Justification

Gemeinsamer Bundesausschuss

to the Resolution of the Federal Joint Committee (G-BA) on an Amendment of the Pharmaceuticals Directive (AM-RL): Annex XII – Resolutions on the Benefit Assessment of Medicinal Products with New Active Ingredients in Accordance with Section 35a SGB V– Ingenol Mebutate (Reassessment Because of New Scientific Knowledge)

of 21 February 2019

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 ingenol mebutate in accordance with Chapter 5, Section 8, number 4 of the Rules of Procedure of the G-BA (VerfO) is 1 September 2018. The pharmaceutical company submitted the final dossier to the G-BA in accordance with Section 4, paragraph 3, number 4 of the Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with Chapter 5, Section 8, number 4 VerfO on 31 August 2018.

After the active ingredient ingenol mebutate was first placed on the market on 15 January 2013 with the present therapeutic indication, the G-BA carried out a benefit assessment of this active ingredient according to Section 35a SGB V. In its resolution of 4 July 2013, as a result of the benefit assessment of the active ingredient ingenol mebutate in accordance with 35a SGB V, the G-BA concluded that an additional benefit compared with the appropriate comparator therapy is not proven for ingenol mebutate for the treatment of adult patients with non-hyperkeratotic, non-hypertrophic actinic keratosis. Because of the lack of directly comparative studies, the pharmaceutical company had carried out an indirect comparison of ingenol mebutate with diclofenac-hyaluronic acid gel with the bridge comparator vehicle gel or isolated comparisons of individual study arms from different studies (unadjusted indirect comparison). No statements on the additional benefit could be deduced from the data

presented, especially against the background that the comparability of the efficacy of the vehicle gels was not given.

At its session on 21 June 2018, the G-BA decided to grant an application of the pharmaceutical company for a renewed benefit assessment on the basis of new scientific knowledge according to Section 35a, paragraph 5 SGB V.

The granting of the application was linked to the condition that the renewed benefit assessment be carried out on the basis of a data basis corresponding to the current generally accepted state of medical and scientific knowledge, including study LP0041-1120 (RCT 0.015% ingenol mebutate vs 3% diclofenac-hyaluronic acid).

With the resolution of 21 June 2018, the pharmaceutical company was requested to submit the evidence required for the benefit assessment according to Section 35a, paragraph 1, sentence 3 SGB V within three months after notification of the decision on Item I.

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 3 December 2018, 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 ingenol mebutate 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, the statements submitted in the written statement and oral hearing procedure, and the addenda to the benefit assessment prepared by the IQWiG. In order to determine the extent of the additional benefit, the G-BA has assessed 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 ingenol mebutate.

In the light of the above and taking into account the 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 ingenol mebutate (Picato®) in accordance with the product information

Picato® is indicated for the cutaneous treatment of non-hyperkeratotic, non-hypertrophic actinic keratosis in adults.

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy for ingenol mebutate for the topical treatment of non-hyperkeratotic, non-hypertrophic actinic keratosis in adults is:

- Diclofenac-hyaluronic acid gel (3%) or 5-fluorouracil (5-FU) in topical application or (surgical) cryotherapy in the treatment of single lesions

[1] General Methods, Version 5.0 dated 10 July 2017. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen [Institute for Quality and Efficiency in Health Care], Cologne.

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.
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:

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

On 1. Active ingredients approved in principle in the therapeutic indication for the treatment of actinic keratosis:

- 5-fluorouracil (5-FU) (topical)
- Diclofenac-hyaluronic acid gel

Partially approved medicinal products in the therapeutic indication:

- 5-fluorouracil plus salicylic acid (topical)
- Imiquimod
- Aminolevulinic acid and methylaminolevulinate (as part of photodynamic therapy (PDT))

On 2. In principle, cryotherapy, curettage, surgical excision, and chemical peeling can be considered as non-medicinal treatment for actinic keratosis in the present therapeutic indication.

On 3. In the therapeutic indication under consideration here, the G-BA has passed the following resolution:

- Resolution on the benefit assessment of medicinal products with new active ingredients according to Section 35a SGB V for the active ingredient ingenol mebutate dated 24 July 2013.

On 4. The generally accepted state of medical knowledge was represented by a guideline search and an evidence search. According to the approved therapeutic indication, 5-fluorouracil (topical) and diclofenac-hyaluronic acid gel (topical) are available for the topical treatment of non-hyperkeratotic, non-hypertrophic actinic keratosis in adults. Other medicinal products with the active ingredients 5-fluorouracil plus salicylic acid (topical), imiquimod, and aminolevulinic acid and methylaminolevulinate (as part of a photodynamic therapy (PDT)) have only partial agreement in the therapeutic indication. Furthermore, in this indication, photodynamic therapy is not covered by the statutory health insurance.

In consideration of the criteria for determining the appropriate comparator therapy according to the G-BA Chapter 5 Section 6, either 5-fluorouracil, diclofenac-hyaluronic acid gel (3%), or (surgical) cryotherapy for individual lesions was considered relevant for topical application. When considering the evidence base, 5-fluorouracil tended to be rated better than diclofenac-hyaluronic acid based on existing studies to determine relapse rates. This should be contrasted with the increased side effect potential of 5-fluorouracil compared with diclofenac-hyaluronic acid gel (3%). In addition, the G-BA also considers (surgical) cryotherapy for single lesions as a non-medicinal option in the treatment of actinic keratosis to be an equally useful therapeutic option in practical application.

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 ingenol mebutate is assessed as follows:

Because Picato® contains two medicinal products with different, approved indications and dosages, each providing a targeted, topical therapy for different forms of non-hyperkeratotic, non-hypertrophic actinic keratosis, a subdivision is made according to the localisation of the lesions and the corresponding patient population in the present benefit assessment.

a) Adult patients with non-hyperkeratotic, non-hypertrophic actinic keratosis on the face and/or scalp

For adult patients with non-hyperkeratotic, non-hypertrophic actinic keratosis on the face and/or scalp, there is a hint for a non-quantifiable additional benefit for ingenol mebutate compared with the appropriate comparator therapy diclofenac-hyaluronic acid.

Justification:

The assessment is based on the results of the LP0041-1120 study. This study is a randomised, open-label, multi-centre, double-arm, parallel group study evaluating topical treatment with ingenol mebutate compared with topical therapy with diclofenac-hyaluronic acid. Adult patients with 4 to 8 non-hyperkeratotic, non-hypertrophic, clinically typical, visible, and discrete actinic keratosis within a 25 cm^2 treatment area on the face or scalp were included. A total of 502 patients were randomised to topical treatment with ingenol mebutate (n = 255) or diclofenac-hyaluronic acid (n = 247). The randomisation was stratified by study centre and anatomical location of the lesions (face or scalp).

During the 120-day (17-week) study period, patients in the ingengol mebutate arm received one or two ingenol mebutate treatment cycles at Week 8 depending on the response to therapy. Patients in the diclofenac-hyaluronic acid arm received one treatment cycle each. According to the information in the respective product information, ingenol mebutate should be applied to the skin surface to be treated once daily for three consecutive days or, in the comparator arm, diclofenac-hyaluronic acid twice daily for 90 days. Patients in the ingenol mebutate arm who did not have complete regression of the lesions by Week 8 were subsequently treated with ingenol mebutate in a second cycle. The primary endpoint of the study was the complete regression of visible lesions after a treatment cycle. This was assessed primarily at Week 8 in the ingenol mebutate arm and at Week 17 in the diclofenac-hyaluronic acid arm. Overall mortality as well as endpoints of the morbidity and side effects

category at Week 8 and Week 17 were also included. The present benefit assessment is primarily based on the results of the study at week 17. The data collected exclusively for the ingenol mebutate arm at Week 8 are also included in the assessment.

Extent and probability of the additional benefit for patient group a

Mortality

In the study presented, no deaths occurred in the ingenol mebutate arm, and 2 deaths occurred in the diclofenac-hyaluronic acid arm. There was no statistically significant difference between treatment groups for the overall mortality endpoint.

Morbidity

Complete regression of visible lesions

Complete regression of visible lesions is a patient-relevant endpoint. The assessment of the endpoint is based on the operationalisation via the proportion of patients in whom no lesions or clinical signs of actinic keratosis were visible at the end of the entire study observation at Week 17 (and in the ingenol mebutate arm regardless of the number of treatment cycles received). For the endpoint of complete remission of visible lesions, there was a statistically significant difference in favour of ingenol mebutate at 17 weeks compared with diclofenac-hyaluronic acid; at Week 17, 45.1% of patients showed complete remission with ingenol mebutate compared with 23.5% for diclofenac-hyaluronic acid [RR: 1.92; 95% CI [1.48; 2.50]; $p < 0.001$].

Limitations must be taken into account with regard to the interpretability of the result. For example, 26% of patients on the ingenol mebutate arm who were lesion-free at Week 8 developed new lesions within 8 weeks. This shows that for some of the patients, no permanent or longer-term freedom from lesions was achieved. For the patients under diclofenac-hyaluronic acid therapy, there are no data on the occurrence of lesions between Week 8 and Week 17 as well as on recurrences after Week 17. This is because neither a round at Week 8 nor a follow-up beyond the end of the study (a priori) was planned. For patients in both the ingenol mebutate and diclofenac-hyaluronic acid arms, it also remains unclear how many patients experienced further relapses or lesions after Week 17. The sustainability of the effect can therefore not be assessed conclusively. The interpretation should also take into account that the optimal therapeutic effect of diclofenac-hyaluronic acid may occur only after 120 days (i.e. when the study is completed).

The additional results presented on the further operationalisation of the endpoint, including the complete regression of visible lesions at Week 8 in the ingenol mebutate arm, do not allow comparative statements to be made with the appropriate comparator therapy diclofenac-hyaluronic acid because no study round/endpoint survey was planned at Week 8 in the diclofenac-hyaluronic acid arm.

Squamous cell carcinoma of the skin

Actinic keratosis is a precancerous disease in which the patient is at risk of developing squamous cell carcinoma. The treatment of actinic keratosis is particularly aimed at reducing the occurrence of squamous cell carcinomas in the long term. The study presented does not address this relevant issue. Thus, for the patient-relevant endpoint “squamous cell carcinoma of the skin” there are no usable data overall. The data from the study documentation cannot

be interpreted for the benefit assessment because of the lack of long-term observations beyond 17 weeks as well as insufficient information on the localisation of squamous cell carcinomas.
The recording of the development of squamous cell carcinomas from actinic keratosis is relevant and would thus have been of particular importance in assessing the additional benefit of ingenol mebutate compared with diclofenac-hyaluronic acid.

Partial healing, reduction (percentage change) of the number of lesions

The endpoints “partial healing” (defined as the regression of ≥ 75% of lesions in the treatment area) and “percentage change in the number of lesions” measure a partial regression of actinic keratosis. For the benefit assessment, the evaluation of the comparison of ingenol mebutate at Week 17 with diclofenac-hyaluronic acid at Week 17 is considered for each of these two endpoints (analogous to the endpoint complete regression of visible lesions) regardless of the number of treatment cycles. There is a statistically significant difference in favour of ingenol mebutate for the endpoint “partial healing” as well as the endpoint “reduction (percentage change) in the number of lesions”. Nevertheless, these endpoints do not allow conclusions to be drawn about the specific effects of remaining visible lesions on affected patients. It remains to be seen what significance a partial regression has for the risk of developing squamous cell carcinoma. For the endpoint “partial healing”, the rationale for the selected threshold of 75% healed lesions is also unclear. Overall, the significance of the results for the two endpoints is unclear for the present benefit assessment.

As a consequence of the aforementioned limitations, the patient-relevant advantage of ingenol mebutate compared with diclofenac-hyaluronic acid in the morbidity category is assessed as non-quantifiable.

Quality of life

Health-related quality of life was not assessed in the LP0041-1120 study.

Side effects

SAE, discontinuation because of AE

For the endpoint SAE, there was no statistically significant difference between ingenol mebutate and diclofenac-hyaluronic acid at Week 17. The results for the endpoint therapy discontinuation because of are not usable because of the different application durations of ingenol mebutate (3 days) compared with diclofenac-hyaluronic acid (90 days).

Reaction at the application site

For the endpoint reaction at the application site, there was also no statistically significant difference between ingenol mebutate and diclofenac-hyaluronic acid at Week 17.

<u>Overall assessment for patient population a</u>

For adult patients with non-hyperkeratotic, non-hypertrophic actinic keratosis on the face and/or scalp, there are evaluations from the randomised, open-label LP0041-1120 RCT. Results on mortality, morbidity, and side effects are available for this study.

In summary, there are no statistically significant advantages or disadvantages for ingenol mebutate compared with the appropriate comparator therapy diclofenac-hyaluronic acid in the endpoint categories mortality and side effects.

In the morbidity category, data on the patient-relevant occurrence of squamous cell carcinomas are missing. Nevertheless, the endpoint of complete remission of visible lesions at Week 17 shows a statistically significant advantage of ingenol mebutate compared with the appropriate comparator therapy diclofenac-hyaluronic acid. Data on quality of life were not surveyed.

According to this, for adult patients with non-hyperkeratotic, non-hypertrophic actinic keratosis of the face and/or scalp, ingenol mebutate had only positive effects compared with the appropriate comparator therapy diclofenac-hyaluronic acid in the endpoint "complete regression of visible lesions" in the endpoint category morbidity. This is not offset by negative results from other categories.

Because of the lack of long-term observations, neither the sustainability of the positive effect nor the potential effects of topical therapy on the development of squamous cell carcinoma can be assessed.

In the overall view, the effects of ingenol mebutate are considered non-quantifiable in the population with actinic keratosis of the face and/or scalp, taking into account the severity of the disease and the therapeutic objective in treatment of the disease. An additional benefit exists but is non-quantifiable because the scientific data basis does not allow this.

Reliability of data (probability of additional benefit)

The LP0041-1120 study is a randomised, open-label Phase IV study for the assessment of the additional benefit. For the LP0041-1120 study, the risk of bias is assessed as low at study level. While there is a low risk of bias at the endpoint level for overall mortality and SAE, the risk of bias for the morbidity endpoints "complete regression of visible lesions at week 17", "partial healing rate", and "reduction (percentage change) in the number of lesions" is rated as high because of the open study design, the short study duration, and unclear blinding in the endpoint survey, among other things.

In the overall view, the uncertainties described justify a classification of the reliability of data as a hint for an additional benefit.

b) Adult patients with non-hyperkeratotic, non-hypertrophic actinic keratosis on the trunk and/or extremities

For adult patients with non-hyperkeratotic, non-hypertrophic actinic keratosis on the trunk and/or extremities, the additional benefit of ingenol mebutate compared with the appropriate comparator therapy is not yet proven.

Justification:

For the patient population of adult patients with non-hyperkeratotic, non-hypertrophic actinic keratosis on the trunk and/or extremities covered by the marketing authorisation, the pharmaceutical company has not submitted a study that would have been suitable for assessing the additional benefit of topical therapy with ingenol mebutate compared with the appropriate comparator therapy.

2.1.4 Limitation of the period of validity of the resolution

The limitation of the period of validity of the resolution on the benefit assessment of ingenol mebutate has its legal basis in Section 35a, paragraph 3, sentence 4 SGB V. Thereafter, the G-BA may limit the validity of the resolution on the benefit assessment of a medicinal product. In this case, the limitation is justified by objective reasons consistent with the purpose of the benefit assessment according to Section 35a, paragraph 1 SGB V.

For the assessment of the additional benefit of ingenol mebutate for the treatment of adult patients with non-hyperkeratotic, non-hypertrophic actinic keratosis, the pharmaceutical company presents the results of the RCT LP0041-1120.
Because of the lack of long-term data on all patient-relevant morbidity endpoints of the study, in particular on the occurrence of squamous cell carcinoma and the complete regression of visible lesions, the evaluations presented in this benefit assessment procedure do not allow a final assessment of the additional benefit of ingenol mebutate with sufficient certainty.
Without long-term data, neither the sustainability of the positive effect (complete regression of visible lesions) nor the potential effects of topical therapy on the development of squamous cell carcinoma or new lesions can be assessed.

The G-BA considers it appropriate to set a time limit on the resolution on the additional benefit of ingenol mebutate. For the renewed benefit assessment after the deadline, long-term data on patient-relevant endpoints, in particular on the occurrence of squamous cell carcinoma and complete regression of lesions, must be submitted in the dossier to assess the sustainability of the effects. The G-BA considers three years to be sufficient in this respect.
The possibility that a benefit assessment for the medicinal product ingenol mebutate can be carried out for other reasons (cf Chapter 5, Section 1, paragraph 2 of the Rules of Procedure of the G-BA (VerfO)) remains unaffected by this.

In accordance with Section 3, number 5 AM-NutzenV in conjunction with Chapter 5, Section 1, paragraph 2, number 7 VerfO, the procedure for the benefit assessment for the medicinal product ingenol mebutate shall recommence when the deadline has expired. For this purpose, the pharmaceutical company must submit a dossier to the G-BA at the latest on the date of expiry to prove the extent of the additional benefit of ingenol mebutate in relation to the appropriate comparator therapy (Section 4, paragraph 3, no. 5 AM-NutzenV in conjunction with Chapter 5 Section 8, no. 5 VerfO).

2.1.5 Summary of the assessment

The present assessment is a renewed benefit assessment of the active ingredient ingenol mebutate in the therapeutic indication “for the topical treatment of non-hyperkeratotic, non-hypertrophic actinic keratosis in adults” based on an application by the pharmaceutical company because of new scientific findings according to Section 14 VerfO.

For the benefit assessment, a distinction was made between two patient groups because of the marketing authorisation of two different medicinal products with different dosages:

a) Adult patients with non-hyperkeratotic, non-hypertrophic actinic keratosis on the face and/or scalp

   and

b) Adult patients with non-hyperkeratotic, non-hypertrophic actinic keratosis on the trunk and/or extremities

Patient group a

The G-BA determined diclofenac-hyaluronic acid gel (3%) or 5-fluorouracil (5-FU) in topical application or (surgical) cryotherapy in the treatment of single cell lesions to be the appropriate comparator therapy. For this patient group, the pharmaceutical company presents the 17-week RCT LP0041-1120 in which ingenol mebutate was compared with diclofenac-hyaluronic acid gel.

In the morbidity category, there was a significant advantage of ingenol mebutate compared with diclofenac-hyaluronic acid in the endpoint “complete regression of visible lesions”. For the benefit category morbidity, there is a non-quantifiable additional benefit because of relevant uncertainties. These include a lack of long-term data on the complete regression of lesions as well as no survey of data on the development of squamous cell carcinomas. In the mortality and side effects categories, there are no statistically significant differences between the two topical treatments. Quality of life was not assessed. Because of the short study duration (17 weeks) and the open study design, there are further uncertainties.

In the overall view, there is a hint for a non-quantifiable additional benefit of ingenol mebutate compared with diclofenac-hyaluronic acid. The resolution is limited to three years because of the lack of long-term data on the development of squamous cell carcinoma.

Patient group b

The G-BA determined diclofenac-hyaluronic acid gel (3%) or 5-fluorouracil (5-FU) in topical application or (surgical) cryotherapy in the treatment of single cell lesions to be the appropriate comparator therapy. The pharmaceutical company does not provide data for this patient group. In the overall view, the additional benefit of ingenol mebutate compared with the appropriate comparator therapy is not proven for this patient group.

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

The patient numbers refer to the target population in the statutory health insurance (SHI). The G-BA bases its resolution on the patient numbers submitted by the pharmaceutical company in the written statement procedure. Although the number of patients in the SHI target population stated there is within a plausible range, it is subject to uncertainties. The lower limit is determined analogously to the initial resolution under the assumption that the 80% patients with actinic keratosis have non-hyperkeratotic, non-hypertrophic actinic keratosis; the upper limit is 90% of patients.

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 Picato® (active ingredient: ingenol mebutate) at the following publicly accessible link (last access: 7 January 2019):

https://www.ema.europa.eu/documents/product-information/picato-epar-product-information_de.pdf

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 February 2019).

It is assumed that one treatment cycle will be used to calculate the costs for all medicinal products. This does not take into account the fact that treatment may be discontinued earlier because of non-response or intolerance. The discontinuation criteria according to the product information of the individual active ingredients shall be taken into account in the application of the medicinal products.

Treatment duration:

Designation of the therapy	Treatment mode	Number of treatments/patient/year	Treatment duration/treatment (days)	Treatment days/patient/ year
Medicinal product to be assessed				
Patient population a)				
Ingenol mebutate (Picato®), topical 150 µg/g gel	1 treatment cycle of 3 consecutive days; 1 × daily	1	3	3
Patient population b)				
Ingenol mebutate (Picato®), topical 500 µg/g gel	1 treatment cycle of 2 consecutive days; 1 × daily	1	2	2
Appropriate comparator therapy for patient population a and b				
Diclofenac-hyaluronic acid gel (3%), topical	1 treatment cycle of 60 to 90 consecutive days; 2 × daily	1	60–90	60–90
5% 5-fluorouracil, topical	1 treatment cycle of 14–28 consecutive days; 2 × daily	1	14–28	14–28
(surgical) cryotherapy	No specification possible			

According to the product information, treatment is carried out topically using ingenol mebutate (Picato®) as well as the appropriate comparator therapy diclofenac-hyaluronic acid gel (3%) or 5-fluorouracil (5%) in the form of treatment cycles.

Picato® (150 µg/g) is approved for the treatment of actinic keratosis of the face and scalp; treatment is performed once daily for 3 consecutive days. In contrast, Picato® (500 µg/g) is

intended for the treatment of actinic keratosis of the trunk and extremities; these are treated once daily for 2 consecutive days. For a treatment area of 25 cm^2, the contents of an entire tube are used. According to the product information, one new tube per 25 cm^2 treatment area must be opened on each day of treatment (irrespective of the potency of 500 µg/g or 150 µg/g). For Picato® (500 µg/g or 150 µg/g), no clinical data are available for more than two treatment cycles of 2 (500 µg/g potency) or 3 (150 µg/g potency) consecutive days.

The treatment of actinic keratosis with diclofenac-hyaluronic acid gel (3%) usually consists of 0.5 g gel applied twice daily over a period of 60 to 90 days; similarly, according to the product information, 5-fluorouracil (5%) is applied twice daily usually over 2 to 4 weeks. The product information for 5-fluorouracil 5% cream and diclofenac-hyaluronic acid 3% gel does not contain any information on the repetition of a treatment cycle.

Picato®, 5-fluorouracil 5% cream, and diclofenac-hyaluronic acid 3% gel are applied topically. The size of the treatment area depends on the spread of the actinic keratosis. The annual treatment costs per patient are standardised for a treatment area of 25 cm^2 and one treatment cycle per year. This does not affect the treatment of larger or more areas or the implementation of several treatment cycles in accordance with the respective product information.

Usage and consumption:

Designation of the therapy	Dosage (per 25 cm^2 treatment area)	Dose/patient/treatment day	Consumption by potency/treatment day	Treatment days/ patient/ year	Average annual consumption
Medicinal product to be assessed					
Patient population a)					
Ingenol mebutate (Picato®), topical 150 µg/g	70 µg	70 µg	0.47 g gel	3	3 tubes of 0.47 g each
Patient population b)					
Ingenol mebutate (Picato®), topical 500 µg/g	235 µg	235 µg	0.47 g gel	2	2 tubes of 0.47 g each
Appropriate comparator therapy for patient population a and b					
Diclofenac-hyaluronic acid gel (3%), topical	2 × 15 mg	30 mg	1 g gel	60	1 tube of 90 g
				90	1 tube of 90 g

Designation of the therapy	Dosage (per 25 cm^2 treatment area)	Dose/patient/treatment day	Consumption by potency/treatment day	Treatment days/ patient/ year	Average annual consumption
5% 5-fluorouracil cream, topical	2 × 25 mg	50 mg	1 g cream	14	1 tube of 20 g
				28	2 tubes of 20 g each
(surgical) cryotherapy	No specification possible				

Costs:

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					
Patient population a)					
Ingenol mebutate 150 µg/g	3 tubes of 0.47 g each	€ 96.33	€ 1.77	€ 0.00	€ 94.56
Patient population b)					
Ingenol mebutate 500 µg/g	2 tubes of 0.47 g each	€ 96.33	€ 1.77	€ 0.00	€ 94.56
Appropriate comparator therapy for patient population a and b					
Diclofenac-hyaluronic acid gel 30 mg/g	1 tube of 90 g	€ 94.70	€ 1.77	€ 3.97	€ 88.96
5-fluorouracil 50 mg/g	1 tube of 20 g	€ 56.03	€ 1.77	€ 2.49	€ 51.77
(surgical) cryotherapy[2]	No specification possible				

Pharmaceutical retail price (LAUER-TAXE®) as last revised: 1 February 2019

Costs for additionally required SHI services:

Only costs directly related to the use of the medicinal product are taken into account. If there

[2] Cryotherapy is covered by the insured/basic flat rate.

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

By letter dated 23 July 2014, received on 25 July 2014, the pharmaceutical company requested consultation in accordance with Section 8 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) on, among other things, the question of appropriate comparator therapy. At its session on 23 September 2014 the Subcommittee on Medicinal Products determined the appropriate comparator therapy. The consultation meeting took place on 25 September 2014.

The appropriate comparator therapy defined by the G-BA was reviewed at the time of the consultation. At its session on 11 September 2018 the Subcommittee on Medicinal Products confirmed the appropriate comparator therapy.

On 31 August 2018, the pharmaceutical company submitted a dossier for the benefit assessment of ingenol mebutate to the G-BA in due time in accordance with Chapter 5, Section 8, number 4 VerfO.

By letter dated 3 September 2018 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 ingenol mebutate.

The dossier assessment by the IQWiG was submitted to the G-BA on 29 November 2018, and the written statement procedure was initiated with publication on the website of the G-BA on 3 December 2018. The deadline for submitting written statements was 24 December 2018.

The oral hearing was held on 7 January 2019.

By letter dated 7 January 2019, the IQWiG was commissioned with a supplementary assessment of data submitted in the written statement procedure. The addendum prepared by IQWiG was submitted to the G-BA on 29 January 2019.

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 12 February 2019, and the proposed resolution was approved.

At its session on 21 February 2019, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee on Medicinal Products	23 September 2014	Determination of the appropriate comparator therapy
Working group Section 35a	4 September 2018	Review of the appropriate comparator therapy after approval of the application according to Section14
Subcommittee on Medicinal Products	11 September 2018	Confirmation of the appropriate comparator therapy
Working group Section 35a	3 January 2019	Information on written statements received; preparation of the oral hearing
Subcommittee on Medicinal Products	7 January 2019	Conduct of the oral hearing Commissioning of the IQWiG with the supplementary assessment of documents
Working group Section 35a	15 January 2019 22 January 2019 5 February 2019	Consultation on the dossier assessment of the IQWiG and evaluation of the written statement procedure
Subcommittee on Medicinal Products	12 February 2019	Concluding discussion of the draft resolution
Plenum	21 February 2019	Adoption of the resolution on the amendment of Annex XII of the AM-RL

Berlin, 21 February 2019

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

Prof. Hecken