Healthcare Improvement Scotland | SMC Advice on new medicines

SMC2651

birch bark extract gel (Filsuvez®)

Chiesi Limited

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The Scottish Medicines Consortium (SMC) has completed its initial assessment of the evidence for the above product using the ultra-orphan framework:

Indication under review: treatment of partial thickness wounds associated with dystrophic and junctional epidermolysis bullosa (EB) in patients 6 months and older.

Key points:

- Epidermolysis bullosa (EB) is a heterogenous group of rare inherited skin disorders that is complex to manage and causes a substantial reduction in quality of life. It is characterised by very fragile skin that is prone to blistering and erosions due to minor trauma or friction, with the resulting wounds usually extending through multiple layers of the skin surface. As well as the high wound burden, there is impaired wound healing and debilitating symptoms such as pain, pruritis, scarring, deformity, and immobility. There are also several systemic complications (for example anaemia, increased risk of infections, osteoporosis, and squamous cell carcinoma). These all can carry considerable morbidity and increased mortality risk.
- In a double-blind, randomised, phase III study, birch bark extract gel led to quicker wound healing than a control gel. Results may also suggest potential improvements in the frequency of dressing changes, and the amount of affected skin.
- The effect of birch bark extract on other relevant outcomes (for example pain and itching) in patients with EB is unclear. There is uncertainty about whether the beneficial effects of birch bark extract gel that were observed in the recessive dystrophic EB (DEB) subgroup, which represented the majority of patients in the EASE study, will be translated to the other subtypes of EB (junctional EB [JEB] and dominant DEB).
- A model-based health economic evaluation indicates that birch extract is associated with improved quality of life. Modelling suggested that birch bark would generate a discounted incremental Quality Adjusted Life Year (QALY) gain of 1.02. However, there were uncertainties associated with the economic results as a result of the data and inputs employed as well as the assumptions used. Additionally, the treatment's cost in relation to its health benefits is high.

Chair
Scottish Medicines Consortium

1. Clinical context

1.1. Background

Birch bark extract (Filsuvez®) is a non-aqueous cutaneous gel consisting of 10% active pharmaceutical ingredient birch bark extract and 90% sunflower oil; the gel has thixotropic properties (that is the viscous gel transforms into a liquid upon application) which is useful for applying to wounds. The precise mechanism of action of birch bark extract in wound healing is unknown[1, 2] but may include modulation of inflammatory mediators and involvement in keratinocyte differentiation and migration.[3]

Birch bark extract (Filsuvez®) cutaneous gel is licensed in the UK for the indication under review. The recommended instructions for birch bark extract (Filsuvez®) cutaneous gel are to apply the gel to the surface of a cleansed wound at a thickness of approximately 1 millimetre and cover with a sterile non-adhesive dressing or apply directly to the dressing, ensuring the gel is in direct contact with the wound. The gel should not be applied sparingly or rubbed in and should be reapplied at each wound dressing change. Each tube is for single use only. The tube should be discarded after use. The posology in paediatric patients (6 months and older) is the same as in adults. This product should not be used concomitantly with other topical products. For further information please see the product Summary of Product Characteristics (SPC).[1]

1.2. Nature of condition

Epidermolysis bullosa (EB) is a heterogenous group of rare inherited skin disorders caused by mutations in the genes that encode skin anchoring proteins of the dermo-epidermal junction. EB can be divided into four major subtypes depending on the level of skin cleavage; birch bark extract is only licensed for the dystrophic and junctional EB subtypes. In junctional EB (JEB), the skin separation occurs in the lamina lucida (or central basement membrane zone) between the epidermis and dermis layers of the skin; whilst in dystrophic EB (DEB), the separation occurs in the sublamina densa or upper dermis. DEB can be inherited as a dominant (only one gene copy is affected) or recessive (both copies are affected) trait; the recessive form is usually more severe but there is considerable overlap between these two forms of DEB. The more severe forms of DEB and JEB are likely to present from birth and are usually diagnosed in babies or children. Life expectancy depends upon disease severity and can range from less than one year of age (for example in severe JEB) to normal life expectance in other types of EB.[2, 4-6] In recessive DEB, particularly the generalised severe form, many patients survive only to their fourth decade as a result of aggressive metastatic squamous cell carcinoma (SCC) that arises within areas of repeated scarring.[2, 7, 8]

EB is characterised by very fragile skin that is prone to blistering and erosions due to minor trauma or friction; the resulting wounds usually extend through multiple layers of the skin surface (partial thickness wounds). As well as the high wound burden, there is impaired wound healing and several wounds may remain unhealed for long periods of time (chronic wounds

persist for >21 days). The presence of many painful wounds, which heal differently and have persisted for different lengths of time, means the management of patients with EB is very complex and involves many hours each week dressing wounds. This has a considerable impact on patients and their family or carers and can massively reduce their quality of life.[9-15] Patients with EB often have debilitating symptoms such as pain, pruritis, scarring, deformity, and immobility; as well as several systemic complications including nutritional issues due to gastrointestinal tract damage, anaemia, increased risk of infections, osteoporosis, and SCC. These all can carry considerable morbidity and increased mortality risk.[2, 11, 16]

There is a high unmet need in patients with EB, there is currently no cure and there are no other treatments licensed for EB. Clinical management of EB focuses on wound management, minimising complications, and improving quality of life where possible. Patients with EB are advised to take precautions to minimise new wounds and prevent new injuries, however this is very challenging, particularly for young children where minor trauma or friction will result in partial thickness wounds.[2, 17, 18] It is usual that parents or carers are involved in the management of patients with EB; their involvement ensures there are heterogeneous management plans that can vary depending on the subtype of EB, wound characteristics (size, severity, age), time of year and the patient's age.[17-20] Clinical experts consulted by SMC, as well as consensus guidelines, advised that the care of patients with EB commonly involves using non-adhesive bandages and topical agents (like the off-label use of antimicrobials and steroids), bathing to aid dressing changes, lancing and draining of blisters, attempts to reduce severe itching and administering pain medicines.[18, 19] Surgical procedures such as oesophageal dilatation, gastrostomy tube insertion, and hand surgery to manage contractures are common in patients with EB; these also place significant care demands on patients and their carers.

Clinical experts consulted by SMC considered that birch bark extract fills an unmet need in this therapeutic area, namely as there are no other specific treatments for EB.

The estimated prevalence for all EB types is less than 80 per 1 million people in the UK[2, 21]; previously a rate of 20 per 1 million people in Scotland has also been reported.[22] The number of patients with DEB and JEB in Scotland is less than 100, and DEB is more common than JEB.

2. Impact of new technology

Comparative efficacy

Evidence to support the efficacy and safety of birch bark extract cutaneous gel comes from the EASE study; study details are summarised in Table 2.1.

Table 2.1 Overview of relevant study.

Criteria	EASE study.[2, 16, 23, 24]
Study design	International, randomised, double-blind, phase III study.
Eligible patients	○ Male and female patients with dystrophic EB or junctional EB. Patients with Kindler EB were eligible but no patients were recruited. ○ ≥ 4 years of age (reduced to ≥ 21 days following an Independent Data Monitoring Committee (IDMC) safety review in 2019). ○ EB target wound 10 to 50 cm^2 in size aged ≥ 21 days and < 9 months outside of the anogenital region. ○ No patients with EB subtype Epidermis bullosa simplex. ○ No patients with clinical signs of local infection in the target wound. ○ No administration of systemic or topical steroids within 30 days. ○ No immunosuppressive or cytotoxic chemotherapy within 60 days. ○ No current and/or former malignancy including BCC/SCC.
Treatments and randomisation	Patients were randomised equally to receive Filsuvez® gel (consisting of 10% active pharmaceutical ingredient birch bark extract and 90% sunflower oil) or the control gel (consisting of 85% sunflower oil, 5% cera flava/yellow wax and 10% carnauba wax). The randomised treatment was administered topically at approximately 1 mm thickness to the EB target wound and to all areas on the patient's body that were affected by EB partial thickness wounds; these wound areas were then covered with a standard of care non-adhesive wound dressing. The randomised treatment was applied during all dressing changes (at least every four days) until the end of the double-blind phase (90 +/-7 days). Randomisation was stratified according to their EB subtype and target wound size: ○ DEB 10 to <20 cm^2 ○ DEB 20 to <30 cm^2 ○ DEB 30 to 50 cm^2 ○ JEB/Kindler 10 to <20 cm^2 ○ JEB/Kindler 20 to <30 cm^2 ○ JEB/Kindler 30 to 50 cm^2 After the 90-day double-blind phase, patients could enter the single-arm, 24-month open-label follow-up phase; patients in the Filsuvez® gel treatment group continued treatment whilst patients in the control group switched to receive Filsuvez® gel. Concomitant treatments that were permitted during the double-blind and open-label phases of the study included: ○ Liquid antiseptics at each dressing change to clean and/or reduce microbial colonisation of target wounds and additional wounds matching target wound criteria prior to study treatment. ○ Bathing (for example with chlorhexidine, diluted bleach, or salt) prior to study treatment at each wound dressing change. ○ Systemic antibiotics, except for the treatment of infections of the EB target wound or additional wounds matching target wound criteria. ○ Inhaled/ophthalmic/topical steroids for oesophageal strictures.

	Silver sulfadiazine, topical antibiotics, or topical steroids were permitted for treatment of any EB wound (except the EB target wound or additional wounds matching target wound criteria). Skin products such as creams, ointments, gels or emollients were not permitted on areas of the body affected by EB wounds during the double-blind phase.
Primary outcome	Proportion of patients with first complete closure[a] of the EB target wound within 45 days following treatment initiation.[b]
Secondary outcomes	Selected secondary outcomes, controlled for multiplicity were: ○ Time to first complete closure[a] of the EB target wound based on clinical assessment until the end of the double-blind phase (day 90). ○ Proportion of patients with first complete closure of the target wound within 90 days. ○ Incidence of target wound infection between baseline and day 90. ○ Maximum severity of target wound infections between baseline and day 90. ○ Change from baseline in total body wound burden at day 90, as per clinical assessment using section I (assessment of the skin activity score except for the anogenital region) of the EBDASI (EB Disease Activity and Scarring Index). ○ Change from baseline in itching at day 90.[c]
Statistical analysis	If the primary analysis of the primary outcome demonstrated superiority at the 5% significance level, hierarchical confirmatory testing of the key secondary outcomes (in the order outlined above) was planned on the FAS. If the primary outcome did not show superiority at the 5% significance level, the analysis of the key secondary outcomes was planned as non-confirmatory and descriptive. An unblinded interim analysis for sample size re-estimation was conducted by the IDMC when approximately 50% of patients had completed day 45 of treatment. The sample size was increased following this interim analysis, but not to the full amount possible under the protocol. Because of the planned sample size re-assessment, the primary analysis was adjusted using the method of Cui, Hung, and Wang (CHW). Since the IDMC deemed it necessary to increase the sample size, the final statistical analysis of the primary outcome will be performed based on the CHW approach to adjust the estimates provided by the CMH test.

[a]defined as the first appearance of complete re-epithelisation without drainage.

[b]the primary outcome was investigator assessed by photographing the EB target wound and any other wounds that match target wound criteria with the ARANTZ silhouette system. A confirmation of complete closure of the EB target wound visit, up to 9 days after first complete closure. Post-treatment assessments would be made within one week of wound closure to determine durability of healing.

[c]assessed using the Itch Man Scale for subjects ≥ 4 to 13 years of age and the Leuven Itch Scale for subjects ≥ 14 years old.
Abbreviations: BCC = basal cell carcinoma; CMH = Cochran-Mantel-Haenszel; DEB = dystrophic epidermolysis bullosa; EB = epidermolysis bullosa; FAS: full analysis set; IDMC = independent data monitoring committee; JEB = junctional epidermolysis bullosa; SCC = squamous cell carcinoma.

The results for the primary and selected secondary outcomes of the EASE double-blind phase (data cut off August 2020) are outlined below in Table 2.2. Birch bark extract gel treatment resulted in a larger proportion of patients achieving target wound closure by day 45 compared with the control gel; this difference was statistically significant. The small difference in the first secondary outcome tested for multiplicity (median time to first complete closure of the EB target wound based on clinical assessment until the end of the double-blind phase) was not statistically significant; hence, subsequent statistical testing was not carried out and the results for the remaining secondary outcomes are descriptive only.

Table 2.2 Results of primary and secondary outcomes in the Full Analysis Set (FAS) from the EASE double-blind phase (data cut off August 2020).[2, 23]

	Birch bark extract gel (n=109)[a]	Control gel (n=114)[a]
Primary outcome: Proportion of patients with first complete closure of EB target wound within 45 (+/- 7) days following treatment initiation.		
n (%)	45 (41%)	33 (29%)
Odds ratio (95% CI), p-value	1.84 (1.02 to 3.30), p=0.013	
p-value using unadjusted CMH test statistic	p=0.041	
Relative Risk (95% CI)[b]	1.44 (1.01 to 2.05)	
Secondary outcome: Median time to first complete closure of the EB target wound based on clinical assessment until the end of the double-blind phase (day 90).		
Median in days (95% CI)	92 days (50 to NE)	94 days (89 to NE)
Treatment difference, p-value	p=0.302	
Secondary outcome: Proportion of patients with first complete closure of the EB target wound within 90 days.		
n, (%)	55 (51%)	50 (44%)
Odds ratio (95% CI)	1.34 (0.78 to 2.32)	
Relative risk (95% CI)	1.16 (0.88 to 1.52)	
Secondary outcome: Incidence of EB target wound infection between baseline and day 90.		
n, (%)	2 (1.8%)	5 (4.4%)
Odds ratio (95% CI)	0.43 (0.08 to 2.33)	
Relative risk (95% CI)	0.44 (0.08 to 2.34)	
Secondary outcome: Maximum severity of EB target wound infections between baseline and day 90.[c]		
n, (%)	1 (0.9%) 'mild'	3 (2.6%) 'moderate' 1 (0.9%) 'severe'
Secondary outcome: Change from baseline in total body wound burden at day 90 (as per clinical assessment using section I of the EBDASI)		
Mean (SD)	n=84 -3.4% (7.2)	n=85 -2.8% (7.5)
LS mean (SE)	n=84 -0.44 (0.90)	n=85 -0.56 (0.85)
Difference in LS means (SE)	0.12 (0.86)	
95% CI of difference in LS means	-1.58 to 1.83	
Secondary outcome: Change from baseline in itching at day 90.		
Mean change in Itch Man Scale (subjects ≥ 4 to 13 years of age)[d]	n=39 -0.44	n=43 -1.0
Leuven Itch Scale[d,e] (subjects ≥ 14 years old)		
Frequency	-8.13	-10.14
Severity	-4.95	-10.76
Duration	-0.93	0.98
Consequence	-4.39	-3.54

Distress	-0.44	-0.26
Surface area	-1.54	0.68
Exploratory outcome: Change from baseline in BSAP (total body surface area affected by EB partial thickness wounds) at day 90.		
Mean (SD)	n=86 -4.32 (7.027)	n=85 -2.53 (8.852)
LS mean (SE)	n=86 -3.41 (0.82)	n=85 -2.13 (0.79)
Difference in LS means (SE)	-1.28 (0.80)	
95% CI of difference in LS means	-2.87 to 0.30	

[a] each treatment group has one patient with EB simplex despite this being an exclusion criterion.
[b] relative risk is the ratio of probabilities for first complete closure of target wound per treatments.
[c] severity of target wound infection between baseline and day 90 was evaluated if a participant had a wound infection event evidenced by adverse event. These were ranked from: mild, moderate, severe, life-threatening, and death.
[d] a reduction in the scale from baseline indicates improvement for the outcome.
[e] results for subjects ≥14 years using the Leuven Itch Scale were presented according to 6 domains rather than an overall score. Some sites used a visual analogue score of incorrect length for the severity and distress domains of the Leuven Itch Scale, so an additional corrected analysis was performed.

Abbreviations: BSAP = body surface area percentage; EB = epidermolysis bullosa; EBDASI = Epidermolysis Bullosa Disease Activity and Scarring Index; LS: least squares; NE = non-estimable; SD = standard deviation; SE = standard error.

Outcomes that assessed wound burden included the change from baseline in body surface area percentage (BSAP) score and Epidermolysis Bullosa Disease Activity and Scarring Index (EBDASI) score; only BSAP was used to inform the economic analyses. BSAP score is one method for measuring EB disease severity, but clinical experts contacted by SMC highlighted that whilst it is an appropriate measure of disease extent, it does not capture the impact or location of wounds in an individual patient. The submitting company highlighted that the full EBDASI instrument data were not collected in the EASE trial data, and as such BSAP was selected as a proxy measure to best represent how wounds across the body healed contemporaneously. At the end of the double-blind phase (day 90), the difference in LS means for both these outcomes that assessed wound burden numerically favoured birch bark extract gel but the absolute differences were small and not statistically significant.[2, 23]

Prespecified subgroup analyses by EB subtype (including JEB, recessive DEB, and dominant DEB) was carried out for the primary outcome and the first secondary outcome tested for multiplicity (median time to first complete closure of the EB target wound based on clinical assessment until the end of the double-blind phase).[24] The largest subgroup in the EASE study were those with recessive DEB (n=175) and for the primary outcome, there was a statistically significant difference in favour of birch bark extract gel for this subgroup; 44% versus 26% (relative risk 1.72, p=0.008).[2, 23] For the recessive DEB subgroup, whilst the median time to first complete closure of the EB target wound by day 90 was numerically shorter for those in the birch bark extract gel group compared with the control gel (64.0 days versus 94.0 days), this was not statistically significant. For patients with JEB (n=26) and dominant DEB (n=20), any numerical differences between treatment groups did not reach statistical significance, and in fact

numerically favoured the control group (for the JEB subgroup only) for both of these outcomes. However, caution should be applied to interpreting these results given the very small patient numbers in these two subtypes.[2, 23]

After the 90-day double-blind phase, patients could enter the single-arm, 24-month open-label follow-up phase; patients in the birch bark extract gel treatment group continued treatment (titled 'former birch bark extract gel group'; n =100) whilst patients in the control group switched to receive birch bark extract gel (titled 'former control gel group'; n=105, consisting of the 99 patients who completed the double-blind phase and the 6 patients who discontinued the double-blind phase prematurely as described above).[2, 16]

Since the primary outcome involved an assessment within 45 days of initiating treatment, it was not included in the open-label phase. All secondary outcomes in the open-label phase were very similar to the those in the double-blind phase, with the addition of new patient reported outcomes assessing changes from the open-label phase baseline (day 0 of the open-label phase) in disease severity (iscorEB; instrument for scoring clinical outcomes of research for EB) and quality of life (EQ-5D). It was noted that there were very small numbers of respondents for these patient reported outcomes.[16, 25]

The EASE study has been completed and the final results from the open-label phase (data cut off July 2022) are available. In general, any improvements observed in the double-blind phase for birch bark extract gel were maintained in the open-label phase.[16] However, none of these secondary outcomes were powered for statistical significance.[16, 25]

Unplanned, post-hoc exploratory analyses were conducted for the frequency of dressing changes. At the end of the double-blind phase (day 90), a higher proportion of patients in the birch bark extract group (21%) had a reduction in the frequency of dressing changes compared with the control gel group (11%)[16]; this equated to one less dressing change every 2 weeks for those receiving birch bark extract gel compared with the control gel.[16, 23]Additionally, more patients in the birch bark extract group (15%) no longer required daily dressings compared with the control gel (6.1%). These reductions in the frequency of dressing changes were maintained in the open-label phase.[16]

Another post-hoc analysis was carried out for the number of tubes of birch bark extract gel used per month. This showed that over the course of the study (both double-blind and open-label phases for patients with available data [n=214]), the median number of birch bark extract tubes used was 381, and the median number of tubes used per month was 19 (ranging from 17 tubes per month for 4 to < 12 years old and 24 tubes per month for those 0 to < 4 years old); there is no data about tube usage available for the control gel group during the double-blind phase.[16] However, it was the mean tube usage per month (across the EASE double-blind phase and 24-month open-label phase) that was used to inform the economics (these results are commercial in confidence).

Comparative safety

At the end of the double-blind phase, a similar proportion of patients in the birch bark extract gel (n=109) and control gel (n=114) groups respectively, reported: adverse events (AEs) (82% versus 81%), serious AEs (6.4% versus 5.3%), AEs leading to drug withdrawal (2.8% versus 3.5%), and serious AEs leading to study withdrawal (2.8% versus 1.8%).[2] Overall, 89% of all patients completed the 90-day double-blind phase of the EASE study; 92% in the birch bark extract gel group and 87% in the control gel group. It should be noted that 6 patients (5.3%) in the control gel group discontinued the double-blind phase prematurely due to worsening of the EB target wound status or due to EB target wound infection and continued into the open-label phase prematurely (at the investigator's discretion).[2, 16]

At the end of the open-label phase, the frequency of AEs was similar to the double-blind phase. From those originally recruited to the study, 69% of patients completed the open-label phase whilst the remaining 31% discontinued the study before the final 24-month visit.[16] The most frequently reported AEs (≥5% of all 205 subjects) were wound complication (41%), anaemia (18%), wound infection (10%), wound infection staphylococcal (10%), pyrexia (9.8%), oesophageal stenosis (9.3%), wound infection bacterial (7.8%), pruritus (6.8%), and dysphagia (6.3%); these events were deemed to be consistent with the course of the disease.[16]

Birch bark extract gel is sterile. However, wound infection is an important and serious complication that can occur during wound healing. In the case of infection, it is recommended to interrupt treatment.[2]

Overall, the safety profile of birch bark extract gel in JEB and DEB patients over the age of 6 months was considered acceptable by regulators.[2, 16, 26] 70% of patients randomised in the EASE study were < 18 years of age (median age of 12 years). 8% of patients were < 4 years of age and 2 patients were < 1 year of age. The adverse reactions observed in the overall population were similar to those observed in the paediatric population.[1]

The safety profile indicates no cause for concern apart from local, mainly wound-related AEs.[2, 16] Limited systemic absorption is expected. Most AEs were of mild or moderate intensity and deemed to mostly be consistent with the course of the disease.[2, 16]

Clinical effectiveness issues

The key strengths and uncertainties of the clinical evidence are summarised below.

Key strengths:

- Birch bark extract gel is the first licensed treatment in this therapeutic area in the UK.[16] Clinical experts consulted by SMC considered that birch bark extract is a therapeutic advancement due to significantly improving wound healing.
- EASE was a randomised, double-blind, phase III study with a large sample size, for a rare condition, of over 200 patients with EB. In the context of an orphan condition, the data

submitted were considered by regulators to be comprehensive as a controlled study has been performed and safety data is available for approximately 140 patients exposed for more than two years.[2, 16]

- The demographics of the recruited patients in the EASE study appear to align with the licensed indication. The median age of participants was 12 years of age (ranging from 6 months to 81 years). Both EB subtypes listed in the licensed indication were also recruited DEB (recessive and dominant) and JEB.[2, 23]
- The treatment effect of birch bark extract gel on the proportion of patients with first complete closure of the EB target wound within 45 days, assessed as the primary outcome, whilst modest in magnitude, was statistically significant and considered clinically meaningful by regulators.[2, 27]
- The EASE study also included an open-label follow-up of up to 24 months. In general, any improvements seen with birch bark extract gel during the double-blind phase were generally maintained during the open-label phase (with most being assessed at month 3 of the open-label phase).[2]
- There were observed reductions in dressing changes associated with birch bark extract gel which would be of benefit to this patient population since this can represent a significant burden to patients and their carers.[16]

Key uncertainties:

- Since the result for the first secondary outcome (median time to first complete closure of the EB target wound based on clinical assessment until the end of the double-blind phase) was not statistically significantly or notably different numerically (92 versus 94 days) between the treatment groups, the results for all of the secondary outcomes were non-confirmatory. This means there were no formally demonstrated positive effects on wound infections, total body wound burden, itch, pain or sleep can be claimed for birch bark extract gel. However, it is acknowledged that in rare diseases, secondary outcomes may be underpowered for formal statistical testing.[16, 23]
- In the pre-specified subgroup analysis, the treatment effect was observed in patients with recessive DEB. Very small patient numbers with JEB (n=26) and dominant DEB (n=20) were recruited to the study and clinical data with these subtypes is limited.[1, 23] This could represent a generalisability issue to these patients within NHSScotland.
- The majority of patients had severe disease, with 79% being diagnosed with recessive DEB (generalised severe recessive DEB was the most common form). This is possibly a result of the study inclusion criteria, including wound sizes (10 to 50 cm^2) and duration, which are characteristic of these subtypes.[23] It is uncertain what proportion of DEB and JEB patients in Scotland this criterion (specifically the wound size of 10 to 50 cm^2) would apply to. The numbers of eligible patients will likely be small but may vary given the unpredictable nature of EB.
- In the EASE study, 31% of patients discontinued the study before the final 24-month visit; this was considered reasonable in a 24-month follow-up study in a severe disease.[16]

However, in the open-label phase the proportion of patients who were lost to follow-up increased at each 3-month visit[16]; loss to follow-up was >10% at month 3, >25% at month 12 and >30% at month 24.[25] It was noted that a higher proportion of people with severe EB were lost to follow-up than those with less severe EB at these later timepoints; this could be because of informative censoring (for example that the severity of a patient's condition may directly influence whether a patient participated in a clinical assessment to provide relevant data).[25]

3. Impact beyond direct health benefits and on specialist services

If the introduction of birch bark extract gel has positive effects on wound healing and a reduction the number of dressing changes this would have considerable benefits for the patient and their carers. Less time spent managing their condition would allow them more time to participate in daily activities for example education. If a reduction in total body wound burden occurred, this may lead to a reduction in long-term complications.

Since the number of patients in Scotland with EB is very small, treatment and care for both adults and children are concentrated in a small number of specialist centres with specialised clinical input and support from dermatologists and nurses. Specialist clinics and outreach nursing support is available in the community.[28] It is anticipated that birch bark extract would be administered by patients, carers, or parents at home. The treatment would likely be started or recommended and monitored by the specialist EB service.[29] Patients/carers would require training in the use of the gel but significant service implications are not expected.

4. Patient and carer involvement

The following information reflects the views of the specified Patient Group.

- We received a patient group submission from DEBRA UK, which is a registered charity.
- DEBRA UK has received 0.39% pharmaceutical company funding in the past two years, including from the submitting company.
- People living with EB live in constant and debilitating pain, and in severe cases it can be fatal. Large areas of skin may be missing, raw and bleeding requiring 2 to 4 hours of specialised dressing changes daily. Chronic pain is a key factor with most people experiencing pain every day. The constant pain and need for often daily painful and invasive care to wounds, can take its toll on the mental health of the person with EB and their family. Schooling can be patchy due to the time it takes for children to have their bandages changed daily, and having to miss school due to ill-health, lack of specialist

equipment available for them, travel to medical appointments and fatigue. Finding appropriate employment can be difficult for adults.

- There are no treatments designed specifically for EB that significantly reduce their pain, wound care, or scarring. People living with EB are subjected to hours of daily bandage changes due to poor wound healing in the condition, so any treatment that promotes faster wound healing could help them live a little better each day.

- Improving wound healing leads to reduced pain, itch and dressing changes, and perhaps longer-term benefits such as less inflammation and improved function in day-to-day life. With reduced pain comes less anxiety and potentially other tangible benefits.

- The impact of a positive change in treatment is not limited to the individual, and the impact on the family, parents, and siblings, is of critical importance. The costs to the NHS of bandages and trying out treatments not designed for EB are considerable. A technology that could reduce the number of bandages for people with EB could also represent a cost-saving to the NHS as well as each of those families. Better wound healing represents less pain, less anxiety, better quality of life, more independence, and more time for whole families to live a better life together.

5. Value for money

5.1. Economic case

The submitting company presented an economic case, summarised in Table 5.1.

Table 5.1 Description of economic analysis

Criteria	Overview
Analysis type	Cost-utility analysis.
Time horizon	80 years, with an assumed starting age of 16 years old.
Population	The submitting company requested SMC consider birch bark extract for the treatment of partial thickness wounds associated with dystrophic epidermolysis bullosa (DEB) and junctional epidermolysis bullosa (JEB) in patients aged 6 months and older.
Comparators	The comparator was current clinical management (CCM). The company noted that there is no curative treatment for DEB or JEB and the mainstay of treatment is wound management, reducing potential for new injury, minimising complications, and improving quality of life. As such, no active comparator treatment was used in the model, but background health state costs were applied in each arm of the model.
Model description	A seven health-state transition model was used, with six health states defined using discrete ranges of patient body surface area percentage (BSAP) and an absorbing death state. In the absence of any clinically defined severity thresholds based on BSAP, health state ranges were defined by dividing BSAP observed in the EASE study into categories ranging from 0% to 4% coverage in the least severe health state to 25% or greater coverage in the most severe state. Patients were initially assumed to be equally distributed across the six BSAP health states. Patients moved between adjacent or non-adjacent health states or to death within a given 30-day model cycle according to transition probabilities.

Clinical data	Clinical data for transition probabilities between BSAP health states for birch bark extract and CCM were drawn from the EASE double-blind phase using data at baseline, day 30, day 60 and day 90.[2, 16, 23, 24] Data from the following 12-month (day 450 relative to double-blind phase baseline) and 24-month (day 810) visits of the EASE open-label phase were used to derive transition long term transition probabilities for patients receiving birch bark extract. Discontinuation from birch bark extract to 90 days was sourced from the EASE double-blind phase, with discontinuation beyond this point estimated at from clinical expert opinion. Survival for dominant DEB, recessive DEB (other), and JEB (non-severe only) patients was assumed equal to the general population. Survival for recessive DEB (severe) patients was sourced from the Kaplan-Meier curve published by Petrof et al., 2022.[21]
Extrapolation	For each 30-day model cycle, up to 90 days, moved patients between health states in each arm based on the estimated transition probabilities from the EASE study. For patients receiving CCM (after day 90), a steady state was assumed whereby patients remained at the last observed level of BSAP severity with no further health state transitions, except for death. The submitting company noted there would be patient level fluctuations in BSAP according to the natural disease cycle of EB (irrespective of treatment), but with the overall distribution of patients across health states remaining constant, hence the steady state assumption used in the model. From day 90 to day 810, further health state transitions were applied to patients in the birch bark extract arm. These were 360-day transition probabilities, with health state membership for model cycles between open-label phase visit dates estimated via interpolation, assuming a linear transition between states. Beyond day 810, a steady state was assumed in both arms. No further health state transitions took place, other than those due to discontinuation of birch bark extract, or death in either arm. Discontinuation from birch bark extract was applied throughout the model. An 8.3% discontinuation rate was applied in the model at 90 days, with an annual discontinuation rate of 1% applied beyond this point. A continuity correction was applied in the base case, to allow for transitions to be estimated where no patients were observed transitioning from a particular health state in the clinical data. This supplemented patient transitions observed in the EASE study with additional transitions from 'hypothetical' patients. The base case distributed these additional transitions equally across cells (reflecting an assumption that subsequent health state is entirely independent of the patient's preceding state), with a scenario restricting to adjacent states (assuming an equal probability of staying in the same state, improving by one state or worsening by one state). In addition, informative censoring (whereby missing data may be more prevalent in higher-severity patients rather than missing at random) was considered in the model. In the base case patients last observed in health states 5 and 6 remained in those health states in subsequent cycles. This was applied when deriving transition probabilities from days 90 to 810.
Quality of life	Health state utility values were derived from pooled data collected during the EASE study open-label phase, using the standardised instruments EQ-5D-5L and EQ-5D-Y. EQ-5D-5L domain scores were mapped to the EQ-5D-3L.[30] In the absence of a validated value set specific to the EQ-5D-Y, the adult EQ-5D-3L tariff was also applied to measurements collected from children and adolescents using the youth version of the instrument. The base case health state utility values were: 0.609 (HS1), 0.482 (HS2), 0.392 (HS3), 0.293 (HS4), 0.191 (HS5), and 0.118 (HS6). The submitting company also presented alternative health state utility values from a cross-sectional survey (CSS) and a time trade-off study (TTO). The CSS utility values were: 0.69 (HS1), 0.64 (HS2), 0.59 (HS3), 0.54 (HS4), 0.49 (HS5), and 0.44 (HS6). The TTO utility values were: 0.82 (HS1), 0.79 (HS2), 0.76 (HS3), 0.61 (HS4), 0.53 (HS5), and 0.54 (HS6). No adverse event disutilities were included.

	Carer utilities were excluded in the base case but were included as a scenario.
Costs and resource use	The model included medicine acquisition costs. These were based on a mean tube usage per month observed across the EASE double-blind phase and 24-month open-label phase (value listed as commercial in confidence). Given the topical application no administration costs were included. No adverse event costs were included. Other costs included were the health state resource costs, that included cost of dressings and formal care costs for time spent changing dressings and outpatient hospital visits. The most substantial of these costs was dressings. Costs associated with wound dressings were derived from PEBLES[31], which reported a mean annual cost of £45,884 per patient. This mean annual cost was combined with dressing application estimates the submitting company's expert elicitation exercise to generate annual dressing costs for each health state.
PAS	A Patient Access Scheme (PAS) was submitted by the company and assessed by the Patient Access Scheme Assessment Group (PASAG) as acceptable for implementation in NHSScotland. Under the PAS, a discount was offered on the list price.

5.2. Results

The base case economic results are shown in Table 5.2, inclusive of the PAS discount on birch bark extract gel. The majority of incremental costs were from medicine acquisition costs. The majority of incremental QALY gain for birch bark extract was from health states 1 and 2.

Table 5.2. Base case results (including birch bark extract gel PAS)

	Total costs (£)	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs	ICER (£/QALY)
Birch bark extract gel	1,188,219	11.75	144,388	0.00	1.02	141,805
CCM	1,043,831	10.74	-	-	-	-

Abbreviations: CCM = current clinical management; ICER = incremental cost effectiveness ratio; Incr = incremental; LYG = life year gain; PAS = Patient Access Scheme; QALY = quality adjusted life year.

5.3. Sensitivity analyses

Results of the sensitivity analysis are shown in Table 5.3. Again, these are inclusive of the PAS discount on birch bark extract gel. The ICER was most sensitive to alternative resource use sources, alternative utility values and informative censoring.

Table 5.3: Scenario analysis results (including birch bark extract gel PAS)

	Parameter	Base case	Scenario	Incr. Costs (£)	Incr. QALYs	ICER (£/QALY)
	Base case	-	-	144,388	1.02	141,805
1	Time horizon	80 years	10 years	55,896	0.39	143,346
2	Informative censoring	No improvement in HS5-6 censoring	Missing at random	86,299	1.27	68,028
3a	Continuity correction	Included (all transitions)	Excluded	103,511	1.21	85,418
3b		Included (all transitions)	Included (adjacent transitions)	124,066	1.10	112,955

4a	Utilities	EASE	Cross-sectional survey	144,388	0.51	285,421
4b		EASE	Time trade-off study	144,388	0.65	221,702
5	Carer utilities	Excluded	Included	144,388	1.57	91,876
6a	Resource use	SEE and Pillay et al. 2020[18]	Angelis 2022[32] (with SEE and Pillay et al. 2020 materials)	153,658	1.02	150,908
6b		SEE and Pillay et al. 2020	Angelis 2022 (including materials)	306,013	1.02	300,538
7a	Baseline health state distribution (both arms)	Equal across 6 health states	EASE baseline pooled	196,953	0.77	254,436
7b			EASE arm-specific	209,433	0.71	294,661
8	Annual change in BSAP after 90 days: RDEB-S	0%	1.3%	146,038	1.01	145,148
9	Discontinuation post-90 days	1%	16.45%	33,843	0.23	146,990

Abbreviations: HS= health state; ICER = incremental cost effectiveness ratio; Incr = incremental; PAS = Patient Access Scheme; QALY = quality adjusted life year; SEE = structured expert elicitation.

5.4. Key strengths:

- The health state transition approach was appropriate to capture wound burden severity transitions for patients receiving treatment for dystrophic and junctional EB.
- The submitting company considered multiple sources of utility values, including EQ-5D-5L and EQ-5D-Y data from the EASE open-label phase, a cross-sectional study, a time-trade-off study. However, these remained a source of uncertainty and additional validation would have been useful.
- The company conducted a structured expert elicitation exercise to obtain UK focussed resource use estimates.
- There was sufficient identification of variables that results were sensitive to in one-way deterministic sensitivity analysis with an appropriate range used.

5.5. Key uncertainties:

- There were limited raw data observations to derive transition probabilities, with no patients observed transitioning between selected health states. A continuity correction was used to account for this, with assumed additional transitions for hypothetical patients were distributed evenly across all health states (reflecting an assumption that subsequent the health state is entirely independent of the patient's preceding state). A scenario restricting to adjacent states was also considered (assuming an equal probability of staying in the

same state, improving by one state or worsening by one state) reducing the ICER to £112,955 (Scenario 3b). The limitation with the continuity correction approaches was they do not account for the distribution of observations, as some transitions may be more likely to occur than others. Removing the continuity correction entirely lowered the ICER to £85,418 (Scenario 3a). In sum, the limited raw data and continuity correction methods used increased uncertainty in the ICER. However, the company did select the most conservative option in the base case from those it presented.

- Informative censoring may have been present in the raw data, whereby missing data may be more prevalent in higher-severity patients rather than missing at random. The company considered a conservative approach to account for informative censoring, where base case patients last observed in health states 5 and 6 remained in those health states in subsequent cycles. This approach was applied when deriving transition probabilities, affecting the long-term health state distribution for birch bark extract. However, given the limited number of raw data observations in the higher health states, there was substantial ICER variation present when excluding the approach to account for informative censoring and assuming missing at random instead. This reduced the ICER to £68,028 (Scenario 2).
- The economic base case assumed that patients were initially evenly distributed across the six BSAP health states. The submitting company noted that this was chosen to reflect the potential under-representation of more severe patients in EASE (due, for example, to exclusion criteria such as the existence of current or former malignancies). However, using alternative distributions from EASE did demonstrate variation in the ICER. Using the EASE baseline pooled distributions increased the ICER to £254,436 (Scenario 7a). Using the EASE arm-specific distributions increased the ICER to £294,661 (Scenario 7b). These alternative scenarios had higher proportions of patients in the least severe health states and less in the most severe health states compared to the base case assumed by the company.
- A steady state assumption was used in the model, whereby patients remained at the last observed level of BSAP severity (beyond 90 days in the CCM arm and beyond 810 days in the birch bark extract arm). This assumption assumed fluctuations in BSAP according to the natural disease cycle of EB (irrespective of treatment), but that the overall distribution of patients across severity states would remain constant. This is a challenging assumption to explore, with only limited additional analysis exploring a 1.3% annual change in BSAP after the transition period in RDEB-S patients in both arms (Scenario 8).
- The utility values derived from the EASE study were subject to limitations. Firstly, the EQ-5D-5L and EQ-5D-Y data collected were only available in the EASE open-label phase and not in the double-blind phase, limiting data collection. Secondly, there is no UK value set for EQ-5D-Y, with the adult EQ-5D-3L UK value set applied to these data, increasing uncertainty in the utility values used in the base case. Thirdly, the utility values used in the base case from the EASE study were lower than those of the alternative cross-sectional study and time trade-off vignette studies, with greater differences observed in worse health states. Although the base case use of prospectively collected EQ-5D data from the study population is preferable, there remains substantial uncertainty from considering

alternative utility values (£285,421 if using the CSS utilities, Scenario 4a, and £221,702 if using the time trade-off utilities, Scenario 4b). The health state utility values were also noted as some of the most sensitive parameters in one-way sensitivity analysis.

- There were uncertainties in the quantities and valuation of dressings. Firstly, the structured expert elicitation exercise used to derive mean dressing use estimates had a limited expert count (n=2). Secondly, the cost of dressings, which used a mean annual cost of £45,884 per patient from Pillay et al. 2020 based on 53 patients with recessive DEB, was not fully reflective of the JEB and DEB population under consideration. Thirdly, there was an assumption that the Pillay cohort was evenly distributed across the six model health states when deriving mean dressing costs for each health state, which may increase uncertainty if this was not the case. Alternative sources for resource use were limited. Applying resource use costs from Angelis et al. 2022 increased the ICER to £300,538 (Scenario 6b), but this study was limited as materials costs were not clearly defined. Blending the Angelis et al. 2022 with dressing costs derived from the structured expert elicitation exercise and Pillay et al. 2020 generated an ICER closer to the base case of £150,908 (Scenario 6a). Although the sources used in the base case likely remain the most appropriate from those available, the ICER demonstrated sensitivity to the dressing costs in scenarios and one-way deterministic sensitivity analysis.
- Utility decrements and costs for adverse events were not included in the economic base case. The company highlighted adverse events associated with birch bark extract usage were mostly of low severity and associated with disease complications (treatment-emergent) rather than being directly associated with birch bark extract or current clinical management (treatment-related). This may be reasonable, but as no exploratory analysis was provided, this cannot be verified.
- The 1% per annum discontinuation rate applied after 90 days in the model was based on clinical opinion and was not aligned with the EASE open-label phase discontinuation data. A pessimistic annual discontinuation rate of 16.45% corresponding to the levels observed in the EASE open-label phase was considered. If running this annual discontinuation rate in the model after 90 days, the ICER increased slightly to £146,990 (Scenario 9).

The economic analysis is subject to uncertainties. These issues are mostly from the limited data available in the ultra-orphan indication being inputted into the model. However, there are further uncertainties regarding resource use and utilities. The treatment's costs in relation to benefits remains high.

6. Costs to NHS and Personal Social Services

With the PAS for birch bark extract gel, the gross impact on the medicines budget was estimated at £229k in year one rising to £234k in year five. As no medicines were assumed to be displaced the net medicines budget impact is equivalent to the gross impact.

*Other data were also assessed but remain confidential.**

7. Guidelines and protocols

A variety of clinical guideline recommendations and expert consensus statements are available for various aspects of EB (for example pain care, managing SCC, nutrition support, psychosocial management); however, none of these are UK specific according to the submitting company.

Clinical experts contacted by SMC confirmed that the International Consensus: Best practice guidelines for skin and wound care in epidermolysis bullosa (published in 2017) are followed by clinicians in Scotland.[18]

In 2022, the West of Scotland Managed Clinical Network for Neonatology approved guidelines titled 'Epidermolysis bullosa (EB) Care of Neonates' that covered the immediate (acute) care of neonates, or neonates provisionally diagnosed with EB, for all neonatal units in the West of Scotland.[33]

8. Additional information

8.1. Product availability date

19 December 2023.

Table 8.1 List price of medicine under review

Medicine	Dose Regimen	Cost per month (£)[a,b]
Birch bark extract cutaneous gel	**One application to the wound surface during each wound dressing change (see section 1.1).**	**4,680.61 to 6,607.92**

[a] *Birch bark extract cutaneous gel is for single use only.*

[b] *Cost range is based on the lowest (17 tubes per month for 4 to <12 years old) and highest (24 tubes per month for 0 to <4 years old) median number of tubes used per month during the double-blind and open-label phases in the EASE study.*[16]

Doses are for general comparison and do not imply therapeutic equivalence. Costs from BNF online on 10 April 2024. Costs do not take any patient access schemes into consideration

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This assessment is based on data submitted by the applicant company up to and including 17 May 2024.

**Agreement between the Association of the British Pharmaceutical Industry (ABPI) and the SMC on guidelines for the release of company data into the public domain during a health technology appraisal:*https://www.scottishmedicines.org.uk/about-us/policies-publications/

Medicine prices are those available at the time the papers were issued to SMC for consideration. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC assessment report.

Patient access schemes: A patient access scheme is a scheme proposed by a pharmaceutical company in order to improve the cost-effectiveness of a medicine and enable patients to receive access to cost-effective innovative medicines. A Patient Access Scheme Assessment Group (PASAG), established under the auspices of NHS National Services Scotland reviews and advises NHSScotland on the feasibility of proposed schemes for implementation. The PASAG operates separately from SMC in order to maintain the integrity and independence of the assessment process of the SMC. When a medicine is available through the ultra-orphan pathway, a set of guidance notes on the operation of the patient access scheme will be circulated to Area Drug and Therapeutics Committees and NHS Boards prior to publication of SMC assessment report.

Assessment report context:

No part of the assessment summary on page one may be used without the whole of the summary being quoted in full.

This assessment represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.