Birch bark extract (treatment of wounds associated with epidermolysis bullosa (6 months and older))

Resolution of: 16 February 2023 valid until: unlimited
Entry into force on: 16 February 2023
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Therapeutic indication (according to the marketing authorisation of 21 June 2022):

Treatment of partial thickness wounds associated with dystrophic and junctional epidermolysis bullosa (EB) in patients 6 months and older.

Therapeutic indication of the resolution (resolution of 16.02.2023):

See therapeutic indication according to marketing authorisation.

1. Extent of the additional benefit and significance of the evidence

Birch bark extract is approved as a medicinal product for the treatment of rare diseases under Regulation (EC) No. 141/2000 of the European Parliament and the Council of 16 December 1999 on orphan drugs. In accordance with Section 35a, paragraph 1, sentence 11, 1st half of the sentence SGB V, the additional medical benefit is considered to be proven through the grant of the marketing authorisation.

The Federal Joint Committee (G-BA) determines the extent of the additional benefit for the number of patients and patient groups for which there is a therapeutically significant additional benefit in accordance with Chapter 5, Section 12, paragraph 1, number 1, sentence 2 of its Rules of Procedure (VerfO) in conjunction with Section 5, paragraph 8 AM-NutzenV, indicating the significance of the evidence. This quantification of the additional benefit is based on the criteria laid out in Chapter 5, Section 5, paragraph 7, numbers 1 to 4 of the Rules of Procedure (VerfO).

Children, adolescents and adults aged 6 months and above with wounds associated with dystrophic or junctional epidermolysis bullosa

Extent of the additional benefit and significance of the evidence of birch bark extract:

Hint for a minor additional benefit

Study results according to endpoints:[1]

Summary of results for relevant clinical endpoints

Endpoint category	Direction of effect/ risk of bias	Summary
Mortality	↔	No deaths occurred.
Morbidity	↑	Advantage in the endpoint of first complete wound closure
Health-related quality of life	n.a.	There are no assessable data.
Side effects	↔	No relevant differences for the benefit assessment.

Explanations:
↑: statistically significant and relevant positive effect with low/unclear reliability of data
↓: statistically significant and relevant negative effect with low/unclear reliability of data
↑↑: statistically significant and relevant positive effect with high reliability of data
↓↓: statistically significant and relevant negative effect with high reliability of data
↔: no statistically significant or relevant difference
∅: There are no usable data for the benefit assessment.
n.a.: not assessable

BEB-13 (EASE) study: pivotal, multicentre, double-blind RCT birch bark extract vs control gel (90-day double-blind period (DBP))

Mortality

Endpoint	
Overall survival	*No deaths occurred during the DBP of the EASE study.*

Morbidity

Endpoint	Birch bark extract		Placebo		Intervention vs control
	N[a]	Patients with event n (%)	N[a]	Patients with event n (%)	Relative risk [95% CI] p value[b]
First complete wound closure of the EB target wound within 45 days					
– according to clinical assessment	109	45 (41.3)	114	33 (28.9)	1.44 [1.01; 2.05]; 0.041
– which is confirmed by a second observation after 7 days	109	19 (17.4)	114	10 (8.8)	2.03 [0.99; 4.18]; 0.048

[1] Data from the dossier assessment of the G-BA (published on 1. Dezember 2022), unless otherwise indicated.

– which did not open again until day 45	109	27 (24.8)	114	23 (20.2)	1.23 [0.76; 2.01] 0.400
Wound infection					
– of the target wound[c]	109	2 (1.8)	114	5 (4.4)	0.44 [0.08; 2.34]; 0.326
– of additional wounds (defined as wounds that met the target wound criteria)[d]	109	2 (1.8)	114	1 (0.9)	-
– of other wounds (defined as wounds that did not meet the target wound criteria)[e]	109	12 (11.0)	114	18 (15.8)	-

Endpoint	**Birch bark extract**			**Placebo**			**Intervention vs control**
	N[a]	Patients with event n (%)	Median time (days) [95% CI]	N[a]	Patients with event n (%)	Median time (days) [95% CI]	Hazard ratio [95% CI] p value[f]
Time to first complete closure of the target wound according to clinical assessment *(presented additionally)*							
	109	50 (50.5)	92.0 [50.0; NE]	114	50 (43.9)	94.0 [89.0; NE]	0.86 [0.57; 1.31]; 0.251

Endpoint	**Birch bark extract**		**Placebo**		**Intervention vs control**
	N[a]	Patients with event n (%)[g]	N[a]	Patients with event n (%)[g]	LS mean difference [95% CI] p value[h]
Wound status: Change in EB target wound size *(presented additionally)*					
Size of EB target wound at baseline [cm^2]	109	107 (98.2) *MV (SD):* 16.7 (17.6)	114	111 (97.4) *MV (SD)*: 17.4 (12.2)	-
Percentage change in target wound size compared to baseline on day 60	109	84 (77.1) *LS mean (SE):* -49.07 (8.70)	114	92 (80.7) *LS mean (SE):* -40.99 (8.08)	-8.09 [-26.61; 10.43]; 0.390
Body surface area percentage (BSAP) affected by partial thickness EB wounds *(presented additionally)*					
BSAP according to Lund-Browder diagram at baseline	109	109 (100.0) *MV (SD):* 12.06 (9.97)	114	113 (99.1) *MV (SD):* 12.18 (12.22)	-
Change in BSAP compared to baseline on day 90	109	86 (78.9) *LS mean (SE):*	114	85 (74.6) *LS mean (SE):*	-1.28

		-3.41 (0.82)		-2.13 (0.79)	[-2.87; 0.30], 0.111
Frequency of dressing change *(presented additionally)*					
Frequency of dressing change per week at baseline	109	106 (97.2) *MV (SD):* 4.81 (1.97)	114	112 (98.2) *MV (SD):* 5.04 (1.96)	-
Change in frequency of dressing changes per week compared to baseline on day 90	109	101 (92.7) *LS mean (SE):* -0.65 (0.21)	114	105 (92.1) *LS mean (SE):* -0.03 (0.20)	-0.62 [-1.03; -0.22]; 0.0027

Endpoint	**Birch bark extract**			**Placebo**		
	N[a]	Patients with event n (%)[g]	Median (min; max)	N[a]	Patients with event n (%)[g]	Median (min; max)
Background pain						
Children < 4 years according to FLACC total score[i]						
Baseline	7	7 (100)	0 (0; 4)	10	10 (100)	0.5 (0; 4)
Change to baseline on day 60	7	7 (100)	0 (-4; 0)	10	8 (80)	0 (-4; 1)
Group difference p value: non-assessable[j]						
Age group ≥ 4 years according to Wong-Baker FACES pain rating scale[i]						
Baseline	102	102 (100)	3 (0; 10)	104	102 (98.1)	2 (0; 10)
Change to baseline on day 90	102	79 (77.5)	0 (-8; 6)	104	79 (76.0)	0 (-8; 6)
Group difference p value: 0.771[k]						
Procedural pain						
Children < 4 years according to FLACC total score[i]						
Baseline	7	7 (100)	3 (2; 10)	10	10 (100)	2 (0; 10)
Change to baseline on day 60	7	7 (100)	-2 (-9; 6)	10	8 (80)	0 (-10; 4)
Group difference p value: non-assessable[j]						
Age group ≥ 4 years according to Wong-Baker FACES pain rating scale[i]						
Baseline	102	98 (96.1)	4 (0; 10)	104	100 (96.1)	2 (0; 10)
Change to baseline on day 90	102	76 (74.5)	-1 (-10; 8)	104	78 (75.0)	0 (-10; 6)
Group difference p value: 0.051[k]						

Endpoint	Birch bark extract			Placebo		
	N[a]	Patients with event n (%)[g]	Median (min; max)	N[a]	Patients with event n (%)[g]	Median (min; max)
Itching according to Itch Man Scale[l] in children in the age group 4-13 years						
Baseline	50	50 (100)	2 (0; 4)	56	55 (98)	2 (0; 4)
Change to baseline on day 90	50	39 (78)	-1 (-4; 3)	56	43 (77)	-1 (-4: 2)
Group difference p value: 0.182[k]						

Endpoint	Birch bark extract			Placebo		
	N[a]	Patients with event n (%)[g]	MV (SD)	N[a]	Patients with event n (%)[g]	MV (SD)
Itching according to Leuven Itch Scale[m] in the age group ≥ 14 years						
Frequency subscale						
Baseline	52	52 (100)	69.2 (25.5)	48	48 (100)	68.8 (26.6)
Change to baseline on day 60	52	40 (76.9)	-11.9 (25.94)	48	39 (81.3)	-9.6 (24.07)
Group difference p value: 0.871[l]						
Change to baseline on day 90	52	40 (76.9)	-8.1 (26.2)	48	37 (77.1)	-10.1 (27.3)
Group difference p value: 0.344[l]						
Duration subscale						
Baseline	52	49 (94.2)	31.3 (43.8)	48	47 (97.9)	24.8 (37.1)
Change to baseline on day 60	52	37 (71.2)	-8.11 (36.35)	48	37 (77.1)	-0.90 (41.19)
Group difference p value: 0.350[l]						
Strength subscale						
Baseline	52	49 (94.2)	54.5 (22.55)	48	47 (97.9)	51.5 (26.29)
Change to baseline on day 60	52	37 (71.2)	-10.5 (24.60)	48	37 (77.1)	-4.3 (33.13)
Group difference p value: 0.400[l]						
Symptom consequences subscale						
Baseline	52	49 (94.2)	28.29 (22.47)	48	47 (97.9)	30.85 (25.56)
Change to baseline on day 60	52	37 (71.2)	-5.59 (14.52)	48	37 (77.1)	-6.22 (16.51)
Group difference p value: 0.113[l]						

Distress subscale[n]						
Baseline	52	49 (94.2)	42.9 (31.09)	48	47 (97.9)	43.2 (32.24)
Change to baseline on day 60	52	37 (71.2)	-9.5 (21.47)	48	37 (77.1)	-2.4 (25.43)
						Group difference p value: 0.116[l]
Symptom localisation subscale						
Baseline	52	49 (94.2)	35.64 (24.26)	48	47 (97.9)	33.55 (24.51)
Change to baseline on day 60	52	37 (71.2)	-3.53 (15.34)	48	37 (77.1)	-1.66 (17.50)
						Group difference p value: 0.916[l]

Endpoint	**Birch bark extract**		**Placebo**		**Intervention vs control**
	N[a]	Patients with event n (%)[g]	N[a]	Patients with event n (%)[g]	LS mean difference [95% CI] p value[h]
Sleep impairment according to 11-point Likert scale in subjects ≥ 14 years of age					
Baseline	52	52 (100) *MV (SD):* 4.6 (3.42)	48	48 (100) *MV (SD)*: 4.4 (3.13)	-
Change to baseline on day 90	52	40 (76.9) *LS mean (SE):* -0.75 (0.50)	48	92 (80.7) *LS mean (SE):* -1.12 (0.46)	0.37 [-0.77; 1.51]; 0.519

Health-related quality of life

Endpoint	
Quality of life	*No data could be considered.*

Side effects

Endpoint	**Birch bark extract**		**Placebo**		**Intervention vs control**
	N[o]	Patients with event n (%)	N[o]	Patients with event n (%)	Relative risk [95% CI] p value[p]
Adverse events (AEs)	108	88 (81)	113	91 (81)	-
Serious AEs (SAEs)	108	7 (6)	113	6 (5)	1.24 [0.43; 3.57]; 0.6909

Severe AEs	108	13 (12)	113	6 (5)	2.40 [0.98; 5.87]; 0.0543
Therapy discontinuations due to AEs[q]	108	3 (3)	113	4 (4)	0.79 [0.18; 3.47]; 0.7537
Adverse events with incidence ≥ 10% according to MedDRA system organ class					
Infections and infestations	108	37 (34)	113	36 (32)	1.08 [0.75; 1.56]; 0.6756
Gastrointestinal disorders	108	11 (10)	113	14 (12)	0.80 [0.38; 1.68]; 0.5495
Skin and subcutaneous tissue disorders	108	11 (10)	113	15 (13)	0.76 [0.36; 1.61]; 0.4776
General disorders and administration site conditions	108	21 (19)	113	25 (22)	0.88 [0.52; 1.49]; 0.6403
- Fever (PT)	108	9 (8)	113	15 (13)	0.62 [0.27; 1.39]; 0.2418
Injury, poisoning and procedural complications	108	68 (63)	113	65 (58)	1.10 [0.89; 1.36]; 0.3814
- Wound complication (PT)	108	66 (61)	113	60 (53)	1.16 [0.92; 1.47]; 0.2017

a. FAS population.
b. Stratified analysis. Cochran-Mantel-Haenszel test stratified by EB subtype and target wound size category.
c. In 1 subject in the intervention group, a wound infection was falsely reported as an infection of the target wound, although it was an infection of a "different" wound. A corrected analysis was performed post hoc with the corrected event rates (1 [0.9%] vs 5 [4.4%]), and no statistically significant difference was observed (relative risk 0.23 [95% CI 0.03; 1.97]; p = 0.142).
d. At baseline, 33 people in the intervention arm and 30 people in the control arm had at least 1 additional wound (Table 10).
e. No information is available on how many people were affected by other wounds; the corrected analysis (see footnote c) showed an incidence of 13 (12%) vs 18 (16%) people with wound infections of other wounds.
f. Cox regression model with treatment group, EB subtype, target wound size category, wound dressing type until day 90, baseline haemoglobin, baseline albumin and age of wound as covariates. p value based on log-rank test stratified by EB subtype.
g. Number of patients evaluated. % share in relation to the randomised study population.
h. Stratified analysis: ANCOVA with treatment group and EB severity and target wound size at baseline as fixed effects and baseline value as covariate.
i. Scale 0–10. A higher score represents greater pain.
j. Due to the small number of subjects, the test statistic including p value was not estimable for the planned analysis (2-sided Wilcoxon rank sum test stratified by EB subtype and target wound size category at baseline).
k. 2-sided Wilcoxon rank sum test using the Van Elteren extension, stratified by EB subtype and target wound size category at baseline.
l. Scale 0–4. A higher score represents more intense itching.
m. Scale 0–100. A higher score represents more intense itching.
n. Some study sites used an incorrect length of continuous VAS for the intensity and stress domains. A corrected analysis was carried out post hoc in which the values recorded with an incorrectly measured scale were converted to the correct scale. The corrected analysis did not produce any results that differed from the analysis shown here.
o. Safety analysis set of the EASE study without subjects with EB simplex (n = 1 per treatment arm).
p. Cochran-Mantel-Haenszel-Chi² hypothesis test stratified according to the factors EB severity and EB target wound size category.
q. The study participants received the study medication until the end of the DBP. When the wound was closed, further treatment was not necessary. Wound status deterioration, infection of the EB target wound, occurrence of unacceptable AEs and use of unauthorised concomitant medications were major protocol-defined reasons for discontinuation. The possible reasons for discontinuation that may occur prior to a potential discontinuation due to AEs represent a competing event for therapy discontinuation due to AEs. Against the background that these events occurred only to a

small extent, they have no impact on the certainty of results and interpretability of the AEs that led to discontinuation of the study medication.

Abbreviations used: ANCOVA: Analysis of covariance; BSAP: Body Surface Area Percentage; DBP: double-blind period; EB: Epidermolysis bullosa; FAS: Full Analysis Set; FLACC: Face, Legs, Activity, Cry, Consolability; HR: hazard ratio; CI: confidence interval; LS: Least Squares; max: maximum; min: minimum; MV: mean value; N: number of patients evaluated; n: Number of patients with (at least one) event; NE: not estimable; SD: standard deviation; SE: standard error; (S)AE: (serious) adverse event; VAS: visual analogue scale

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

Children, adolescents and adults aged 6 months and above with wounds associated with dystrophic or junctional epidermolysis bullosa

Approx. 270 to 860 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 Filsuvez (active ingredient: birch bark extract) at the following publicly accessible link (last access: 1 February 2023):

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

4. Treatment costs

Annual treatment costs:

Designation of the therapy	Annual treatment costs/ patient
Medicinal product to be assessed:	
Birch bark extract	Different from patient to patient

Costs after deduction of statutory rebates (LAUER-TAXE®) as last revised: 1 February 2023)

Costs for additionally required SHI services: not applicable

5. Medicinal products with new active ingredients according to Section 35a, paragraph 3, sentence 4 SGB V that can be used in a combination therapy with birch bark extract

Medicinal products with new active ingredients pursuant to Section 35a, paragraph 3, sentence 4 SGB V are medicinal products with the following new active ingredients that can be used in a combination therapy with birch bark extract for the treatment of partial thickness wounds associated with dystrophic and junctional epidermolysis bullosa (EB) in patients 6

months and older on the basis of the marketing authorisation granted under Medicinal Products Act:

Children, adolescents and adults aged 6 months and above with wounds associated with dystrophic or junctional epidermolysis bullosa

- No active ingredient that can be used in a combination therapy that fulfils the requirements of Section 35a, paragraph 3, sentence 4 SGB V.