best supportive care, to be an appropriate comparator therapy for spesolimab for the treatment of an acute flare of GPP.

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 spesolimab is assessed as follows:

Adults with generalised pustular psoriasis with an acute flare

For adult patients with an acute flare of generalised pustular psoriasis, the additional benefit is not proven.

Justification:

The pharmaceutical company submits the EFFISAYIL 1 study for the assessment of the additional benefit of spesolimab. The EFFISAYIL 1 study included by the pharmaceutical company is unsuitable for making statements on the additional benefit of spesolimab in comparison with the appropriate comparator therapy for patients with generalised pustular psoriasis. This is explained below.

The EFFISAYIL 1 study is a double-blind, randomised, multicentre study comparing spesolimab with placebo. Adult patients with generalised pustular psoriasis with an acute moderate to severe flare were enrolled.

Allocation to treatment with spesolimab or placebo occurred in the study with the onset of the flare. This could either already be present at the time of enrolment in the study or the patients were observed for 6 months after enrolment for the occurrence of a flare. Randomisation and treatment occurred in the last case with the onset of a flare.

A total of 53 patients were enrolled and assigned in a 2:1 ratio to treatment with spesolimab (N = 35) or placebo (N = 18). Randomisation was stratified by region (Japan vs rest of the world).

If the patients were receiving a basic therapy with methotrexate, ciclosporin and/or retinoids for the treatment of generalised pustular psoriasis at the time of enrolment in the study, this could initially be continued until the onset of the flare in the study. However, the basic therapy had to be discontinued at the latest with the onset of the flare before the first administration of spesolimab or placebo. Other systemic basic therapies for the treatment of generalised pustular psoriasis, such as infliximab, cyclophosphamide or corticosteroids, already had to be discontinued with a certain lead time before the flare treatment. Approximately 50% of the patients enrolled in the study were receiving a basic therapy at the time of enrolment in the study, which had to be discontinued either with a certain lead time or at the latest with the onset of the flare before the first administration of spesolimab or placebo. The extent to which this could have led to an additional deterioration of the disease - especially in the absence of an alternative therapy - cannot be assessed in retrospect. Overall, this approach is considered inappropriate in the present therapeutic indication, especially because more than 80% of the patients for whom corresponding retrospective surveys are available had received flare therapy for typical flares that had occurred in the past.

The patients received 900 mg spesolimab intravenously (IV) or placebo IV for flare therapy in the study. In addition, if the disease worsened, both study arms had the option of receiving an alternative medication according to the doctor's instructions, which was not subject to any restrictions. Thus, according to the study design, up to day 8, it was possible in both study arms to administer an alternative medication according to the doctor’s instructions and the principal investigator's assessment in the event of a worsening of the disease. However, according to the study protocol, in the case of stable disease, it was recommended waiting until the primary endpoint of the study was recorded on day 8, as an unblinded administration of spesolimab could take place on this day in both study arms – provided that the patients had not previously received an alternative medication. In fact, only a few patients in the study received an alternative medication until day 8. In contrast, especially in the placebo arm, a large percentage of patients received unblinded treatment with spesolimab due to a lack of symptomatic improvement on day 8.

The comparator analyses for the EFFISAYIL 1 study therefore only refer to a period of 8 days, as the majority of patients in the placebo arm received unblinded spesolimab on day 8 (15 of 18 patients [83.3%]). Subsequent surveys in the study therefore mainly refer to the comparison of immediate flare therapy with spesolimab versus delayed therapy with spesolimab. However, a comparator analysis over only 8 days is considered too short in the present indication despite the consideration of the flare therapy. A typical GPP flare lasts about one to four weeks. Against this background, the comparator analyses over a period of 8 days, as available for the EFFISAYIL 1 study, are insufficient.

In addition, it cannot be ruled out that - due to the short duration of the study - patients decided to "wait and see" for a few days instead of initiating active therapy. Especially with the severity of the disease, it must be assumed that these patients would have been treated outside of a study.

As already described, in the EFFISAYIL 1 study, patients were given the option of receiving an alternative medication, if necessary, according to the doctor's instructions. The choice of this alternative medication was not limited, so that in principle there was also the possibility of flare therapy with systemic glucocorticoids or other therapies. However, only 1 of the 18 patients included in the placebo arm of the study actually received an alternative medication (including systemic glucocorticoids) by day 8.

Even if, as clarified in the written statement procedure, regular therapy with systemic glucocorticoids is unsuitable for patients (e.g. due to the risk of a rebound effect) or could be

rejected by patients, the study design is viewed critically with regard to the implementation of the appropriate comparator therapy, as this design recommended that patients do not receive therapy for the period of 8 days. This is particularly critical in light of the fact that 80% of patients have received therapy for flares in the past.

In summary, the EFFISAYIL 1 study is unsuitable for making a statement on the additional benefit of spesolimab for the treatment of flares in adult patients with generalised pustular psoriasis due to the short comparative study duration of 8 days in the present case as well as the inappropriate discontinuation of the previous therapies for flare control, and possibly the associated provocation of flares.

2.1.4 Summary of the assessment

The present assessment concerns the benefit assessment of the new medicinal product Spevigo with the active ingredient spesolimab.

Spesolimab is approved for the treatment of flares in adult patients with generalised pustular psoriasis (GPP) as monotherapy. The G-BA determined the appropriate comparator therapy to be a therapy according to doctor's instructions under consideration of systemic glucocorticoids and best supportive care.

The pharmaceutical company submits the EFFISAYIL 1 study for the assessment of the additional benefit of spesolimab. This is a double-blind, randomised, multi-centre study comparing spesolimab with placebo. Adult patients with generalised pustular psoriasis with an acute moderate to severe flare were enrolled.

Approximately 50% of the patients enrolled in the study were receiving a basic therapy at the time of enrolment in the study, which had to be discontinued either with a certain lead time or at the latest with the onset of the flare before the first administration of spesolimab or placebo. The extent to which this could have led to an additional deterioration of the disease - especially in the absence of an alternative therapy - cannot be assessed in retrospect. Overall, this approach is considered inappropriate in the present therapeutic indication.

The comparator analyses for the EFFISAYIL 1 study only refer to a period of 8 days, as the majority of patients in the placebo arm received spesolimab on day 8 in an unblinded manner. However, a comparator analysis over only 8 days is considered too short in the present indication despite the consideration of the flare therapy. A typical GPP flare lasts about one to four weeks.

In summary, due to the short comparator study duration of 8 days in the present case and the inappropriate therapy for flare control, the EFFISAYIL 1 study is unsuitable for making a statement on the additional benefit of spesolimab for the treatment of flares in adult patients with generalised pustular psoriasis.

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 A23-05). The G-BA takes into account the patient numbers stated in the

pharmaceutical company's dossier, which are, however, subject to uncertainty due to the exclusive consideration of inpatients and the possibility that those affected may suffer more than one flare per year. Overall, an underestimation of the number of patients can be assumed.

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 Spevigo (active ingredient: spesolimab) at the following publicly accessible link (last access: 4 July 2023):

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

Treatment with spesolimab should only be initiated and monitored by doctors experienced in the treatment of inflammatory skin disorders.

2.4 Treatment costs

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

The calculation of the annual treatment costs was based on the assumption that a patient receives only one flare therapy per year; further treatments due to recurring flares are therefore not included in the annual treatment costs.

Treatment period:

According to the product information for the flare treatment of GPP with spesolimab, a further dose (after 8 days) can be administered after the initial dose in the case of persistent flare symptoms. For the cost representation, only the dosages of the general case are considered.

According to the product information, no recommendations are given on the duration of therapy with the glucocorticoids prednisone and prednisolone. The duration of therapy depends on the individual patient's response and varies from patient to patient.

Designation of the therapy	Treatment mode	Number of treatments/ patient/ flare	Treatment duration/ treatment (days)	Treatment days/ patient/ flare
Medicinal product to be assessed				
Spesolimab	1 x per flare	1	1	1
Appropriate comparator therapy				
Therapy according to doctor's instructions				

Designation of the therapy	Treatment mode	Number of treatments/ patient/ flare	Treatment duration/ treatment (days)	Treatment days/ patient/ flare
Prednisone	1 x daily	1	Varies from patient to patient	Varies from patient to patient
Prednisolone	1 x daily	1	Varies from patient to patient	Varies from patient to patient
Best supportive care[2]	Different from patient to patient			

Consumption:

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment day	Consumption by potency/ treatment day	Treatment days/ patient/ flare	Average annual consumption by potency
Medicinal product to be assessed					
Spesolimab	900 mg	900 mg	900 mg	1 - 2	900 mg – 1800 mg
Appropriate comparator therapy					
Therapy according to doctor's instructions					
Prednisone	10 mg - 100 mg	10 mg - 100 mg	10 mg - 100 mg	Varies from patient to patient	Varies from patient to patient
Prednisolone	10 mg - 100 mg	10 mg - 100 mg	10 mg - 100 mg	Varies from patient to patient	Varies from patient to patient
Best supportive care[2]	Different from patient to patient				

[2] In the case of a comparison with best supportive care, also to be used additionally for the medicinal product to be assessed.

Costs:

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

Costs of the medicinal products:

Designation of the therapy	Packaging size	Costs (pharmacy sales price)	Rebate Section 130 SGB V	Rebate Section 130a SGB V	Costs after deduction of statutory rebates
Medicinal product to be assessed					
Spesolimab	900 mg	€ 23,713.63	€ 2.00	€ 2,316.00	€ 21,395.63
Appropriate comparator therapy					
Therapy according to doctor's instructions					
Prednisone	Different from patient to patient				
Prednisolone	Different from patient to patient				
Best supportive care[2]	Different from patient to patient				

LAUER-TAXE® last revised: 01 July 2023

Costs for additionally required SHI services:

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

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

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

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

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 27 October 2020, the Subcommittee on Medicinal Products determined the appropriate comparator therapy.

On 20 January 2023, the pharmaceutical company submitted a dossier for the benefit assessment of spesolimab to the G-BA in due time in accordance with Chapter 5 Section 8, paragraph 1, number 1, sentence 2 VerfO.

By letter dated 25 January 2023 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 spesolimab.

The dossier assessment by the IQWiG was submitted to the G-BA on 24 April 2023, and the written statement procedure was initiated with publication on the G-BA website on 2 May 2023. The deadline for submitting statements was 23 May 2023.

The oral hearing was held on 5 June 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 11 July 2023, and the proposed resolution was approved.

At its session on 20 July 2023, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal products	27 October 2020	Determination of the appropriate comparator therapy
Working group Section 35a	30 May 2023	Information on written statements received; preparation of the oral hearing
Subcommittee Medicinal products	5 June 2023	Conduct of the oral hearing
Working group Section 35a	14 June 2023 21 June 2023 4 July 2023	Consultation on the dossier assessment by the IQWiG, assessment of the written statement procedure
Subcommittee Medicinal products	11 July 2023	Concluding discussion of the draft resolution
Plenum	20 July 2023	Adoption of the resolution on the amendment of Annex XII AM-RL

Berlin, 20 July 2023

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

Prof. Hecken