Resolution

Gemeinsamer Bundesausschuss

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 According to Section 35a SGB V – Ingenol Mebutate (Reassessment Because of New Scientific Knowledge)

of 21 February 2019

At its session on 21 February 2019, the Federal Joint Committee (G-BA) resolved to amend the Directive on the Prescription of Medicinal Products in SHI-accredited Medical Care (Pharmaceuticals Directive, AM-RL) in the version dated 18 December 2008/22 January 2009 (Federal Gazette, BAnz. No. 49a of 31 March 2009), as last amended on 17 January 2019 (Federal Gazette, BAnz AT 8 March 2019 B1), as follows:

I. Annex XII will be amended as follows:

1. The information relating to ingenol mebutate as amended by the resolution of 4 July 2013 (Federal Gazette, BAnz AT 1 August 2013 B5) is hereby repealed.

2. Annex XII shall be amended in alphabetical order to include the active ingredient ingenol mebutate as follows:

Ingenol mebutate

Resolution of: 21 February 2019
Entry into force on: 21 February 2019
Federal Gazette, BAnz AT DD MM YYYY Bx

Therapeutic indication (according to the marketing authorisation of 14 November 2012):

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

1. Additional benefit of the medicinal product in relation to the appropriate comparator therapy

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

Appropriate comparator therapy:

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

Extent and probability of the additional benefit of ingenol mebutate compared with diclofenac-hyaluronic acid:

Hint for a non-quantifiable additional benefit

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

Appropriate comparator therapy:

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

Extent and probability of the additional benefit of ingenol mebutate compared with the appropriate comparator therapy:

Additional benefit not proven

Study results according to endpoints:[1]

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

[1] Data from the dossier assessment of the IQWiG (A18-55) as well as from the addendum (A19-02) of the IQWiG unless otherwise indicated.

LP0041-1120 study: RCT 0.015% ingenol mebutate vs 3% diclofenac-hyaluronic acid

Study LP0041-1120 Endpoint category Endpoint	Ingenol mebutate		Diclofenac-hyaluronic acid		Ingenol mebutate vs diclofenac-hyaluronic acid
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]; p value[a]
Mortality					
Overall mortality	247	0 (0)	234	2 (0.9)	0.19 [0.01; 3.93]; 0.155

Study LP0041-1120 Endpoint category Endpoint	Ingenol mebutate		Diclofenac-hyaluronic acid		Ingenol mebutate vs diclofenac-hyaluronic acid
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]; p value[a]
Morbidity					
Complete regression of visible lesions at Week 17	255	115 (45.1)	247	58 (23.5)	1.92 [1.48; 2.50]; < 0.001
Complete regression of visible lesions at Week 8 (presented additionally)	255	88 (34.5)	not collected		---
Relapse at Week 17 (presented additionally)	88[b]	23 (26.1)[c]	not collected		---
Morbidity					
Squamous cell carcinoma of the skin	No usable data[d]				
Partial healing[e] at Week 17	255	176 (69.0)	247	107 (43.3)	1.59 [1.35; 1.88]; < 0.001[a]

Study LP0041-1120 Endpoint category Endpoint	Ingenol mebutate			Diclofenac-hyaluronic acid			Ingenol mebutate vs diclofenac-hyaluronic acid
	N	Values at the start of study MV (SD)	Reduction of the number of lesions % [95% CI]	N[f]	Values at the start of study MV (SD)	Reduction of the number of lesions % [95% CI]	Rate ratio [95% CI]; p value[g]
Morbidity							
Reduction (percentage change) of the number of lesions at Week 17[h]	255	6.12 (1.26)	77.2 [73.0; 80.8]	246	5.96 (1.25)	57.7 [52.4; 62.5]	0.52 [0.42; 0.63]; < 0.001
Health-related quality of life							
No data collected							

Study LP0041-1120 Endpoint category Endpoint	Ingenol mebutate		Diclofenac-hyaluronic acid		Ingenol mebutate vs diclofenac-hyaluronic acid
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]; p value[a]
Side effects					
AE (presented additionally)	247	122 (49.4)	234	95 (40.6)	-
SAE	247	9 (3.6)	234	10 (4.3)	0.85 [0.35; 2.06]; 0.776
Discontinuation because of AE	No usable data[i]				
Reaction at the injection site (AE)	247	59 (23.9)	234	45 (19.2)	1.24 [0.88; 1.75]; 0.248

a: p value: own calculation of the IQWiG (exact unconditional test, CSZ method according to Martin Andrés et al., 1994).
b: The value describes the total of all patients who were lesion-free at Week 8 and were thus able to develop a relapse up to Week 17.
c: Own calculation of the IQWiG. For 1 patient without visible lesions after Week 8, no values were available at Week 17. In accordance with the BLOCF replacement, this patient was included in the evaluation as a patient with relapse.
d: Because of a lack of long-term observations and insufficient information on the localisation of squamous cell carcinoma during the observation period, the data on the endpoint squamous cell carcinoma of the skin are not usable (for the justification, see IQWiG benefit assessment).
e: ≥ 75% recovery of all forms of actinic keratosis on the treatment area
f: In 1 patient, the information on the number of lesions at the start of study was missing. This patient was not included in the evaluation.
g: Negative binomial regression model, adjusted for treatment and anatomical location of lesions as fixed effects and study centre as random effect and log (number of lesions to baseline) as offset.
h: Result of the least-squares estimate for the mean difference (LS-MD) presented by the pharmaceutical company in Module 4 A from an unspecified model: −19.62 [−25.49; −13.75], p < 0.001, Hedges' g: −0.57 [−0.75; −0.40].
i: Available results on discontinuation because of AE are not usable because of significantly different application durations of ingenol mebutate and diclofenac-hyaluronic acid (for the justification see IQWiG benefit assessment).

Abbreviations used: CI: confidence interval; LS: least squares; n: number of patients with (at least 1) event; MD: mean difference; MV: mean value; N: number of patients evaluated; RCT: randomised controlled trial; RR: relative risk; SAE: serious adverse event; AE: adverse event; vs: versus

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

No relevant data are available.

2. Number of patients or demarcation of patient groups eligible for treatment

Adult patients with non-hyperkeratotic, non-hypertrophic actinic keratosis (a + b)

approx. 990,000 to 1,114,000 patients

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: 31 January 2019):

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

4. Treatment costs

Annual treatment costs:

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

Designation of the therapy	Annual treatment costs/patient
Medicinal product to be assessed:	
Ingenol mebutate, topical	€ 94.56
Appropriate comparator therapy	
Diclofenac-hyaluronic acid gel (3%), topical	€ 88.96
5-fluorouracil (5-FU; 5%), topical	€ 51.77 – 103.54
(surgical) cryotherapy in the treatment of single lesions[2]	No specification possible

Costs after deduction of statutory rebates (LAUER-TAXE®) as last revised: 1 February 2019

Costs for additionally required SHI services: not applicable

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

Designation of the therapy	Annual treatment costs/patient
Medicinal product to be assessed:	
Ingenol mebutate, topical	€ 94.56
Appropriate comparator therapy	
Diclofenac-hyaluronic acid gel (3%), topical	€ 88.96
5-fluorouracil (5-FU; 5%), topical	€ 51.77 – 103.54
(surgical) cryotherapy in the treatment of single lesions[2]	No specification possible

Costs after deduction of statutory rebates (LAUER-TAXE®) as last revised: 1 February 2019

Costs for additionally required SHI services: not applicable

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

II. Entry into force

1. The resolution will enter into force on the day of its publication on the internet on the website of the G-BA on 21 February 2019.

2. The period of validity of the resolution is limited to 28 February 2022.

The justification to this resolution will be published on the website of the G-BA at www.g-ba.de.

Berlin, 21 February 2019

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

Prof. Hecken