Gemeinsamer Bundesausschuss

Justification

of the Resolution of the Federal Joint Committee 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

Afamelanotide (Reassessment after the deadline: Phototoxicity in erythropoietic protoporphyria (EPP))

of 1 July 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.

For medicinal products for the treatment of a rare disease (orphan drugs) that are approved according to Regulation (EC) No. 141/2000 of the European Parliament and the Council of 16 December 1999, the additional medical benefit is considered to be proven through the grant of the marketing authorisation according to Section 35a paragraph 1, sentence 11, 1st half of the sentence SGB V. Evidence of the medical benefit and the additional medical benefit in relation to the appropriate comparator therapy do not have to be submitted (Section 35a, paragraph 1, sentence 11, 2nd half of the sentence SGB V). Section 35a, paragraph 1, sentence 11, 1st half of the sentence SGB V thus guarantees an additional benefit for an approved orphan drug, although an evaluation of the orphan drug in accordance with the principles laid down in Section 35a paragraph 1, sentence 3, No. 2 and 3 SGB V in conjunction with Chapter 5 Sections 5 et seq. of the Rules of Procedure (VerfO) of the G-BA has not been carried out In accordance with Section 5, paragraph 8 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV), only the extent of the additional benefit is to be quantified indicating the significance of the evidence.

However, the restrictions on the benefit assessment of orphan drugs resulting from the statutory obligation to the marketing authorisation do not apply if the turnover of the medicinal product with the SHI at pharmacy sales prices and outside the scope of SHI-accredited medical care, including VAT exceeds €50 million in the last 12 calendar months. According to Section 35a paragraph 1, sentence 12 SGB V, the pharmaceutical company must then, within three months of being requested to do so by the G-BA, submit evidence according to Chapter 5, Section 5, subsection 1–6 VerfO, in particular regarding the additional medical benefit in relation to the appropriate comparator therapy as defined by the G-BA according to Chapter 5 Section 6 VerfO and prove the additional benefit in comparison with the appropriate comparator therapy.

In accordance with Section 35a paragraph 2 SGB V, the G-BA decides whether to carry out the benefit assessment itself or to commission the Institute for Quality and Efficiency in Health Care (IQWiG). Based on the legal requirement in Section 35a paragraph 1 sentence 11 SGB V that the additional benefit of an orphan drug is considered to be proven through the grant of the marketing authorisation the G-BA modified the procedure for the benefit assessment of orphan drugs at its session on 15 March 2012 to the effect that, for orphan drugs, the G-BA initially no longer independently determines an appropriate comparator therapy as the basis for the solely legally permissible assessment of the extent of an additional benefit to be assumed by law. Rather, the extent of the additional benefit is assessed exclusively on the basis of the approval studies by the G-BA indicating the significance of the evidence.

Accordingly, at its session on 15 March 2012, the G-BA amended the mandate issued to the IQWiG by the resolution of 1 August 2011 for the benefit assessment of medicinal products

with new active ingredients in accordance with Section 35a paragraph 2 SGB V to that effect that, in the case of orphan drugs, the IQWiG is only commissioned to carry out a benefit assessment in the case of a previously defined comparator therapy when the sales volume of the medicinal product concerned has exceeded the legal limit of €50 million and is therefore subject to an unrestricted benefit assessment (cf. Section 35a paragraph 1, sentence 12 SGB V). According to Section 35a paragraph 2 SGB V, the assessment by the G-BA 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 online and is part of the Pharmaceuticals Directive.

2. Key points of the resolution

The pharmaceutical company submitted a dossier for the early benefit assessment for the active ingredient afamelanotide (Scenesse) to be assessed for the first time on 9 February 2016. For the resolution of 4 August 2016 made by the G-BA in this resolution, a limitation of the period of validity of 1 January 2021 was pronounced.

In accordance with Section 4, paragraph 3 paragraph 5 of the Ordinance on the Benefit Assessment of Pharmaceuticals (AM- NutzenV) in conjunction with Chapter 5 Section 8, paragraph 1, number 5 VerfO, the procedure for the benefit assessment of the medicinal product Scenesse recommences when the deadline has expired.

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 30 December 2020.

Afamelanotide indicated for prevention of phototoxicity in adult patients with erythropoietic protoporphyria (EPP)is approved as a medicinal product for the treatment of a rare disease under Regulation (EC) No 141/2000 of the European Parliament and the Council of 16 December 1999.

In accordance with section 35a, paragraph 1, sentence 11, 1st half of the sentence German Social Code, Book Five (SGB V), the additional benefit is considered to be proven through the grant of the marketing authorisation. The extent of the additional benefit and the significance of the evidence are assessed on the basis of the authorisation studies carried out by the G-BA.

The G-BA carried out the benefit assessment and commissioned the IQWiG to evaluate the information provided by the pharmaceutical company in Module 3 of the dossier on treatment costs and patient numbers. The benefit assessment was published on 1 April 2021 together with the IQWiG assessment on the G-BA website (www.g-ba.de), thus initiating the written statement procedure. In addition, an oral hearing was also held.

The G-BA has adopted its resolution on the basis of the dossier of the pharmaceutical company, the dossier evaluation carried out by the G-BA, the assessment of treatment costs and patient numbers (IQWiG G21-01) 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 studies relevant for the marketing authorisation with regard to their therapeutic relevance (qualitative) in accordance with the criteria laid down in Chapter 5, Section 5, paragraph 7, sentence 1, numbers 1 – 4 VerfO. The methodology proposed by the IQWiG in accordance with the General Methods 1 was not used in the benefit assessment of afamelanotide.

2.1 Additional benefit of the medicinal product

2.1.1 Approved therapeutic indication of afamelanotide (Scenesse) in accordance with the product information

Scenesse is indicated for prevention of phototoxicity in adult patients with erythropoietic protoporphyria (EPP).

Therapeutic indication of the resolution (resolution of 1 July 2021):

see approved therapeutic indication

2.1.2 Extend of the additional benefit and significance of the evidence

Adult patients with erythropoietic protoporphyria for the prevention of phototoxicity

In conclusion, there is a hint for a non-quantifiable additional benefit, since the scientific data does not allow a quantification.

Justification:

The assessment of the G-BA is based on the data of the phase III study CUV039 and the post-authorisation safety study (PASS) submitted by the pharmaceutical company. Further studies (CUV029, CUV030) have already been rejected by the EMA in the approval procedure due to relevant deviations from the methodological requirements. Therefore, they cannot be used as a basis for the benefit assessment. No test subjects were recruited for the retrospective study to collect long-term safety data and efficacy CUV-RCR-001.

The multicentre, double-blind, randomised controlled trial CUV039 included 93 patients with erythropoietic protoporphyria. Participants were randomised in a 1:1 ratio to two treatment arms (afamelanotide and placebo) and treated to a maximum of 201 days. The efficacy endpoints Sunlight exposure and/or Pain experience were collected via standardised patient diaries. In addition, quality-of-life questionnaires were used, and side effects were recorded. A high risk of bias must be assumed for the study because there is no guarantee that blinding could be completely maintained for the study participants and medical personnel until the

1 General Methods, version 6.0 of 5.11.2020. Institute for Quality and Efficiency in Health Care (IQWiG), Cologne.

individual end of the study: Discoloration of the skin at the implant site occurred in 19% (n=9) of participants in the verum arm, which was not observed in any participant in the placebo arm. The tanning effect that occurred as a result of the treatment (increase in melanin density by 6 to 30%) could also lead to unblinding in the study. Therefore, it cannot be ruled out that both patients and study physicians received knowledge of the group allocation, which could lead to an influence on the behaviour of the study participants towards sunlight as well as in their self-assessment in the diary entries. In particular, the assessment of subjective data such as quality of life and other patient-reported data may be significantly biased as a result.

The PASS study is a non-interventional study in people on afamelanotide treatment that has been ongoing since 2016. As a control group, individuals should also be included for whom afamelanotide may be considered but who choose not to use it. However, all but one patient consented to the use of afamelanotide, so only single-arm data are available. Afamelanotide was administered every two months before expected and increased sunlight exposure (spring to fall). The maximum number of implants per year was four. At the time of the database closure for the 4th interim report from the 30.6.2019, 297 subjects were included. Primary endpoints are long-term safety and compliance with risk minimisation. In addition, quality of life, daily activity and phototoxicity were recorded as further patient-relevant endpoints.

Mortality

There were no deaths in the studies.

Morbidity

The CUV039 study evaluated the ITT population of 46 participants in the afamelanotide arm and 43 participants in the placebo arm, consisting of all randomised subjects who received at least one dose of study medication and for whom at least one proof of concept was available post-baseline. The primary endpoint of the study was the amount of time patients were able to spend in sunlight (between 10:00 am and 6:00 pm) on days when they did not experience EPP-related pain. The duration of sunlight exposure was operationalised by self-recording in a patient diary using multiple data collection points (15-minute intervals); pain was rated daily by participants on a Likert scale (0 to 10 points). There is a statistically significant advantage of afamelanotide. Patients in this arm spent 24 hours longer (estimated median difference) in the sun than patients in the placebo arm during the total study duration of about 180 days. In contrast, the test for patient-individual differences in minutes per study day between the two treatment arms was not statistically significant. More detailed evaluations of this endpoint, e.g. by referring only to days with sunlight exposure, were not performed.

The time that could be spent in sunlight (between 10:00 and 18:00) on days when no EPP-related pain was felt is considered relevant to the patient, as pain represents the patient's perceived symptoms during or after sunlight exposure. The pain can already occur after a short stay in the sun (sometimes also in artificial light). However, the validity of the patient diary can only be assumed with limitations, as neither pre-test results nor psychometric properties are known. In addition, patients' highly individual handling of this disease and its varying manifestations make it difficult the investigations in clinical studies. It cannot be ruled

out that - especially in the case of endpoints collected subjectively by diaries - partial unblinding biases the results in favour of afamelanotide. Other endpoints also considering the components pain and sunlight exposure (phototoxic episodes and pain in phototoxic episodes) did not statistical significance. In addition, photoprovocation measurements were performed under laboratory conditions. These endpoints are not used for the benefit assessment because the patient relevance, e.g. with regard to the effects of artificial light sources, was not presented. The validity of the provocation test as a patient-relevant surrogate parameter has not been established. Due to the uncertainties described above, the additional benefit of afamelanotide is non-quantifiable on the basis of the morbidity results.

In the PASS study, phototoxicity was also assessed via patient diaries and a recall-based recording of the last two months at each study visit. The severity of phototoxic reaction was assessed by Likert scale from 0-10 and was to be recorded in the case of patient diaries one week before baseline and then at week 1 and 5 after afamelanotide application. The results have to be considered as potentially highly biased, as far as the subjects had to indicate the number of phototoxic reactions in the last 2 months only on the basis of their memory. It is unclear what data went into the evaluations. Data on patient diaries are not available (at least for baseline due to lack of compliance). Due to these uncertainties in operationalisation, the endpoint cannot be used for the assessment of the extent of additional benefit.

Daily activity is generally relevant to patients and was assessed in the PASS study using the "Daily Activity Inventory", for which, however, insufficient information is available for validation.

Quality of life

The pharmaceutical company presents the results of two health-related quality of life survey instruments in the CUV039 study. Of these, only the data of the Dermatology Quality of Life Index (DLQI) can be used for the benefit assessment. The questionnaire is validated and established for the assessment of the impact of skin disease on quality of life, but transferability of the results to individuals with erythropoietic protoporphyria (EPP) is questionable. Ten items are recorded, each with four values (0 to 3) and the option "not relevant"; a total score is calculated (values from 0 to 30). The lower the score, the better the health-related quality of life. Changes in the total DLQI score were not different between the two study arms after statistical adjustment. The second instrument used to assess quality of life in both studies was the disease-specific EPP-Quality of Life (EPP-QoL) questionnaire. No information is available on the validation and psychometric quality of this questionnaire. In addition, two different versions of the questionnaire were used. The results of the questionnaire can therefore not be used to assess the additional benefit.

Side effects

Differences between study arms in terms of moderate or severe AE and serious AE in the CUV039 study were not statistically tested. Overall, few serious AEs and no AEs leading to discontinuation of study medication occurred in both treatment arms. The most frequent AEs at PT level under afamelanotide were headache (40%), nausea (19%) and discolouration of

the skin at the implantation site (19%), but no statistical analysis is available for these either. An assessment with regard to the quantification of the additional benefit is not possible on this basis. The data from the PASS study yield side effect frequencies in the same range and no indication of particular risks not observed in the CUV039 study. Since only single-arm data are available, no comparative evaluation is possible here either.

Overall view

In summary, the mortality, morbidity, quality of life, and side effects data do not provide a quantification of the additional benefit of afamelanotide. Overall, the uncertain evidence base resulting from the high risk of bias in study CUV039 makes interpretation of the data difficult. Only one operationalisation of the endpoint of sunlight exposure (duration of direct sunlight exposure between 10:00 and 18:00 on days without pain, patient-individual total time in the study) had a statistically significant result in favour of afamelanotide. There was no statistically significant confirmation of this effect in other operationalisations or in other patient-relevant endpoints. Because of this, and because statistical evaluation of the data on side effects are not available, the results are not sufficient for a quantification of the additional benefit. There is an additional benefit, but it is not quantifiable because the scientific data basis does not allow a quantifiable statement on the extent of the additional benefit.

Significance of the evidence

Due to the high risk of bias in the CUV039 study and the non-comparative data in the PASS study, the strength of the evidence is rated as hint.

2.1.3 Summary of the assessment

The active ingredient afamelanotide (Scenesse) was subject to a new benefit assessment after the expiry of the limitation of the resolution of 4 August 2016.

Afamelanotide is approved as an orphan drug under exceptional circumstances for the prevention of phototoxicity in adult patients with erythropoietic protoporphyria (EPP).

The pharmaceutical company presents the results of the CUV039 study, in which afamelanotide was compared to placebo, as well as results of a non-interventional post-authorisation safety study (PASS).

There were no deaths in the studies. In the morbidity endpoint "time spent in sunlight (between 10:00 and 18:00) on days without EPP-related pain" (CUV039 study), there is a statistically significant result in favour of afamelanotide. Patients in this arm spent 24 hours longer in the sun than those in the placebo arm during the study period of about 180 days in total. Further evaluations, which also considered the components pain and sunlight exposure, did not reach statistical significance. A high risk of bias can be assumed for the results due to possible unblinding (skin discolouration at the implantation site, increase in melanin density), and there are also uncertainties in the validity of the patient diary.

Data on quality of life, collected using the DLQI, showed no differences relevant to the benefit assessment.

An assessment with regard to the quantification of additional benefit is not possible on the basis of the data on side effects, as the data of the CUV039 study were not statistically evaluated, and only single-arm data are available in PASS.

Overall, there is a non-quantifiable additional benefit, since the scientific data does not allow a quantification. The significance of the evidence is rated as hint due to the limitations of the CUV039 study and the non-comparative data of the PASS study mentioned above.

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

The indication regarding patient numbers (approximately 540 to 1 090 patients) follows that of the resolution of 4 August 2016. Due to uncertain literature data, the lack of restriction to adult patients and to patients who are insured in the SHI system, an overall overestimation 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 Scenesse (active ingredient: afamelanotide) at the following publicly accessible link (last access: 8 June 2021):
https://www.ema.europa.eu/en/documents/product-information/scenesse-epar-product-information_de.pdf

Afamelanotide should only be prescribed by specialised doctors in recognised porphyria centres and only by a doctor who has been trained and accredited by the marketing authorisation holder in the application of the implant.

As a risk minimisation measure, all medical professionals likely to use the product will be trained by the marketing authorisation holder. The following prescribed information material shall be made available: Summary of the characteristics of the medicinal product, face-to-face training material, information video and a register information sheet.

This medicinal product was approved under "exceptional circumstances". This means that due to the rarity of the disease, it was not possible to obtain complete information on this medicinal product. The European Medicines Agency will assess any new information that becomes available on an annual basis, and, if necessary, the summary of product characteristics will be updated.

Depending on the duration of protection required, three implants per year are recommended. A maximum of four implants per year is recommended. The total duration of treatment is at the discretion of the specialist doctor.

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 June 2021).

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 patient-individual 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.

Treatment duration:

Designation of the therapy	Treatment mode	Number of treatments/patient/year	Treatment duration/treatment (days)	Days of treatment/patient/ year
Medicinal product to be assessed				
Afamelanotide	every 2 months (before the expected sun exposure as well as in case of increased sun exposure)	3 – 4	1	3 – 4

Consumption:

Designation of the therapy	Dosage/ application	Dosage/patient/days of treatment	Usage by potency/day of treatment	Treatment days/ patient/ year	Average annual consumption by potency
Medicinal product to be assessed					
Afamelanotide	16 mg	16 mg	1 x 16 mg	3 - 4	3 – 4 x 16 mg

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 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.

Cost of medicinal product:

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					
Afamelanotide 16 mg	1 implant	€ 17,293.72	€ 1.77	€ 0.00	€ 17,291.95

Last revised LAUER-TAXE®: 15 June 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 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 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.

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

On 30 December 2020 the pharmaceutical company submitted a dossier for the benefit assessment of afamelanotide to the G-BA in due time in accordance with Chapter 5, Section 8, paragraph 1, number 5 VerfO.

The benefit assessment of the G-BA was published on 1 April 2021 together with the IQWiG assessment of treatment costs and patient numbers on the G-BA website (www.g-ba.de), thus

initiating the written statement procedure. The deadline for submitting written statements was 22 April 2021.

The oral hearing was held on 10 May 2021.

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 22 June 2021, and the draft resolution was approved.

At its session on 1 July 2021, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal products	23 June 2020	Information of the benefit assessment of the G-BA
Working group Section 35a	5 May 2021	Information on written statements received; preparation of the oral hearing
Subcommittee Medicinal products	10 May 2021	Conduct of the oral hearing
Working group Section 35a	19.05.2021; 19.05.2021; 16/6/2021	Consultation on the dossier evaluation by the G-BA, the assessment of treatment costs and patient numbers by the IQWiG, and the evaluation of the written statement procedure
Subcommittee Medicinal products	22 June 2021	Concluding discussion of the draft resolution
Plenum	1 July 2021	Adoption of the resolution on the amendment of Annex XII AM-RL

Berlin, 1 July 2021

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

Prof. Hecken