Justification

Gemeinsamer Bundesausschuss

to the Resolution of the Federal Joint Committee (G-BA) on an Amendment of the Pharmaceuticals Directive (AM-RL): Annex XII – Benefit Assessment of Medicinal Products with New Active Ingredients According to Section 35a SGB V Trifarotene (Acne Vulgaris)

of 4 February 2021

Contents

1. Legal basis

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

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

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

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

2. Key points of the resolution

The relevant date for the first placing on the market of the active ingredient trifarotene in accordance with Chapter 5, Section 8, paragraph 1, number 1, sentence 2 of the Rules of Procedure of the G-BA (VerfO) is 15 August 2020. 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 13 August 2020.

The G-BA commissioned the IQWiG to carry out the assessment of the dossier. The benefit assessment was published on the website of the G-BA (www.g-ba.de) on 16 November 2020, 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 trifarotene 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 written statements presented on this in the written and oral hearing procedure. In order to determine the extent of the additional benefit, the G-BA assessed the data justifying the finding of an additional benefit on the basis of their therapeutic relevance (qualitative) according to 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 set aside in the benefit assessment of trifarotene.

In light of the above and taking into account the written statements received and the oral hearing, the G-BA has arrived at 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 trifarotene (Selgamis) in accordance with the product information

Selgamis is indicated for the topical treatment of acne vulgaris on the face and/or trunk in patients 12 years of age and older if many comedones, papules, and pustules are present.

Therapeutic indication of the resolution (resolution of 4 February 2021)

See approved therapeutic indication

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

Patients 12 years of age and older with acne vulgaris on the face and/or trunk if many comedones, papules, and pustules are present

Appropriate comparator therapy:

- A topical combination therapy of adapalene + benzoyl peroxide

or

- A topical combination therapy of clindamycin + benzoyl peroxide

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 according to 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.
3. As comparator therapy, medicinal applications or non-medicinal treatments for which the patient-relevant benefit has already been determined by the Federal Joint Committee shall be preferred.

[1] General Methods, Version 6.0 dated 5 November 2020. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care), Cologne.

4. According to the generally recognised state of medical knowledge, the comparator therapy should be part of the appropriate therapy in the therapeutic indication.

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

On 1. In the present therapeutic indication for the treatment of acne vulgaris, the following active ingredients are approved in the context of topical therapy: Tretinoin, adapalene, azelaic acid, erythromycin, clindamycin, and nadifloxacin. The active ingredients benzoyl peroxide and sodium bituminosulfonate, which are also approved in the present therapeutic indication, are pharmacy-only medicinal products that are not reimbursable if the patient is older than 12 years or, in the case of people with developmental disorders, older than 18 years (Sections 31, paragraph 1, sentence 1 SGB V in conjunction with Section 34, paragraph 1, sentence 5, Nos. 1 and 2 SGB V). In the fixed combination with adapalene, however, benzoyl peroxide is reimbursable (e.g. Epiduo® proprietary medicinal product).
The retinoid isotretinoin and the antibiotics doxycycline and minocycline are approved for the treatment of acne vulgaris as part of a systemic therapy.

On 2. Non-medicinal measures for the treatment of acne vulgaris are not indicated as the sole appropriate comparator therapy.

On 3. No resolutions of the G-BA have been made in the therapeutic indication considered here.

On 4. The general accepted state of medical knowledge on which the decision of the G-BA are based was illustrated by systematic research for guidelines and reviews of clinical studies in this indication.

It is assumed that the patients covered by the therapeutic indication have a moderately severe form of acne vulgaris. In accordance with guidelines, a topical combination therapy of the retinoid adapalene and benzoyl peroxide or a topical combination therapy of the antibiotic clindamycin and benzoyl peroxide is recommended for patients with moderate or moderately severe acne vulgaris. Both combination therapies are mentioned with the same recommendation grade; both combination therapies are thus considered equally appropriate options for the treatment of moderate acne vulgaris. The respective marketing authorisation of the medicinal products must be considered.
It is assumed that adequate cleansing and care of the skin is performed equally in both arms of the study and that no comedogenic preparations are used.
It is also assumed that the patients in the present therapeutic indication are not yet eligible for systemic therapy. The appropriate comparator therapy therefore includes only topical therapies.

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

2.1.3 Extent and probability of the additional benefit

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

For patients 12 years of age and older with acne vulgaris on the face and/or trunk if many comedones, papules, and pustules are present, the additional benefit is not proven.

Justification:

For the benefit assessment, the pharmaceutical company submits the PERFECT-1 and PERFECT-2 pivotal studies as well as data from the single-arm SATISFY study.

The double-blind, placebo-controlled PERFECT-1 and PERFECT-2 studies investigate the efficacy and safety of trifarotene in patients aged 9 years and older with acne vulgaris compared with placebo over 12 weeks. Approx. 1,200 patients aged 9 years and older with moderate acne on the face and trunk were included. Patients with severe (e.g. acne conglobata, acne fulminans) or secondary forms of acne (e.g. chloracne or medication-induced acne) were excluded from the studies. During the 12-week treatment phase, trifarotene or the active ingredient-free vehicle cream was applied once a day by the patients to the affected skin areas on the face and trunk.

The single-arm SATISFY study investigates the treatment of trifarotene in the present therapeutic indication over 52 weeks.

Because of a lack of comparison with the appropriate comparator therapy, both the placebo-controlled studies PERFECT-1 and PERFECT-2 and the single-arm study SATISFY are not suitable for the benefit assessment according to Section 35a SGB V. An additional benefit of trifarotene compared with the appropriate comparator therapy is therefore not proven.

2.1.4 Summary of the assessment

The present assessment refers to the benefit assessment of the new medicinal product Selgamis with the active ingredient trifarotene. Selgamis is indicated for the topical treatment of acne vulgaris on the face and/or trunk in patients 12 years of age and older if many comedones, papules, and pustules are present.

A topical combination therapy of adapalene and benzoyl peroxide or a topical combination therapy of clindamycin and benzoyl peroxide was determined as an appropriate comparator therapy by the G-BA.

For the benefit assessment, the pharmaceutical company presents the PERFECT-1 and PERFECT-2 pivotal studies, which investigate the efficacy and safety of trifarotene compared with placebo over 12 weeks in patients aged 9 years and older with moderate acne vulgaris. It also presents supplementary data from the single-arm SATISFY study.

Because of a lack of comparison with the appropriate comparator therapy, both the placebo-controlled PERFECT-1 and PERFECT-2 studies and the single-arm SATISFY study are not suitable for the benefit assessment.

In the overall view, it is concluded that for trifarotene in patients 12 years of age and older with acne vulgaris on the face and/or trunk if many comedones, papules, and pustules are present, the additional benefit is not proven.

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

This information on the number of patients refers to the target population in the statutory health insurance.

The derivation of the patient numbers in the dossier appears plausible overall; however, it is subject to uncertainties. The lower limit of prevalence for the indication acne vulgaris is determined from a publication based on a voluntary skin cancer study of 16- to 70-year-old workers in Germany; the pharmaceutical company transfers the prevalence of 16- to 20-year-old persons for the age range 12 to 15 years, which is not taken into consideration. The approach is understandable; however, it is unclear to what extent the prevalence of the age groups is comparable or transferable. Furthermore, because only employed persons were included in the present study, the distribution of age groups in the study is not representative

of the population as a whole. For the upper limit, a Chinese cross-sectional study of 1- to 99-year-olds is used to derive the prevalence. The transferability of the results to Germany is unclear. In addition, the derivation of the proportion of people with moderate acne vulgaris is subject to uncertainties, and the underlying sources do not have any definitions of acne.

Overall, the range of patient numbers (approx. 887,500–1,950,700 patients) is subject to uncertainties.

2.3 Requirements for a quality-assured application

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

2.4 Treatment costs

The treatment costs are based on the contents of the product information and the information listed in the LAUER-TAXE® (last revised: 15 January 2021).

For the cost representation, only the dosages of the general case are considered. If the treatment duration is unlimited, initial induction regimens are to be disregarded in the representation of costs. Patient-individual dose adjustments (e.g. because of side effects or co-morbidities) are not taken into account when calculating the annual treatment costs.

The cost presentation only drew on the costs of proprietary prescription medicinal products. Topical treatment with glucocorticoids often involves the use of formulations that were not taken into consideration in the present calculation.

Treatment duration:

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 is different for each individual patient and/or is shorter on average. The time unit “days” is used to calculate the “number of treatments/patient/year”, the time between individual treatments, and the maximum treatment duration if specified in the product information.

Topical therapy options are employed on a patient-individual basis depending on the severity and site of the disease. The therapy, in particular, is adapted to patient-individual incidences of flares, with the result that treatment duration is patient-individual.

Designation of the therapy	Treatment mode	Number of treatments/patient/year	Treatment duration/treatment (days)	Treatment days/patient/year
Medicinal product to be assessed				
Trifarotene	1 × daily	different for each individual patient		
Appropriate comparator therapy				
Topical combination therapy of adapalene + benzoyl peroxide	1 × daily	different for each individual patient		

Designation of the therapy	Treatment mode	Number of treatments/patient/year	Treatment duration/treatment (days)	Treatment days/patient/ year
Topical combination therapy of clindamycin + benzoyl peroxide	1 x daily for max. 12 weeks	different for each individual patient		

Usage and 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					
Trifarotene	different for each individual patient				
Appropriate comparator therapy					
Topical combination therapy of adapalene + benzoyl peroxide	different for each individual patient				
Topical combination therapy of clindamycin + benzoyl peroxide	different for each individual patient				

Costs:

In order to improve comparability, the costs of the medicinal products were approximated based on the pharmacy sales price level as well as less the statutory rebates according to Sections 130 and 130a SGB V. To calculate the annual treatment costs, the required number of packs of a particular potency was first determined based on consumption. Having determined the number of packs of a particular potency, the costs of the medicinal products were then calculated based on the costs per pack after deduction of the statutory rebates.

Costs of the medicinal product:

Designation of the therapy	Package 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					

Designation of the therapy	Package size	Costs (pharmacy sales price)	Rebate Section 130 SGB V	Rebate Section 130a SGB V	Costs after deduction of statutory rebates
Trifarotene 0.05 mg	75 g CRE	€ 71.73	€ 1.77	€ 3.36	€ 66.60
Appropriate comparator therapy					
Adapalene 1 mg + benzoyl peroxide 25 mg	60 g GEL	€ 51.06	€ 1.77	€ 5.37	€ 43.92
Adapalene 3 mg + benzoyl peroxide 25 mg	45 g GEL	€ 49.84	€ 1.77	€ 2.15	€ 45.92
Clindamycin 10 mg + benzoyl peroxide 30 mg	60 g GEL	€ 51.05	€ 1.77	€ 2.21	€ 47.07
Clindamycin 10 mg + benzoyl peroxide 50 mg	60 g GEL	€49,75	€ 1.77	€ 3.67	€ 44.31
Abbreviations: CRE = cream, GEL = gel					

Pharmaceutical selling price (LAUER-TAXE®) as last revised: 15 January 2021

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 assessed 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 standard expenditure in the course of the treatment are not shown.

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

3. Bureaucratic costs

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 9 July 2019, the Subcommittee on Medicinal Products determined the appropriate comparator therapy.

On 13 August 2020, the pharmaceutical company submitted a dossier for the benefit assessment of trifarotene to the G-BA in due time in accordance with Chapter 5, Section 8, paragraph 1, number 1, sentence 2 VerfO.

By letter dated 13 August 2020 in conjunction with the resolution of the G-BA of 1 August 2011 concerning the commissioning of the IQWiG to assess the benefits 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 trifarotene.

The dossier assessment by the IQWiG was submitted to the G-BA on 12 November 2020, and the written statement procedure was initiated with publication on the website of the G-BA on 16 November 2020. The deadline for submitting written statements was 7 December 2020.

The oral hearing was held on 21 December 2020.

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 were discussed at the session of the subcommittee on 26 January 2021, and the proposed resolution was approved.

At its session on 4 February 2021, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee on Medicinal Products	9 July 2019	Determination of the appropriate comparator therapy
Working group Section 35a	16 December 2020	Information on written statements received; preparation of the oral hearing
Subcommittee on Medicinal Products	21 December 2020	Conduct of the oral hearing
Working group Section 35a	6 January 2021 20 January 2021	Consultation on the dossier assessment by the IQWiG, evaluation of the written statement procedure
Subcommittee on Medicinal Products	26 January 2021	Concluding discussion of the draft resolution
Plenum	4 February 2021	Adoption of the resolution on the amendment of Annex XII of the AM-RL

Berlin, 4 February 2021

Federal Joint Committee
in accordance with Section 91 SGB V
The Chair

Prof. Hecken