5.29 BIRCH TRITERPENES (BIRCH BARK DRY EXTRACT), Gel containing 100 mg per 1 g, 23.4 g Filsuvez®, Chiesi Australia Pty Ltd

1 Purpose of submission

1.1 The Category 1 submission requested a Section 85, Authority Required (Written) listing for birch triterpenes topical gel for the treatment of patients with partial thickness skin wounds caused by dystrophic epidermolysis bullosa (DEB) or junctional epidermolysis bullosa (JEB). Each 1 g of gel contains 100 mg birch bark dry extract (10% w/w) which is composed of a mixture of triterpenes (84-95% w/w).

1.2 The submission stated that birch triterpenes gel accelerates wound healing (when used alongside standard dressings), potentially reducing overall wound burden, with associated improvements in quality of life for patients and caregivers.

1.3 Listing was requested on the basis of a cost-effectiveness analysis versus best supportive care (BSC).

Table 1: Key components of the clinical issue addressed in the submission

Component	Description
Population	Patients with partial thickness wounds associated with dystrophic or junctional epidermolysis bullosa.
Intervention	Birch triterpenes 10% topical gel applied liberally at a thickness of approximately 1 mm to the wound surface and covered by a sterile non-adhesive wound dressing or applied to the dressing in direct contact with the wound. The gel should be reapplied at each wound dressing change. Birch triterpenes gel is used as an adjunct to best supportive care.
Comparator	Best supportive care, comprising wound dressings, blister care, infection prevention, pain/itch relief, nutrition support and surgery for complications.
Outcomes	Proportion of patients with first complete closure of the target wound within 45 days, time to first complete closure of the target wound within 90 days, incidence of infection, wound burden, wound size, frequency of dressing changes, quality of life and adverse events.
Clinical claim	Birch triterpenes topical gel (as an adjunct to best supportive care) is superior in terms of efficacy and non-inferior in terms of safety compared to best supportive care.

Source: Table 1.1-1, p24 of the submission.

2 Background

Registration status

2.1 The submission was made under the TGA/PBAC Parallel Process and with the review being under the Comparable Overseas Regulator (COR-B) pathway. The TGA Delegate's Overview was finalised on 8 April 2026. Birch triterpenes gel (birch bark dry extract (84-95% triterpenes) 100 mg/g gel tube) was listed on the Australian Register of Therapeutic Goods on 5 May 2026 for the treatment of partial thickness wounds

associated with dystrophic and junctional epidermolysis bullosa (EB) in patients aged 6 months and older.

Previous PBAC consideration

2.2 This is the first PBAC consideration of birch triterpenes topical gel.

2.3 This item was initially submitted for consideration at the March 2026 PBAC meeting as the TGA Delegate's Overview was expected prior to that meeting, however the PBAC consideration occurred at the July 2026 meeting following receipt of the TGA Delegate's Overview in April 2026.

3 Requested listing

MEDICINAL PRODUCT medicinal product pack	DPMQ	Max. qty packs	Max. qty units	№.of Rpts	Available brands
Birch triterpenes 10% (w/w) topical gel, 23.4 g, 10 tubes	$[redacted][a]	1	10	5	FILSUVEZ
Birch triterpenes 10% (w/w) topical gel, 23.4 g, 30 tubes	$[redacted][a]	1	30	5	
Category / Program: Section 85 General Schedule					
Prescriber type: ☒Medical Practitioners					
Restriction type: ☒Authority Required (in writing only via post/HPOS upload)					
Condition: Dystrophic epidermolysis bullosa or junctional epidermolysis bullosa.					
Indication: Treatment of partial thickness wounds associated with dystrophic epidermolysis bullosa or junctional epidermolysis bullosa					
Treatment Phase: Initial treatment					
Treatment criteria: Must be prescribed by a dermatologist or a paediatrician experienced in epidermolysis bullosa management					
Clinical criteria:					
Patient must have a confirmed diagnosis of dystrophic epidermolysis bullosa (recessive or dominant) or junctional epidermolysis bullosa					
AND					
Clinical criteria:					
The patient must have one or more partial-thickness wound(s) that: • have been present for ≥21 days despite standard care, AND • are not infected or requiring systemic antibiotic treatment, AND • constitute a chronic wound field of ≥10 cm² or a discrete wound ≥10 cm².					
AND					
Clinical criteria:					
The patient must not have full-thickness wounds as the treatment target					
AND					
Clinical criteria:					
Treatment must be initiated by or in consultation with a specialist experienced in epidermolysis bullosa management (e.g. dermatologist, paediatrician)					
Prescribing Instructions:					

Each tube is for single use only. Once opened, the product should be used immediately and discarded after use, even if there is some topical gel remaining. At the time of the application, prescribers must request the appropriate number of tubes based on the total wound area to be covered with gel at a thickness of approximately 1mm, to provide sufficient drug for 4 weeks of treatment, according to the specified dosage in the Therapeutic Goods Administration (TGA) approved Product Information.
Category / Program: Section 85 General Schedule
Prescriber type: ☒Medical Practitioners ☒Nurse practitioners
Restriction Level / Method: ☒ Streamlined
Condition: Treatment of partial thickness wounds associated with dystrophic or junctional epidermolysis bullosa.
Indication: Treatment of partial thickness wounds associated with dystrophic or junctional epidermolysis bullosa.
Treatment Phase: Continuing treatment
Treatment criteria:
Must be prescribed by a dermatologist or a paediatrician experienced in EB management. A nurse practitioner may prescribe continuing therapy under the supervision of dermatologist or a paediatrician experienced in EB management.
Clinical criteria:
Reassessment must occur at 45–60 days after initiation - The patients must have achieved any one of the following: • Complete re-epithelialisation of the treated wound • ≥ 50% reduction in wound area • Any two of the following supportive improvements: - ≥ 30% reduction in frequency of dressing changes, - ≥ 2-point reduction in procedural pain, - Visible reduction in wound exudate, odour, or infection-related intervention - If no response or signs of deterioration, treatment must be discontinued - One 30-day extension may be permitted for partial improvement at high-risk anatomical sites
Prescribing Instructions:
Each tube is for single use only. Once opened, the product should be used immediately and discarded after use, even if there is some topical gel remaining. At the time of the application, prescribers must request the appropriate number of tubes based on the total wound area to be covered with gel at a thickness of approximately 1mm, to provide sufficient drug for 4 weeks of treatment, according to the specified dosage in the Therapeutic Goods Administration (TGA) approved Product Information.

[a] The DPMQ was calculated based on an AEMP of $[redacted] for 10 tubes and an AEMP of $[redacted] for 30 tubes, equivalent to $[redacted] per tube.

3.1 The submission proposed pack sizes of 10 tubes and 30 tubes. The gel should be reapplied at a thickness of approximately 1 mm at each wound dressing change and the tube discarded after use.

3.2 The proposed restriction specified that prescribers must request the appropriate number of tubes based on the total wound area to be covered, to provide enough for 4 weeks of treatment. The submission stated that when applied at the recommended thickness that a 23.4 g tube of gel will cover an area roughly the size of a business envelope, measuring 10.48 cm x 24.13 cm. An average of 26.23 tubes of gel per 30-day cycle were used in the birch triterpenes gel arm of the key EASE trial based on the overall study duration (3 months double blind, 24 months open label). Usage in the trial varied considerably, with a median number of tubes per 30-day cycle of 18.7 (range, 6 to 198).

3.3 The submission did not propose a special pricing arrangement. The requested ex-manufacturer price was $[redacted] per tube.

3.4 The submission stated that diagnosis is complex, requiring specialist confirmation, and that a Written Authority for treatment initiation would allow prescribers to submit supporting documentation. The evaluation considered that a Written Authority would be appropriate; however, noted that no documentation requirements were specified in the proposed restriction. The National Epidermolysis Bullosa Dressing Scheme (NEBDS) requires proof of clinical diagnosis by an approved specialist or multidisciplinary epidermolysis bullosa clinic with at least one of the following as supporting evidence: skin biopsy testing results, genetic testing results or genetic testing results of a family member. It may be appropriate for similar diagnostic and evidence requirements to be specified in the PBS restrictions. The Pre-PBAC Response stated that for the initial Written Authority it would be appropriate for an EB specialist to confirm a diagnosis of DEB or JEB on the basis of any one of: (i) genetic testing, histology (immunofluorescence mapping or electron microscopy), or (ii) expert clinical opinion, consistent with practice within the NEBDS. The Response proposed that "Genetic testing should not be mandated, and confirmation should be documented in the patient's medical record rather than submitted to the PBS. Where confirmatory diagnostics are pending, which in neonates can take up to six months, a specialist should be able to initiate treatment on the basis of expert clinical opinion".

3.5 The submission proposed an age-agnostic restriction although the TGA approved indication is for patients aged 6 months and older. The proposed restriction was narrower than the TGA approved indication in terms of specifying a minimum wound age of 21 days and a minimum discrete wound size or chronic wound field of at least 10 cm^2.

3.6 The submission claimed that there is a clinical need for birch triterpenes gel in patients aged less than 6 months, as severe forms of epidermolysis bullosa, including DEB and JEB, usually present shortly after birth and require immediate wound care. The submission acknowledged the lack of safety and efficacy data in this age group but claimed that there is no biologically plausible reason that these patients would not benefit, and that no evidence of harm has emerged. The submission also claimed there would be equity concerns should this group be ineligible for treatment and an age-agnostic listing would allow for clinician judgement when deciding on use among infants. No patients under 6 months were enrolled in the EASE trial, despite a protocol amendment including patients ≥21 days old and <4 years. The Pre-Sub-Committee Response (PSCR) stated that the EASE trial did not include patients less than 6 months due to feasibility constraints, and that epidemiological estimates suggest that there would be no more than 10 patients who would be initiated under 6 months of age. The ESC noted the lack of data in patients aged less than 6 months in the EASE trial, but considered that as the disease can start at birth that an age agnostic listing may be reasonable.

3.7 The submission acknowledged that the proposed wound size thresholds were artefacts of the EASE trial design and would be difficult to implement in practice. The submission also noted that a fixed wound size threshold may not be clinically appropriate given the fluctuating and dynamic nature of epidermolysis bullosa wounds and having an arbitrary threshold may contradict good practice in wound management and infection risk. The evaluation stated that these claims appeared to be inconsistent with the inclusion of wound size thresholds in the restriction.

3.8 The submission claimed that international HTA agencies (NICE[1], SMC[2]) have not applied wound size thresholds in their recommendations for birch triterpenes gel. The NICE recommendation was aligned with its marketing authorisation (for treating partial thickness wounds associated with dystrophic and junctional epidermolysis bullosa in people aged 6 months and over). Similarly, the SMC recommended birch triterpenes gel for treatment of partial thickness wounds due to DEB or JEB in patients who are 6 months or older. Recommendations from both agencies do not include any wound criteria in terms of size, infection status or chronicity.

3.9 The submission stated that the intent of the wound eligibility criteria (age and size) was to identify patients with clinically significant, persistent wounds with a meaningful symptom burden and to avoid use in minor wounds, typically present in patients with epidermolysis bullosa simplex. The evaluation considered that the proposed wound criteria would be difficult to implement in clinical practice and that they do not appear necessary should there be sufficient evidence to support a confirmed diagnosis of DEB and JEB. The ESC agreed with the evaluation that the proposed wound criteria (minimum age and size) for treatment initiation may be difficult to implement in clinical practice and considered that it may be reasonable to allow for flexibility through clinician judgement. The Pre-PBAC Response stated that it would be reasonable for the listing to require confirmed DEB or JEB diagnosis, at least one partial-thickness wound, prescribing by an EB-experienced dermatologist or paediatrician, and treatment consistent with the TGA-approved Product Information.

3.10 The submission proposed a continuing restriction with objective response criteria to determine if patients are deriving a clinically meaningful treatment benefit, based on efficacy endpoints in the key EASE trial. The ESC considered the requirement for patients to demonstrate a clinically meaningful benefit based on objective response criteria for continuing treatment to be impractical, given fluctuations in both size and

[1] NICE recommendation: https://www.nice.org.uk/guidance/hst28/chapter/1-Recommendations
[2] SMC assessment: https://scottishmedicines.org.uk/medicines-advice/birch-bark-extract-filsuvez-uo-pathway-smc2651/public-summary/

number of wounds and challenges in seeking a dermatological review within a fixed timeframe.

3.11 Neither the economic model nor financial estimates presented in the submission included stopping rules based on treatment response.

3.12 The Pre-PBAC Response proposed that adequate response should be defined qualitatively as: "complete re-epithelialisation; or a significant reduction in wound area; or at least two of the following: a reduction in procedural pain, a significant reduction in dressing-change frequency, or a visible reduction in wound exudate, odour or infection-related intervention". The Response suggested that reassessment should align with routine 3-monthly specialist review, that 2 repeats would be appropriate for initial treatment, and supported removal of the mandatory discontinuation rule and one-off 30-day extension, allowing for clinician judgement. The Response requested that the maximum quantity at continuation be permitted to exceed the initial quantity where clinically required, because responders may extend treatment from a few wounds to a broader wound area.

3.13 The proposed Authority level for continuing therapy was inconsistent within the submission, with both Authority required (Telephone/electronic) and Authority required (Streamlined) listings proposed. Given that Telephone approval would be required for any quantities above the listed maximum, the evaluation considered that a Streamlined listing may be inadequate.

For more detail on PBAC's view, see section 7 PBAC outcome.

4 Population and disease

4.1 Epidermolysis bullosa is a group of rare, inherited, lifelong disorders caused by pathogenic variants that result in certain skin anchoring proteins being expressed incorrectly or disrupted. This results in very fragile skin that easily blisters and breaks, particularly after minor trauma or friction. Many of the wounds associated with epidermolysis bullosa are partial thickness wounds, which extend through multiple different layers of the skin. Epidermolysis bullosa can also manifest internally, affecting the eyes, mouth and stomach. Other complications include the development of aggressive skin cancers (squamous cell carcinomas), dental problems and nutritional compromise.

4.2 Four major subtypes of epidermolysis bullosa are recognised, classified according to where in the body the blistering occurs, and the layer of skin affected. Symptoms can vary significantly across the subtypes.

- Epidermolysis bullosa simplex (EBS): this is the most common type of epidermolysis bullosa, accounting for approximately 70% of all cases, and is typically milder, with a low risk of major complications.

- Dystrophic epidermolysis bullosa (DEB): this is the second most common type of epidermolysis bullosa, accounting for approximately 25% of cases. DEB can be either dominantly or recessively inherited, with dominant DEB associated with milder symptoms and recessive DEB more severe symptoms.
- Junctional epidermolysis bullosa (JEB): this is a rare type of epidermolysis bullosa and typically the most severe. JEB is recessively inherited and characterised by blistering above the basement membrane zone. JEB is classified as either generalised intermediate or generalised severe. Severe JEB can result in blistering covering large regions of the body, including the lining of the mouth and digestive tract.
- Kindler syndrome: this is a very rare, typically mild type of epidermolysis bullosa, recessively inherited and characterised by blistering at multiple levels of the skin, as well as pigmentation and photosensitivity.

4.3 Diagnosis of epidermolysis bullosa involves a detailed clinical history (including family history), comprehensive clinical examination, immunofluorescence antigen mapping and/or transmission electron microscopy of skin biopsy, pathogenic variant identification, and prenatal testing (offered when a familial pathogenic variant has been identified in a previously affected individual).

4.4 The submission noted the lack of contemporary Australian data on the incidence and prevalence of epidermolysis bullosa. Based on 2006-2008 data from the Australasian Epidermolysis Bullosa Registry (AEBR) the prevalence of epidermolysis bullosa in Australia was estimated to be 5.6 cases per million for epidermolysis bullosa simplex, 0.7 per million for JEB and 3.9 per million for DEB (Kho 2010). The study authors noted limitations faced by the registry due to limited recruitment time, geographical limitations and under-recruitment of patients with less severe forms of epidermolysis bullosa. The authors noted higher prevalence estimates in New South Wales, with 10.5 cases per million for epidermolysis bullosa simplex, 2.1 per million for JEB and 8.0 per million for DEB. An analysis of an England and Wales database using data collected prospectively from 2002 to 2021 and retrospectively for cases prior to 2002 (Petrof 2022), suggested minimum point-prevalence estimates of 10.7 per million for DEB and 1.0 per million for JEB and an incidence of 26.1 per million live births for DEB and 8.9 per million live births for JEB. Data from the England and Wales database were used in the budget impact estimates.

4.5 Life expectancy in epidermolysis bullosa varies widely according to epidermolysis bullosa subtype and disease severity. Severe forms of JEB (particularly generalised severe JEB) are associated with very high infant mortality, most commonly due to sepsis, respiratory failure, and failure to thrive (Bardhan 2020, Fine 2010). Individuals with recessive DEB typically survive into adolescence or adulthood but have substantially reduced life expectancy due to the very high lifetime risk of aggressive cutaneous squamous cell carcinoma (Fine 2010). Dominant DEB and most forms of

EBS and Kindler syndrome are associated with a normal or near-normal lifespan (Petrof 2022), although quality of life can be significantly affected (So 2022).

4.6 There is no cure or disease-modifying treatment for epidermolysis bullosa, with current treatment options aiming to manage symptoms. This includes wound management (bathing wounds, lancing and draining blisters, use of creams and non-adhesive dressings to manage open wounds; with topically-applied steroid creams and antimicrobial creams used in the event of infection); surgical procedures (to manage complications of epidermolysis bullosa, such as fusion of fingers and oesophageal strictures); pain management (pharmacological and non-pharmacological interventions to manage the pain from epidermolysis bullosa and associated surgical and wound management procedures); and monitoring and management of complications (including itching, nutritional deficiencies and squamous cell carcinoma). Treatment options are often personalised, based on disease subtypes and patient characteristics, involving a multidisciplinary team of healthcare professionals (including dermatologists, specialist nurses, paediatricians, gastroenterologists, geneticists, dentists, pain specialists, endocrinologists, plastic surgeons, podiatrists, dieticians, psychologists, occupational therapists, physiotherapists, and social workers).

4.7 The submission highlighted the significant burden that epidermolysis bullosa places on patients, their caregivers and families. The submission provided links to case studies highlighting the impact of epidermolysis bullosa. Patients experience blistering, wounds, itching, chronic pain, infection risk, nutritional challenges, and significant functional limitations. Daily wound care is time consuming and is physically and emotionally demanding. Epidermolysis bullosa can have a significant impact on the education, employment and personal lives of patients and caregivers. Patients may experience poor self-esteem, anxiety and depression and their caregivers often face stress and fatigue.

4.8 The submission requested listing of birch triterpenes gel for partial thickness wounds in patients with DEB or JEB only, on the basis that these 2 subtypes represent the most severe and clinically burdensome forms.

4.9 Birch triterpenes gel is a topical, non-aqueous gel. Each 1 g of gel contains 100 mg birch bark dry extract (10% w/w) of which 84-95% is composed of a mixture of triterpenes (84-95 mg) including betulin, betulinic acid, erythrodiol, lupeol and oleanolic acid. The mechanism of action in the treatment of wounds associated with epidermolysis bullosa is unknown.

4.10 The submission's clinical algorithm provided a summary of the general principles of skin and wound care in patients with DEB or JEB but did not provide specific indications for the wide range of wound care products used for debridement, moisture management, wound perimeter protection and care mentioned in international guidelines (Denyer 2017) and available through the NEBDS in Australia.

4.11 The submission did not clearly define the role of birch triterpenes gel for wound management, in terms of addressing specific barriers to healing (e.g. debridement, moisture management). The Approved Product Information recommends that the gel be applied to a non-adhesive wound dressing that is placed directly over the wound, or direct application to the wound surface covered by the dressing. It is unclear how the role of birch triterpenes gel differs from other products that are used directly on the wound.

For more detail on PBAC's view, see section 7 PBAC outcome.

5 Comparator

5.1 The submission nominated BSC as the main comparator. The main arguments provided in support of this nomination were that there are no agents currently listed on the PBS for the treatment of partial thickness wounds in DEB/JEB, and birch triterpenes gel will be used as an adjunctive therapy alongside BSC. The evaluation considered that BSC is an appropriate comparator.

5.2 BSC is focused on wound management, pain/itch control and monitoring and management of complications. Wound management includes bathing wounds, lancing and draining blisters, use of creams and non-adhesive dressings to manage open wounds; with topically applied steroid creams and antimicrobial creams used in the event of infection. Pain and itch control includes pharmacological and non-pharmacological interventions to manage the pain and itch from epidermolysis bullosa and associated surgical and wound management procedures. Monitoring and management of complications includes surgical procedures (e.g., to manage the fusion of fingers and oesophageal strictures), nutrition support, and monitoring for squamous cell carcinoma.

5.3 The NEBDS provides a broad range of wound care products including primary layer dressings for direct wound contact (silicone/non-silicone dressings, hydrogels, honey/medicated/silver dressings), secondary layer dressings for absorption and protection (exudate transfer dressings, foam, gauze, absorbent padding), enzymatic/antimicrobial products, barrier films and creams, bandages and securement dressings, debriding solutions and other accessories (needles and lancets).

For more detail on PBAC's view, see section 7 PBAC outcome.

6 Consideration of the evidence

Sponsor hearing

6.1 The sponsor requested a hearing for this item. The clinician discussed their experience managing patients with chronic severe DEB and JEB over many years and described the high mortality rate in this patient group. The clinician explained that death

typically occurs: 1) when wounds develop squamous cell carcinomas, 2) when wounds result in severe septicaemia, or 3) when other systemic complications arise. The clinician described how birch triterpenes gel is the first treatment to have approval for this indication and that it reduces the duration of chronic wounds, as well as the time required for caregivers to change dressings. The clinician highlighted that wound closure in EB is especially important because if wounds become chronic, the wounds are at higher risk of developing squamous cell carcinomas, which can metastasise. The clinician stated that if wounds are closing, they are biologically less harmful, even if they open again. The clinician explained that earlier wound healing means a lower risk of developing septicaemia. In relation to the EASE trial, the clinician stated that patients treated with birch triterpenes gel had reduced wound size compared to control gel from day 14 - day 75, and that by 90 days (an arbitrary time point chosen for the trial) wounds may reopen as patients begin moving around. The PBAC considered that the hearing was informative as it provided an expert clinical perspective on the treatment of patients with this chronic and severe condition.

Consumer inputs

6.2 The PBAC noted and welcomed the input from health care professionals (2) and organisations (Australasian College of Dermatologists, National Paediatric Medicines Forum and Dystrophic Epidermolysis Bullosa Research Association (DEBRA) Australia Ltd). The input from health professionals and organisations supported the PBS listing of birch triterpenes gel. The input stated that living with EB has been likened to living with third-degree burns and that most individuals with EB have extensive dressings on both the trunk and the limbs that involve a lengthy and often extremely painful process of dressing changes, wound management and dressing replacement every one or two days. The input stated that birch triterpenes gel helps with wound healing and reduces complications. The input stated that there is a high need for an effective treatment.

6.3 Input from health care professionals reported their experience from clinical trial participation, compassionate access and clinical practice, noting improved wound closure; reduced itch and pain; fewer dressing changes; reduced dressing use; and no reported worsening of wounds among treated patients. Input from health care professionals considered faster wound healing to be important “because chronic wounds may contribute to: scarring; infection; anaemia; nutritional depletion; renal complications; and squamous cell carcinoma risk, particularly in severe EB subtypes”.

6.4 Input from DEBRA Australia described a strong clinical need for new treatments. It was stated that based on the experience of patients treated with birch triterpenes gel that some patients derive benefit from using the therapy, but others will discontinue it after some months of use because they do not consider it sufficiently helpful.

Clinical trials

6.5 The submission was based on the phase 3 EASE trial, which included a 90-day head-to-head, randomised, double blind phase comparing birch triterpenes gel and a control gel for the treatment of partial-thickness wounds in patients with DEB or JEB and a 24-month open label phase, during which all patients received treatment with birch triterpenes gel.

6.6 Details of the trial presented in the submission are provided in Table 2.

Table 2: Trials and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
EASE (NCT03068780)	Double blind, randomised, vehicle-controlled, phase III, efficacy and safety study with 24-month open label follow-up of Oleogel-S10 in subjects with inherited epidermolysis bullosa.	Internal study report: February 2021; March 2021; and December 2022
	Kern et al. (2023). Efficacy and safety of Oleogel-S10 (birch triterpenes) for epidermolysis bullosa: results from the phase III randomized double blind phase of the EASE study.	British Journal of Dermatology 2023; 188(1):12-21.
	Murrell et al. (2025). Long-term safety and efficacy of Oleogel-S10 (birch bark extract) in epidermolysis bullosa: 24-month results from the phase III EASE study.	British Journal of Dermatology 2025; 192(6):1007-1017.

Source: Table 2.2-1, pp57-58 of the submission.

6.7 The key features of the included trial are summarised in Table 3.

Table 3: Key features of the included evidence

Trial	N	Design/ duration	Risk of bias	Patient population	Outcomes	Use in modelled evaluation
Birch triterpenes gel versus control gel						
EASE	223	Phase 3, multicentre, head-to-head, randomised, double blind trial (3 months) with open label extension phase (24 months)	Low	Patients aged 4 years or older [a] with confirmed DEB or JEB, and an epidermolysis bullosa wound meeting the target criteria (i.e., a partial thickness wound of 10 cm^2 to 50 cm^2 in size that is aged ≥21 days and <9 months)	Proportion of patients with first complete closure of the target wound within 45 days, time to first complete closure of the target wound within 90 days, incidence of infection, BSAP, wound burden, wound size, frequency of dressing changes, quality of life and adverse events	Baseline characteristics, BSAP, EQ-5D-5L, EQ-5D-Y-3L

Source: Table 2.3-1, pp60-69; Table 2.2 1, p57-58 of the submission.
Abbreviations: BSAP, body surface area percentage affected by partial thickness wounds; DEB, dystrophic epidermolysis bullosa; JEB, junctional epidermolysis bullosa.
[a] Age of trial participants was reduced to >21 days following an independent data monitoring committee safety review in February 2019.

6.8 In the EASE trial, a single epidermolysis bullosa wound that met the target wound criteria (a partial thickness wound of 10 cm^2 to 50 cm^2 in size and ≥21 days to <9 months in age) was selected for assessment of the primary endpoint and the first key secondary endpoint. In addition to the target wound, up to 4 other wounds that met the target wound criteria were selected as 'additional wounds' and were evaluated for closure, along with the target wound, based on clinical assessment and blinded evaluation of photographs. Some of the efficacy assessments (e.g., total body surface

area affected, wound infections) were based on all wounds, including the target wound, additional wounds that met the target wound criteria, and all other partial-thickness wounds that did not meet target wound criteria (referred to as 'other wounds').

6.9 Most patients enrolled in the EASE trial had recessive DEB (78.5%) with dominant DEB and JEB accounting for 9.0% and 11.7% of patients respectively. Data from the Australasian Epidermolysis Bullosa Registry (Kho 2010) suggests that the distribution of DEB and JEB types and subtypes in Australia may differ from that in the EASE trial, with Kho 2010 reporting that 37.5% of those on the registry had recessive DEB, 17.8% dominant DEB and 10.8% dominant JEB. The evaluation considered the impact of differences between the EASE trial and Australian population is unclear.

6.10 The submission stated that the population in the EASE trial consisted predominantly of patients with established severe recessive DEB with large chronic wounds, predicting that the Australian population would be a mix of patients with newly diagnosed and established disease. The submission stated that early disease often features multiple smaller wounds that persist and merge.

6.11 The submission claimed that the use of BSC in the EASE trial was in line with Australian clinical practice. However, the EASE trial specified a limited number of permitted dressings and did not allow use of silver dressings or dressings containing topical emollients, nor were skin products such as creams, ointments, gels, emollients, and silver sulfadiazine, or systemic steroids or systemic antibiotics allowed. The evaluation and the ESC noted that the restrictive requirement for dressing materials and concomitant treatment is unlikely to be representative of clinical practice and may affect the magnitude of benefit observed with birch triterpenes gel in the Australian setting.

Comparative effectiveness

6.12 Table 4 presents results for the primary endpoint of proportion of patients with first complete closure of target wound (based on clinical assessment) within 45 days in the EASE trial.

Table 4: Proportion of patients with first complete closure of target wound (based on clinical assessment) within 45 days in the double-blind phase of the EASE trial (full analysis set)

Outcome	Birch triterpenes gel N=109	Control gel N=114	Odds ratio (95% CI)
First complete closure of target wound within 45 days; n (%)	45 (41.3)	33 (28.9)	**1.84 (1.02, 3.30)**

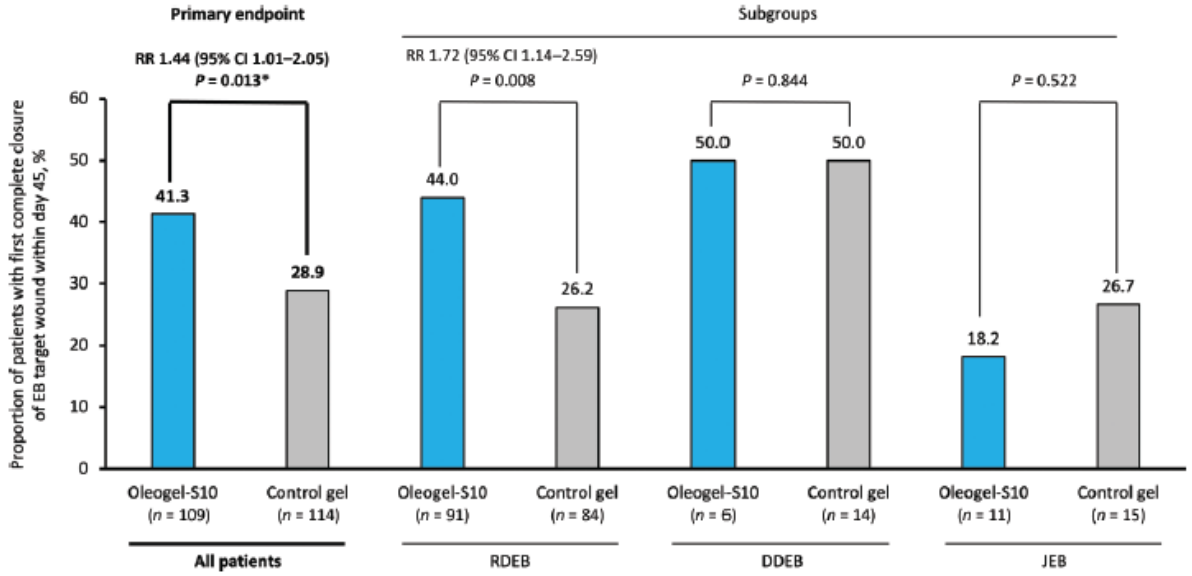
Source: Table 2.5-1, p86 of the submission; Table 24, p117 of the EASE clinical study report (v1; 11 June 2020 data cut-off); Table 14.2.1.1.1, pp247-248 of the EASE clinical study report Section 14 tables (v1; 11 June 2020 data cut-off).
Abbreviations: CI, confidence interval.
Note: The wound was rated as 'closed' at first appearance of complete re-epithelialisation without drainage.
Note: Bold indicates statistically significant, with an odds ratio >1 representing a favourable outcome for the birch triterpenes gel arm.

6.13 Treatment with birch triterpenes gel was associated with a statistically significantly higher proportion of patients achieving first complete closure of the target wound within 45 days compared to the control gel arm. However, a supportive analysis of the

primary outcome based on first complete closure of the target wound within 45 days AND no re-opening of the target wound suggested a smaller numerical benefit for birch triterpenes gel versus the control gel (birch triterpenes gel 24.8%, control gel 20.2%; Odds ratio 1.32; 95% CI 0.69, 2.51).

6.14 Figure 1 below presents results of the primary outcome by epidermolysis bullosa subgroup. The analysis shows that treatment effects associated with birch triterpenes were primarily driven by patients with recessive DEB, with limited representation of patients with dominant DEB and JEB in the trial.

Figure 1: Proportion of patients with first complete closure of the target wound within 45 days, based on clinical assessment (all patients and by epidermolysis bullosa subgroup)



Source: Figure 1, p14 of the EASE double blind phase trial publication (Kern 2023).
Abbreviations: CI, confidence interval; DDEB, dominant dystrophic epidermolysis bullosa; JEB, junctional epidermolysis bullosa; RDEB, recessive dystrophic epidermolysis bullosa.
* Pre-specified adjustment to account for the independent data monitoring committee interim sample size re-estimation.
Note: The 'All patients' group includes 2 patients with epidermolysis bullosa simplex (one in each treatment arm).
Note: Oleogel-S10 refers to birch triterpenes gel.

6.15 Table 5 presents the results of the key secondary outcomes of the EASE trial.

Table 5: Summary of results of secondary wound outcomes in the EASE double blind phase (full analysis set)

Outcome	Birch triterpenes gel (N=109)	Control gel (N=114)
Time to first complete closure of the target wound (based on clinical assessment) within 90 (±7) days		
Target wound closure, n (%)	55 (50.5)	50 (43.9)
Target wound non-closure, n (%)	54 (49.5)	64 (56.1)
Median time to first closure, day (95% CI)[a]	92.0 (50.0, NE)	94.0 (89.0, NE)
Log-rank test, p-value	0.302	
Patients with first complete closure of target wound based on clinical assessment		
Patients with target wound closure at day 90, n (%)	55 (50.5)	50 (43.9)
Odds ratio (95% CI)	1.34 (0.78, 2.32)	
Target wound infection up to day 90, based on adverse event reporting and/or use of antibiotics		
Patients with wound infection, n (%)	2 (1.8%)	5 (4.4%)
Odds ratio (95% CI)	0.43 (0.08, 2.33)	

Outcome	Birch triterpenes gel (N=109)	Control gel (N=114)
Maximum severity of target wound infection up to day 90 based on adverse event reporting		
Patients with wound infection, by severity, n (%)	Mild: 1 (0.9) Moderate: 0 Severe: 0 Life threatening: 0 Death: 0	Mild: 0 Moderate: 3 (2.6) Severe: 1 (0.9) Life threatening: 0 Death: 0
EBDASI Skin Activity Score (maximum score 100)[b]		
Baseline EBDASI Skin Activity Score, mean (SD)	19.6 (11.26)	19.6 (12.55)
Least squares mean change from baseline at day 90 (SE)	-0.44 (0.90)	-0.56 (0.85)
Difference in least squares mean change (95% CI)	0.12 (-1.58, 1.83)	
Itching, based on the Itch Man Scale for patients aged ≥4 to <14 years[c]		
Baseline Itch Man Scale, mean (SD)	N=50 2.0 (1.04)	N=56 2.5 (1.07)
Mean change from baseline to day 90 (SD)	-0.4 (1.31)	-1.0 (1.31)
Itching, based on the Leuven Itch Scale for patients ≥14 years[d]		
Baseline Leuven Itch Scale, mean (SD) - Frequency subscore - Duration subscore - Severity subscore - Consequences subscore - Distress subscore - Surface area subscore	N=52 69.2 (25.54) 31.3 (43.78) 54.5 (22.55) 28.3 (22.47) 42.9 (31.09) 35.6 (24.26)	N=48 68.8 (26.55) 24.8 (37.08) 51.5 (26.29) 30.9 (25.559) 43.2 (32.24) 33.6 (24.50)
Mean change from baseline to day 90 (SD) - Frequency subscore - Duration subscore - Severity subscore - Consequences subscore - Distress subscore - Surface area subscore	 -8.1 (26.18) -0.9 (35.17) -4.7 (19.05) -4.4 (14.07) -0.3 (22.03) -1.5 (12.35)	 -10.1 (27.3) 1.0 (39.77) -10.3 (32.24) -3.5 (19.40) 0.0 (34.38) 0.7 (17.08)

Source: Table 14.2.2.1.1.1, pp316-317; Table 14.2.2.1.1.2, p 318-319; Table 14.2.2.3.5, pp406; Table 14.2.2.4.2, pp416; Table 14.2.2.5.1, pp417-420; Table 14.2.2.6.4, pp720-722; Table 14.2.2.6.5, pp724-747 of the EASE clinical study report Section 14 tables (v1; 11 June 2020 data cut-off).

Abbreviations: CI, confidence interval; EBDASI, Epidermolysis Bullosa Disease Activity and Scarring Index; SD, standard deviation; SE, standard error.

[a] If wound closure did not occur prior to the end of the 90-day double blind phase, time to first complete closure was censored at the end of the double-blind phase visit date of at last assessment date.

[b] Total body wound burden was assessed using the EBDASI Skin Activity Score, assessing the number and size of wounds at 10 skin locations (the anogenital region was excluded), scored from absent (0) to entire area covered (10), with a maximum score of 100, with higher scores indicative of greater wound burden.

[c] Itch Man Scale measures the intensity of itching among children, featuring drawings of stick figures with varying facial expressions and red dots representing itch levels from 0 (no itch) to 4 (worst itch).

[d] Leuven Itch Scale is a patient-reported outcome instrument to assess the severity and multidimensional impact of itch, evaluating 6 domains (occurrence, severity, treatment, consequences, sensory characteristics, and distress), with each domain scored from 0 to 100 and higher scores indicating more severe or burdensome itch.

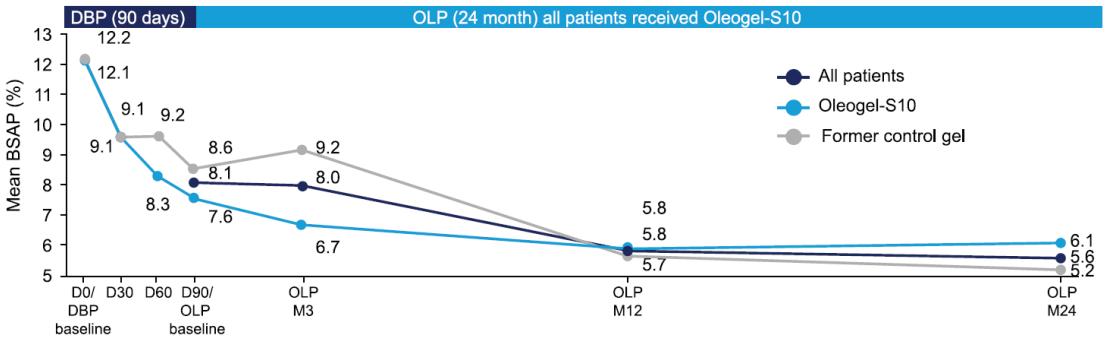
6.16 The results of the first key secondary outcome, median time to first closure of the target wound within 90 (±7) days, were similar between treatment arms (92 days in the birch triterpenes gel arm compared with 94 days in the control gel arm) and did not achieve statistical significance (p=0.302). As this first key secondary outcome failed to reach statistical significance, subsequent statistical testing was not carried out and the results for the remaining secondary outcomes are descriptive only.

6.17 In general, point estimates for the other secondary wound outcomes numerically favoured the birch triterpenes gel arm, although confidence intervals were wide for many of the outcome measures.

6.18 Over the 24-month duration of the open label phase, there were 7 target wound infections (2 mild; 3 moderate; 2 severe). The incidence of additional and other wound infections remained low over the open label phase. Total wound burden measured using the EBDASI Skin Activity Score fluctuated over the open label phase but results at 24 months were generally consistent with the baseline (Day 90) of open label phase, and lower than the double-blind phase baseline. Reductions in itching observed in both treatment arms during the EASE double blind phase, were maintained over the first 3 months of the open label phase (no further assessment of itching outcomes was undertaken).

6.19 The economic analysis presented in the submission used clinical inputs based on individual patient data from the EASE double blind and open label phases for body surface area percentage affected by partial thickness wounds. Figure 2 presents the average body surface area percentage affected by partial thickness wounds by visit over the double blind and open label phases of the EASE trial.

Figure 2: Mean body surface area percentage affected by partial thickness wounds from baseline of the EASE double blind phase to month 24 of the open label phase



Oleogel-S10 (*n*)	109	100	98	100	85	67	59
Former control gel (*n*)	113	100	100	97	87	73	70
All patients (*n*)	–	–	–	197	172	140	129

Source: Figure 2.5-10, p102 of the submission.
Abbreviations: D, day; DBP, double blind phase; M, month; OLP, open label phase.
Note: Oleogel-S10 refers to birch triterpenes gel.
Note: Assessments recorded within open label phase visit windows were lower than expected largely due to the COVID-19 pandemic. Therefore, a *post hoc* analysis was produced without visit windows in the open label phase.
Note: D90/OLP refers to the last assessment before the first open label treatment and at day 90 of double-blind phase (eight patients did not have a day-90 visit).

6.20 At baseline the mean body surface area percentage affected by partial thickness wounds was 12.1% in the birch triterpenes gel arm and 12.2% in the control gel arm. There was a reduction in body surface area percentage from baseline to 90 days in both treatment arms (-4.3% in the birch triterpenes arm; -2.5% in the control gel arm),

with no apparent difference between treatment arms (difference in least squares mean -1.28, 95% CI -2.87, 0.30).

6.21 In the open label phase, mean body surface area percentage in patients who remained on treatment with birch triterpenes gel improved from 7.6% at open label phase baseline to 6.7% at month 3, and then stabilised at a reduced level for the remainder of the open label phase (5.8% at month 12; 6.1% at month 24). In patients who switched from the control gel to birch triterpenes gel, the mean body surface area percentage increased from 8.6% at open label phase baseline to 9.2% at month 3 and decreased to 5.7% at month 12 and 5.2% at month 24.

6.22 Results for other patient reported outcomes in terms of quality of life during the EASE double blind phase showed similar improvements in both treatment arms in terms of background pain (defined as pain between dressing changes), sleep, treatment satisfaction and missed school/workdays. Patient-reported estimates of procedural pain (defined as pain resulting from removal of wound dressings and application of new dressings) numerically favoured the birch triterpenes gel arm compared to the control gel arm (a 1.3 point reduction versus a 0.2 point reduction, based on the Wong-Baker FACES scale [0=no pain; 10=worst pain], measured in patients aged 4 and older).

6.23 In the open label phase, reductions in procedural pain and background pain observed in the double-blind phase were maintained to 3 months; there was an increase in the proportion of patients reporting missed school or work between the open label phase baseline and 3 months; and the proportion of patients reporting satisfaction with treatment was stable.

6.24 The Instrument for Scoring Clinical Outcome of Research for Epidermolysis Bullosa (iscorEB) and EQ-5D-5L (for patients aged 16 years and older) and EQ-5D-Y-3L (for patients younger than 16, with proxy responses for patients younger than 4 years provided by parents or caregivers) were added following a protocol amendment approximately 2.5 years after the trial was initiated. As the instruments were not collected from the outset of the open label study, overall completion rates were low.

6.25 Results for EQ-5D-5L and EQ-5D-Y-3L index scores were not reported in the submission or EASE clinical study reports. No clear trends were observed over the 24-month open label phase for the iscorEB and EQ-5D VAS outcomes. Results are difficult to interpret given the low numbers of patients completing these assessments, particularly at open label phase baseline.

6.26 The frequency of dressing changes at baseline in the EASE trial was on average, every 1.4 days. There were nominally significant differences in changes from baseline in dressing frequency between treatment arms at Days 7, 45, 60 and 90, favouring the birch triterpenes arm (at Day 90, average dressing change frequency was every 1.4 days in the birch triterpenes arm and every 1.6 days for the control gel arm). The frequency of dressing changes remained steady during the open label phase (every 1.5-1.6 days).

6.27 The PSCR highlighted that patient reported outcomes in the EASE trial were exploratory secondary endpoints that were not powered to detect short-term symptomatic changes associated with accelerated wound closure.

Comparative harms

6.28 Table 6 presents a summary of adverse events in the double blind and open label phases of the EASE trial.

Table 6: Summary of key adverse events in the EASE double blind and open label phases (safety analysis set)

Adverse events, n (%) [number of events]	EASE double blind phase (90 days)		EASE open label phase (24 months) N=205
	Birch triterpenes gel N=109	Control gel N=114	
Any adverse events	89 (81.7) [282]	92 (80.7) [277]	158 (77.1) [833]
Serious adverse events	7 (6.4) [10]	5 (4.4) [7]	50 (24.4) [116]
Grade 3/4 adverse events	13 (11.9) [19]	6 (5.3) [7]	37 (18.0) [91]
Fatal serious adverse events	0	0	8 (3.9) [8]
Any adverse events leading to study withdrawal	3 (2.8) [4]	2 (1.8) [2]	16 (7.8) [16]
Any serious adverse events leading to study withdrawal	2 (1.8) [3]	0	12 (5.9) [12]
Any adverse events leading to drug withdrawal	3 (2.8) [4]	4 (3.5) [4]	16 (7.8) [16]
Adverse events due to wound complications	67 (61.5) [100]	61 (53.5) [88]	84 (41.0) [107]
- Increase in wound size compared to baseline	32 (29.4) [40]	37 (32.5) [47]	29 (14.1) [29]
- Wound re-opening	31 (28.4) [38]	20 (17.5) [23]	40 (19.5) [45]
- Increase in wound size compared to the previous visit	12 (11.0) [16]	7 (6.1) [8]	12 (5.9) [12]
- Injury to the wound	1 (0.9) [1]	4 (3.5) [5]	1 (0.5) [1]
- Wound worsening compared to baseline	0	1 (0.9) [1]	4 (2.0) [4]
- Other [a]	4 (3.7) [5]	3 (2.6) [4]	13 (6.3) [16]

Source: Table 2.5-9, p112 of the submission; Table 39, p182; Table 56, p213 of the EASE clinical study report (v1; 11 June 2020 data cut-off), Table 6, p72; Table 11, p87 of the EASE clinical study report (v3; 27 May 2022 data cut-off).
[a] Other events included increase in wound burden, worsening of epidermolysis wound pain, and wound odour.

6.29 The proportion of patients experiencing any adverse event was similar between treatment arms. The most frequently reported adverse events in the EASE double blind phase for the birch triterpenes gel and control gel arms were wound complication (61.5% and 53.5%), pyrexia (8.3% and 13.2%), wound infection (7.3% and 8.8%), pruritus (7.3% and 5.3%), anaemia (7.3% and 3.5%), and cough (2.8% and 7.0%).

6.30 In the EASE open label phase, the most frequently reported adverse events were wound complication (41.0%), anaemia (18.0%), wound infection (10.2%), wound infection staphylococcal (10.2%), pyrexia (9.8%), oesophageal stenosis (9.3%), wound infection bacterial (7.8%), pruritus (6.8%), and dysphagia (6.3%). A total of 9 subjects died during the EASE open label phase due to sepsis (2 patients), pneumonia (2 patients), EB progression, cardiac failure, cardiorespiratory arrest, intestinal ischemia, and acute renal failure (1 patient each). None of the deaths were considered related to study treatment. One of the deaths was due to sepsis, with onset more than 30 days after the last date of birch triterpenes gel administration.

6.31 In the birch triterpenes gel arm, serious adverse events of infections and infestations were reported in 4 patients (1 each of sepsis, bacterial wound infection, device related infection, and pneumonia), anaemia in 3 patients, and wound haemorrhage, squamous cell carcinoma and haematuria were each reported in one patient. In the control gel arm, serious adverse events of infections and infestations were reported in 5 patients (2 patients with sepsis, and one each with bacterial wound infection, erysipelas, upper respiratory tract infection and wound infection), and increased gamma-glutamyl transferase in one patient. There were no deaths reported in the EASE double blind phase.

6.32 In the EASE open label phase, a total of 116 serious adverse events occurred in 50 patients (24.4%). The most commonly reported serious adverse events were oesophageal stenosis and anaemia, each with 15 events in 10 patients (4.9%); and malnutrition, septic shock, squamous cell carcinoma and wound infection, each reported in 3 patients (1.5%).

6.33 In the EASE double blind phase, the incidence of wound complication-related adverse events was higher in the birch triterpenes gel arm than in the control gel arm (61.5% versus 53.5%). The incidence of wound re-opening and increase in wound size compared to the previous visit were higher in the birch triterpenes gel arm than the control gel arm. The PSCR stated that while wound-complication adverse events were higher in the birch triterpene gel arm than in the control arm, wound re-opening can only occur in previously closed wounds (and earlier wound closure was more frequent in the birch triterpene gel arm), so that the probability of observing re-opening events was inherently higher in the birch triterpene gel arm.

6.34 The incidence of wound complication-related adverse events was lower in the open label phase (41.0%) compared to the double-blind phase. The most frequently reported wound complication-related adverse events were wound re-opening and increase in wound size compared to baseline.

6.35 In addition to wound complications, other adverse events of interest in the EASE trial were hypersensitivity, skin malignancies, haemorrhages, and anaemia, which were assessed in patients exposed to birch triterpenes gel in the double blind or open label phases of the EASE trial:

- 12 patients experienced hypersensitivity events; 2 events were considered severe (rash, anaphylactic reaction).
- 4 patients (all adults with recessive DEB) reported an adverse event of squamous cell carcinoma; all of which were serious and severe in intensity.
- 15 patients had 23 adverse events of haemorrhage, including one patient with a serious wound haemorrhage adverse event.
- 45 patients experienced 70 anaemia-related adverse events; 19 events in 12 patients were classified as serious adverse events.

6.36 The lack of comparative event rates limits the interpretation of other adverse events of interest.

6.37 No new safety signals were identified during the reporting period of Periodic Safety Update Report. Identified important potential risks include wound infection, particularly those resulting in serious consequences such as sepsis, septic shock, and fatal outcomes, as well as squamous cell carcinoma and other skin malignancies. Missing information includes use in patients with different skin types regarding ethnic origin/Fitzpatrick skin types.

Benefits/harms

6.38 On the basis of direct evidence presented in the submission, in patients with partial thickness skin wounds associated with DEB or JEB, for every 100 patients treated with birch triterpenes gel in comparison with control gel:

- Approximately 12 additional patients would achieve first complete closure of a chronic (onset of ≥21 days and <9 months), partial thickness (skin-deep) wound of moderate to large size (10 cm^2 to 50 cm^2) within 45 days.
- There would be no difference in time to wound closure within 90 days.
- There would be no difference in wound burden, itching, and pain over 90 days.
- Approximately 8 additional patients would experience wound complications within 90 days.

Clinical claim

6.39 The submission described birch triterpenes gel in addition to BSC as superior in terms of efficacy compared to BSC. The ESC considered this claim was supported in terms of short-term wound closure but was not well-supported for longer-term wound closure, infection, other measures of wound burden (number and size of wounds, dressing changes) and patient-reported outcomes (itching, work/school attendance and quality of life).

6.40 The submission described birch triterpenes gel in addition to BSC as non-inferior in terms of safety compared to BSC. The ESC considered the claim of non-inferior safety was not supported. The Pre-PBAC Response highlighted that excess wound complications in patients treated with birch triterpenes gel were mainly due to re-opening, which only occurred in previously closed wounds. The Response argued that earlier and more frequent closure in the birch triterpenes arm increased re-opening opportunities and that events showing net deterioration (wound enlargement or injury) did not increase. The Response highlighted that wound-complication rates declined in the open-label phase (41.0%) compared to the double-blind phase (61.5%). The Response maintained that safety is comparable to BSC when re-opening of previously treated wounds is considered in context.

6.41 The ESC considered the clinical benefit of birch triterpenes gel compared to the control gel to be modest. While the EASE trial demonstrated an acceleration in wound closure within 45 days, the difference between treatment arms was substantially reduced when subsequent wound re-opening was assessed. Additionally, the ESC noted that data at 90 days suggested no apparent difference in wound closure rates between treatment arms, which was also reflected in patient reported outcomes which indicated a small or no improvement in itching, pain, and impact on sleep and work/school attendance with birch triterpenes gel treatment. The Pre-PBAC Response stated that the benefit with birch triterpenes gel is accelerated wound closure and that in patients with DEB and JEB, faster wound closure is clinically meaningful. The Response highlighted that open wounds increase the risk of infection and pain. The Response stated that EB specialists have noted that chronic non-healing wounds are linked to metastasising cutaneous squamous cell carcinoma. The Response further stated that as patients often have multiple wounds, that the single target-wound endpoint understates the overall reduction in wound burden, including total body surface area. The Pre-PBAC Response acknowledged that disease modification was not demonstrated and stated that convergence of outcomes by Day 90 reflects delayed closure in patients treated with control gel, and not a loss of effect of birch triterpenes gel. The Pre-PBAC Response and the PSCR stated that results at Day-90 numerically favoured birch triterpenes.

6.42 The ESC noted that there is a lack of comparative long-term efficacy and safety data beyond 90 days. The Pre-PBAC Response stated that "a long-term randomised comparison in EB is not feasible or ethical due to extreme skin fragility, infection risk, and the inability to deny effective treatment to controls after benefit is shown (prompting open-label roll-over)". The Pre-PBAC Response stated that the 90-day timepoint for assessment of outcomes was aligned with the FDA wound-healing guidance. The Pre-PBAC Response further stated that sustained reductions in the proportion of body surface area affected by wounds were demonstrated with open-label treatment with birch triterpenes gel for 24 months. The ESC noted there is uncertainty in the clinical benefit of birch triterpenes gel in patients with dominant DEB and in patients with JEB (the most severe subtype), who represented only 9.0% (N=20) and 11.7% (N=26) of patients in the EASE trial, respectively.

6.43 The ESC noted that the applicability of the EASE trial to the Australian setting is uncertain given a comparison with Australian registry data (Kho 2010) indicates that the EASE trial enrolled a substantially higher proportion of patients with recessive DEB (78.5% versus 37.5% in the Australian registry data) and lower proportions of patients with dominant DEB and JEB compared to available Australian data. Patients with recessive DEB typically have a relatively severe disease course with a markedly increased risk of aggressive squamous cell carcinoma and substantially reduced life expectancy.

6.44 The PBAC considered that the claim of superior comparative effectiveness was supported for accelerated wound closure at 45 days, but was not adequately

supported for longer-term wound closure, infection, broader wound burden outcomes, or patient-reported outcomes.

6.45 The PBAC considered that the claim of non-inferior comparative safety was not adequately supported by the data in the double-blind phase of the EASE trial. The PBAC noted that wound complications for patients treated with birch triterpenes gel reduced in the open-label phase of the EASE trial.

Economic analysis

6.46 The submission presented a modelled economic evaluation of birch triterpenes gel in addition to BSC versus BSC alone for the treatment of partial thickness wounds in patients with DEB or JEB. The economic evaluation was based on the results of the EASE trial with additional modelled data. The economic evaluation was presented as a cost-effectiveness/cost-utility analysis.

6.47 Key components of the economic evaluation are summarised in Table 7.

Table 7: Key components of the economic evaluation

Component	Description
Type of analysis	Cost effectiveness/cost utility analysis
Outcomes	Proportion of patients with wound closure, quality adjusted life years
Time horizon	40 years
Methods used to generate results	Markov cohort analysis
Treatments	Birch triterpenes gel in addition to best supportive care; best supportive care
Health states	6 disease burden health states defined by body surface area percentage (BSAP) affected by epidermolysis bullosa partial thickness wounds: - BSAP 1 (0 to ≤4%) - BSAP 2 (>4 to ≤7%) - BSAP 3 (>7 to ≤10%) - BSAP 4 (<10 to ≤18%) - BSAP 5 (>18% to ≤25%) - BSAP 6 (>25%) and a dead state
Cycle length	30 days

Component	Description
Transition probabilities	Transition matrices between BSAP health states in the first 3 model cycles were derived from individual patient data from the double-blind phase of the EASE trial for the birch triterpenes gel and best supportive care treatment arms. From cycle 3 (Day 90) in the best supportive care arm of the model, patients were assumed to be in a steady state, with no further change in disease burden (as measured by BSAP) over the 40-year model time horizon. In the birch triterpenes gel arm, transition matrices between BSAP health states between cycles 3 and 15 (Days 90 and 450) and between cycles 15 and 27 (Days 450 and 810) were derived from individual patient data from the open label extension phase of the EASE trial. Where no data were available to inform health state transitions, it was assumed that patients had an equal probability of transitioning to each of the 6 health states in the next model cycle. Linear interpolation was used to allocate patients to health states in between cycles 3 and 15 and cycles 15 and 27. Beyond cycle 27 (Day 810), steady state was assumed for patients in the birch triterpenes gel arm, with no further change in disease burden (as measured by BSAP) over the 40-year model time horizon. In the first 3 model cycles, a probability of treatment discontinuation of 2.85% was applied to the birch triterpenes gel arm, based on the proportion of patients in the birch triterpenes gel arm who discontinued during the double-blind period of the EASE trial at 90 days (8.3%). In subsequent cycles, a probability of treatment discontinuation of 0.08% was applied, based on an annual discontinuation rate of 1% from UK clinical expert opinion. Patients discontinuing birch triterpenes treatment in a given cycle are redistributed across health states according to the distribution of patients in the best supportive care arm for that cycle (with the cycle 3 distribution used for all cycles after cycle 3). In subsequent cycles, discontinued patients have the same transitions as best supportive care patients. The model did not incorporate the costs and quality of life impacts associated with birch triterpenes gel adverse events. Mortality was estimated based on Australian general population life tables (ABS Life tables 2021-2023), with no difference in mortality assumed between treatment arms.
Utility values	Health state utilities were derived using pooled EQ-5D-5L and EQ-5D-Y-3L data from the EASE open label extension phase. The EQ-5D-5L data were indexed using the Norman 2023 value set. In the absence of a validated value set for EQ-5D-Y-3L, the adult Australian EQ-5D-3L value set (Viney 2011) was used. A generalised linear model was used to estimate patient utility as a function of BSAP. Health state utilities were calculated from the regression analysis results using the midpoint value of the BSAP range for each health state, with a midpoint of 30% assumed for the BSAP 6 health state (BSAP >25%). Resulting utilities were: BSAP 1, 0.6807; BSAP 2, 0.6159; BSAP 3, 0.5642; BSAP 4, 0.4978; BSAP 5, 0.4177; BSAP 6, 0.3376. Carer utilities were not collected in the EASE study and were included in the economic evaluation based on a sponsor-commissioned time trade-off analysis conducted in 120 adults from the UK general population. It was assumed that one caregiver would be required per patient across all health states. The resulting carer utilities were: BSAP 1 and 2, 0.85; BSAP 3 and 4, 0.76; BSAP 5 and 6, 0.64. Adverse event disutilities were not included.

Component	Description
Costs	The cost of birch triterpenes gel treatment was based on an average cost per tube of $[redacted] (assuming that 30% of use will be from packs of 10 tubes and 70% from packs of 30 tubes) and 25.7 tubes per 30-day period (derived from a post hoc analysis of utilisation in the EASE trial and open label extension).[a] Disease management costs by health state were estimated based on costs of hospital outpatient visits (numbers of visits based on UK clinical expert opinion; unit costs based on MBS 105, subsequent specialist attendance), formal dressing care (hours of care per month based on UK clinical expert opinion, unit costs based on MBS 82216, nurse practitioner attendance ≥60 minutes), and dressing materials (average monthly dressing costs of $5,000 based on a 2021 Australian government press release, inflated to 2025 dollars based on the CPI, with relative use between health states derived from UK clinical expert opinion). Adverse event costs were not included.
Discount rate	5% for costs and outcomes
Software package	Microsoft Excel

Source: Table 3.1.1, p120; and Sections 3.3-3.6, pp132-145 of the submission.
Abbreviations: ABS, Australian Bureau of Statistics; BSAP, body surface area percentage; CPI, consumer price index; MBS, Medicare Benefits Schedule; UK, United Kingdom.
[a] Although the utilisation estimate was based on 30-day data, it was assumed that the data were from a calendar month (30.4375 days per month) and adjusted to the 30-day cycle length. This resulted in a cost per 30-day cycle of $[redacted] rather than $[redacted].

Baseline BSAP distribution

6.48 At the start of the model, patients were assumed to be equally distributed among 6 health states defined by the body surface area percentage (BSAP) affected by partial thickness wounds (Table 8).

Table 8: BSAP distribution in the model base case and the EASE trial population at baseline

Health state	Economic model	EASE trial baseline		
		Birch triterpenes gel arm (N=109)	Control gel arm (N=114)	All patients (N=223)
BSAP 1 (0% to ≤4%)	16.67%	20 (18.3%)	28 (24.6%)	48 (21.5%)
BSAP 2 (>4% to ≤7%)	16.67%	33 (30.3%)	29 (25.4%)	62 (27.8%)
BSAP 3 (>7% to ≤10%)	16.67%	8 (7.3%)	21 (18.4%)	29 (13.0%)
BSAP 4 (>10% to ≤18%)	16.67%	23 (21.1%)	12 (10.5%)	35 (15.7%)
BSAP 5 (>18% to ≤25%)	16.67%	12 (11.0%)	9 (7.9%)	21 (9.4%)
BSAP 6 (>25%)	16.67%	13 (11.9%)	15 (13.2%)	28 (12.6%)

Source: Constructed during the evaluation based on data in the 'FILSUVEZ EB PBAC Nov 2025 CE Model' spreadsheet provided with the submission.
Abbreviations: BSAP, body surface area percentage.

6.49 Compared to the EASE trial population, assuming an equal distribution of patients among BSAP health states results in smaller proportions of patients in the lower disease burden health states and higher proportions of patients in higher disease burden states than in the EASE trial.

6.50 The submission stated that this distribution was used to account for the potential under-representation of more severe patients in the EASE trial (due to exclusion criteria such as the existence of current or former malignancies, for example); and that this would help minimise the potential influence of low transition matrix cell counts on transition probabilities. The evaluation considered the assumption that the distribution of BSAP health states can be changed without modifying other patient

characteristics was not adequately supported. Additionally, a higher proportion of patients in more severe health states would increase the influence of data sparseness issues associated with the higher severity health states. In their PSCR the sponsor stated that "an equal baseline distribution of patients across BSAP health states is an imperfect representation of the underlying Australian population and introduces uncertainty. However, dividing the population into severity states based on equal numbers of observations rather than equal intervals helped to minimise the potential under-representation of more severe patients in the EASE trial (because of exclusion criteria such as the existence of current or former malignancies), and the potential influence of low transition matrix cell counts on generating robust transition probabilities".

6.51 The ESC considered that it was not appropriate to change the baseline distribution of patients across health states based on body surface area percentage (BSAP) affected by partial thickness wounds (based on an assumed equal distribution). The ESC noted that this approach was inconsistent with the clinical trial data, assumes independence of BSAP from other modelled patient characteristics and exacerbates issues associated with data sparseness.

Baseline health state transitions

6.52 Health state transitions were derived from individual patient data from the EASE trial and open label extension. These transitions were affected by data sparseness, with small numbers of patients informing multiple transition probabilities, particularly for the more severe health states. The extent to which the resulting transition matrices reflect the clinical pathway of the disease and birch triterpenes gel treatment effects or are artefacts of data sparseness is unclear (e.g. there appeared to be implausible transition patterns whereby patients could transition to non-adjacent health states, but not to adjacent health states).

6.53 Smaller numbers of patients informed health state transitions at later time points (e.g. 89.9% of patients in the birch triterpenes gel arm of the EASE trial inform transitions from Day 0 to Day 30; 48.6% of patients inform transitions from Day 450 to Day 810). Data from the sponsor indicate there were higher proportions of discontinuations from patients in more severe health states The model base case assumed that discontinuations were at random and therefore would equally affect all BSAP health states. This assumption was not adequately justified.

6.54 From cycle 3 (Day 90) in the BSC arm and cycle 27 (Day 810) in the birch triterpenes gel arm, patients were assumed to be in a steady state, with no further change in disease burden (as measured by body surface area percentage) over the 40-year model time horizon. The submission noted that this does not imply that individual patients do not continue to transition between severities, but that the overall distribution of the cohort across severities does not change. This does not appear consistent with advice from clinical experts which indicated that patients with severe JEB and severe recessive DEB would experience disease progression over time.

6.55 The use of data from the open label phase for the birch triterpenes gel arm leads to greater incremental effects compared to BSC than observed in the EASE double blind phase.

Utilisation of birch triterpenes gel

6.56 The economic model assumed no differences in use of birch triterpenes gel between the BSAP health states, with patients in the BSAP 1 health state (with 0 to ≤4% of their body surface area affected by partial thickness wounds) assumed to use the same number of tubes per month as patients in the BSAP 6 health state (with >25% of their body surface area affected by partial thickness wounds). This assumption did not appear plausible and means that changing the distribution of patients among health states at baseline so that a higher proportion of patients have more of their body surface area affected by partial thickness wounds compared with the EASE trial, has no impact on use of birch triterpenes gel. The PSCR noted that data on average monthly tube use of birch triterpenes gel stratified by BSAP affected by partial thickness wounds were not available and the submission assumed the quantity of birch triterpenes gel used by each patient was independent of their BSAP. The PSCR presented the results of a sensitivity analysis assuming patients in BSAP health states 3 and 4 used the average number of tubes of birch triterpenes per month derived from the EASE trial, patients in BSAP 1 and 2 used 20% less than the average and patients in BSAP 5 and 6 used 20% more than average. No justification was provided for the selected values, which resulted in a 16% reduction in the base case ICER. The model also did not account for the impact of growth in children on utilisation of birch triterpenes gel.

Mortality

6.57 Mortality was estimated based on Australian general population life tables (ABS Life tables 2021-2023). This is inconsistent with advice from clinical experts indicating that most patients with severe recessive DEB (who represent 55.6% of the EASE trial population) would be deceased by the age of 55 years, with squamous cell carcinoma a key cause of death. The assumption of general population life expectancy results in a substantial underestimate of mortality in JEB and DEB patients, based on data from the EASE trial and open label phase, with 9 deaths observed over 27 months. However, the economic model was not sensitive to alternative estimates of mortality.

Utilities

6.58 There were limited EQ-5D-5L (in patients 16 years and older) and EQ-5D-Y-3L data (in patients younger than 16 years, with proxy responses provided by parents or caregivers for patients younger than 4 years). The ESC noted that these measures were only included in the EASE study as outcomes following a protocol amendment approximately 2.5 years after the trial was initiated. The EQ-5D-5L and EQ-5D-Y-3L utilities were pooled and a log-link function within a generalised linear model was used to estimate patient utility as a function of body surface area percentage, with the

midpoint value of the body surface area percentage range for each health state used to derive health state utilities. The submission did not justify the pooling of adult and child/adolescent utility values which was not appropriate given the different instruments used during the trial, the different value sets used and apparent different relationships between utility values and body surface area percentage (adults appeared to maintain higher utility scores at higher body surface area percentages) between the two patient groups. The PSCR acknowledged that pooling utility values for adults and children might generate additional uncertainty, however maintained that the utility estimates applied in the submission were appropriate, noting that a detailed technical report of the analysis was available. The ESC considered the approaches for scoring and pooling the EQ-5D-5L and EQ-5D-Y-3L used in the submission were inappropriate.

6.59 There were large differences in the health state utilities derived using Australian versus UK value sets and based on a sponsor-commissioned time trade-off analysis.

6.60 The ESC considered the utility values used in the model to be highly uncertain. The ESC noted that the submission did not justify the pooling of adult and child/adolescent utility values to derive health state utilities, and considered this approach was inappropriate. The ESC considered that modelling QALYs introduced significant uncertainty and that a better approach may be to focus on short term outcomes using a trial-based analysis.

6.61 The submission stated that carer utilities were included in the economic evaluation base case given the pivotal role of family carers in managing patient care (including changing bandages and supporting patients in daily activities) that contributes to health outcomes in patients with epidermolysis bullosa, and the impact on carers' quality of life. The evaluation and the ESC noted that inclusion of carer utilities in the base case of the economic model is not consistent with PBAC Guidelines, which specify that health-related outcomes in people other than the patient receiving treatment (such as quality-of-life benefits for family) should not be included in the base case evaluation, but presented as supplementary analyses. During the evaluation, the base case of the economic evaluation was revised excluding carer utilities, which were included in a sensitivity analysis.

Comparison of body surface area affected by wounds in the EASE trial versus the model

6.62 At the end of the 90 day double blind phase of the EASE trial, body surface area percentage was 7.41 in the birch triterpenes gel arm and 8.14 in the control gel arm, a difference of -0.73. In the economic model, based on the EASE trial baseline distribution, the difference between treatment arms in body surface area percentage was -1.53 at 90 days, -2.71 at 450 days and -2.49 at 810 days, illustrating the impact of allowing further improvements beyond 90 days for the birch triterpenes gel arm, but not for the BSC arm. When an equal distribution of patients among health states is assumed, the economic model generates even larger differences between treatment arms; -2.05 at 90 days, -3.43 at 450 days and -3.32 at 810 days.

Time horizon

6.63 The submission nominated a 40-year time horizon given the long-term, potentially life-limiting nature of the disease and requirement for ongoing management of patients, and to capture the potential long-term costs and benefits of birch triterpenes gel. However given the majority of patients in the EASE trial had severe recessive DEB, with a life expectancy of approximately 30 years, and the model was based on an assumption of a steady state, with no further health state transitions besides death beyond 90 days for the BSC arm and 27 months for the birch triterpenes gel arm, a shorter time horizon is likely to reduce the uncertainty associated with extrapolation beyond the EASE study duration.

6.64 Key drivers of the economic model are summarised in Table 9.

Table 9: Key drivers of the model

Description	Method/Value	Impact
Baseline BSAP distribution	The submission assumed that patients at baseline would be equally distributed among 6 BSAP health states. The ESC considered that it was not appropriate to change the baseline distribution of patients across BSAP health states.	High, favours birch triterpenes gel
BSAP health state transitions	Health state transitions derived from individual patient data from the EASE trial and open label extension were affected by data sparseness, with small numbers of patients informing multiple transition probabilities, particularly for the more severe health states. Smaller numbers of patients informed health state transitions at later time points. From cycle 3 (Day 90) in the best supportive care arm and cycle 27 (Day 810) in the birch triterpenes gel arm, patients were assumed to be in a steady state, with no further change in disease burden. This does not appear consistent with advice from clinical experts which indicated that patients with severe JEB and severe recessive DEB would experience disease progression over time. The use of data from the open label phase for the birch triterpenes gel arm leads to greater incremental effects compared to best supportive care than observed in the EASE double blind phase.	High, favours birch triterpenes gel

Source: Constructed during the evaluation.
Abbreviations: BSAP, body surface area percentage

Model results

6.65 The submission presented the results of a trial based economic analysis, based on the proportion of patients with first complete closure of the target wound by day 45, and drug costs over 45 days (step 1) and the proportion of patients with first complete closure of the target wound by day 90, and drug costs over 90 days (step 2). The incremental cost per additional patient with first complete wound closure by day 45 was $155,000 to < $255,000, and the incremental cost per additional patient with first complete wound closure by day 90 was $555,000 to < $655,000. The results of the trial-based analysis are shown in Table 10.

Table 10: Results of the trial-based economic evaluation

Economic analysis	Birch triterpenes gel	Best supportive care	Increment
Costs	$[redacted]	$0	$[redacted]
Patients with first EB wound closure at 45 days	41.3%	28.9%	12.4%
Incremental cost/patient with first EB wound closure at 45 days			$[redacted][1]
Costs	$[redacted]	$0	$[redacted]
Patients with first EB wound closure at 90 days	50.5%	43.9%	6.6%
Incremental cost/patient with first EB wound closure at 90 days			$[redacted][2]

Source: Table 3.8.1, p149 of the submission and calculated during preparation of the ESC Advice based on 26.23 tubes of birch triterpenes gel used every 30 days, as cited from Post-Hoc Table 14.1.5.6, page 5 of 6, BEB-13-section 14 of the EASE trial CSR. The submission utilised the tube quantity of 25.7 per 30 days, which was the quantity for all patients, irrespective of whether they used birch triterpenes gel or control gel.

The redacted values correspond to the following ranges:

[1] *$155,000 to < $255,000*

[2] *$555,000 to < $655,000*

6.66 The result of the modelled economic evaluation, revised during the evaluation to remove carer utilities, is summarised in Table 11.

Table 11: Results of the economic evaluation (revised to remove carer utilities)

Economic analysis	Birch triterpenes gel	Best supportive care	Increment
Costs	$[redacted]	$1,137,377	$[redacted]
QALYs	10.8064	10.1046	0.7018
Incremental cost/QALY gained			$[redacted][1]

Source: Table 3.8.5, p151 of the submission.

Abbreviations: QALY, quality adjusted life year.

The redacted values correspond to the following ranges:

[1] *> $1,055,000*

6.67 The submission applied a cost for birch triterpenes gel based on a mean of 25.7 tubes per 30-day cycle, which was the mean number of tubes across both treatment arms in the EASE trial. The ESC noted this was inappropriate as the mean number of tubes per 30-day cycle for patients who used birch triterpenes gel was 26.23.

6.68 Based on the economic evaluation, treatment with birch triterpenes gel was associated with an incremental cost per QALY gained of > $1,055,000 compared to BSC for the treatment of partial thickness wounds in patients with DEB or JEB.

6.69 The submission acknowledged that the incremental cost effectiveness ratio for birch triterpenes gel of > $1,055,000 per QALY gained (with the inclusion of carer utilities; Table 12) is significantly higher than ICERs normally accepted by the PBAC, but stated that this should be placed in the context of the rare nature of epidermolysis bullosa as a disease, the high clinical need for new therapies for epidermolysis bullosa, and the clinical benefit of birch triterpenes gel at a low to moderate budget impact.

6.70 The ESC considered the economic model presented to have limited reliability given the modest short-term benefits and assumptions made to translate the trial data to a longer time horizon.

6.71 The Pre-PBAC Response stated that the sponsor recognizes that the modelled ICER is high and uncertain, with significant uncertainty arising from the extrapolation of short-term wound-burden effects over time. The Response stated that the model is highly sensitive to carer utilities, which it considered are crucial in EB, where family members deliver wound care. The Pre-PBAC Response stated that "the cost-utility model quantifies health outcomes as QALYs but may not capture all downstream cost offsets of faster wound closure, such as fewer dressing changes, reduced infections and hospitalisations, and lower long-term skin-cancer surveillance. Accounting for these offsets would improve cost-effectiveness from a health-system perspective".

6.72 The results of key sensitivity analyses presented in the submission and conducted during the evaluation are summarised in Table 12.

Table 12: Results of key sensitivity analyses

Analysis	Incremental cost	Incremental QALYs	ICER	% change
Revised base case	**$[redacted]**	**0.7018**	**$[redacted][1]**	**-**
Scenario analysis including carer utilities (submission's base case)	$[redacted]	1.1786	$[redacted][1]	-[redacted]%
Discount rate (base case: 5% costs and outcomes)				
0%	$[redacted]	1.4767	$[redacted][1]	-[redacted]%
3.5%	$[redacted]	0.8493	$[redacted][1]	-[redacted]%
Time horizon (base case: 40 years)				
5 years	$[redacted]	0.1855	$[redacted][1]	+[redacted]%
10 years	$[redacted]	0.3378	$[redacted][1]	+[redacted]%
20 years	$[redacted]	0.5348	$[redacted][1]	+[redacted]%
30 years	$[redacted]	0.6431	$[redacted][1]	+[redacted]%
Baseline health state distribution (base case: patients assumed to be equally distributed between health states; 16.7% in each health state)				
Distribution among health states based on EASE trial[a]	$[redacted]	0.5368	$[redacted][1]	+[redacted]%
Use of EASE study data and extrapolation (base case: birch triterpenes gel transitions based on EASE double blind phase and open label extension, with steady state assumed after 810 days; best supportive care transitions based on EASE double blind phase, with steady state assumed after 90 days)				
Birch triterpenes gel arm based on EASE double blind phase only, with steady state assumed after 90 days	$[redacted]	0.3314	$[redacted][1]	+[redacted]%
Handling of discontinuations in transition matrices (base case: patients are assumed to be missing at random)				
Patients in BSAP 5 and BSAP 6 health states who discontinued during the EASE open label phase assumed to remain in the same health state at later timepoints	$[redacted]	0.5656	$[redacted][1]	+[redacted]%
Continuity correction for sparse data in transition matrices (base case: no continuity correction)				
Continuity correction applied to all health states	$[redacted]	0.5897	$[redacted][1]	+[redacted]%
Continuity correction applied to adjacent health states	$[redacted]	0.5444	$[redacted][1]	+[redacted]%
Treatment discontinuation (base case: 8.3% over the first 90 days of the model [2.85% per 30-day cycle]; 1% per year [0.08% per 30-day cycle] for subsequent cycles)				
Subsequent discontinuations based on discontinuations in the EASE open label phase (31.2%; 1.53% per 30-day cycle)	$[redacted]	0.1886	$[redacted][1]	+[redacted]%
Subsequent discontinuation based on discontinuations due to adverse events in the EASE open label phase (7.8%; 0.33% per 30-day cycle)	$[redacted]	0.4949	$[redacted][1]	+[redacted]%
Mortality (base case: general population mortality)				

Analysis	Incremental cost	Incremental QALYs	ICER	% change
Revised base case	**$[redacted]**	**0.7018**	**$[redacted][1]**	**-**
Mortality SMR applied so that 50% of patients have died by age 30 (after 13.3 years; SMR 117.7)	$[redacted]	0.4185	$[redacted][1]	+[redacted]%
Health state utilities (base case: derived from pooled EQ-5D-5L and EQ-5D-Y-3L data from the EASE open label phase; valued using Australian value sets)				
Health state utilities derived from TTO analysis	$[redacted]	0.7461	$[redacted][1]	-[redacted]%
Health state utilities derived from the EASE study, based on UK value sets (NICE submission)	$[redacted]	1.0983	$[redacted][1]	-[redacted]%
Drug cost (base case: 25.7 tubes per 30-day cycle, based on the average use across both arms from the EASE double blind phase and open label phase				
30 tubes per 30-day cycle, to account for the higher proportion of patients in more severe health states at baseline in the economic model compared to the EASE trial	$[redacted]	0.7018	$[redacted][1]	+[redacted]%
Disease management costs (associated with dressings, formal dressing care, and specialist outpatient visits)				
Remove disease management costs	$[redacted]	0.7018	$[redacted][1]	+[redacted]%
Increase dressing costs by 50%	$[redacted]	0.7018	$[redacted][1]	-[redacted]%
Decrease dressing costs by 50%	$[redacted]	0.7018	$[redacted][1]	+[redacted]%
Increase formal dressing care costs by 50%	$[redacted]	0.7018	$[redacted][1]	-[redacted]%
Decrease formal dressing care costs by 50%	$[redacted]	0.7018	$[redacted][1]	+[redacted]%
Increase outpatient visit costs by 50%	$[redacted]	0.7018	$[redacted][1]	-[redacted]%
Decrease outpatient visit costs by 50%	$[redacted]	0.7018	$[redacted][1]	+[redacted]%

Source: Table 3.9.2, p153 of the submission. 'FILSUVEZ EB PBAC Nov 2025 CE Model' spreadsheet provided with the submission.
Abbreviations: ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life year; TTO, time trade-off.
The redacted values correspond to the following ranges:
[1] *> $1,055,000*

6.73 The ESC noted that based on submission's requested price, the incremental cost per additional patient with first complete wound closure by day 45 would be $155,000 to < $255,000 (based on average number of tubes used per patient per 30-day cycle in the EASE trial of 26.23 and an additional 12.3% of patients would achieve first wound closure within this timeframe; Table 13).

Drug cost/patient/year

Table 13: Drug cost per patient for birch triterpenes gel

	EASE trial	Economic model	Financial estimates
Cost/patient/year	-	$[redacted][a]	$[redacted][b]
Treatment discontinuation	8.3% at 90 days	8.3% at 90 days 1% per year after 90 days	1% per year

[a] Calculated during preparation of the ESC Advice based on the mean of 26.23 tubes of birch triterpenes gel used every 30 days, (319.08 tube per year) as cited from Post-Hoc Table 14.1.5.6, page 5 of 6, BEB-13-section 14 of the EASE trial CSR. The submission utilised the tube quantity of 25.7 per 30 days, which was the quantity for all patients, irrespective of whether they used birch triterpenes gel or control gel. The cost was calculated using the average DPMQ of $[redacted]. Cost/patientyear using AEMP of $[redacted] per tube = $[redacted].

[b] May be underestimated as based on an average of 25.7 tubes per 30 days from the EASE trial and open label phase (rather than 26.23 tubes as noted in note a above), equivalent to 312.9 tubes per year, requiring 31.29 scripts of birch triterpenes gel 10 tube pack (=25.7/30×365.25/10) or 10.43 scripts of birch triterpenes gel 30 tube pack (=25.7/30×365.25/30). Assuming the 30% of use from 10 tube packs and 70% from 30 tube packs, the cost per year was calculated as $[redacted]×31.29×30%+$[redacted]×10.43×70%.

Estimated PBS usage & financial implications

6.74 This submission was not considered by the DUSC. The submission used an epidemiological approach to estimate the utilisation and financial implications associated with the PBS listing of birch triterpenes gel for the treatment of partial thickness wounds in patients with DEB or JEB.

6.75 Table 14 summarises the data sources and parameter values applied in the utilisation and financial estimates.

Table 14: Data sources and parameter values applied in the utilisation and financial estimates

Parameter	Value applied and source	Comment
Eligible population		
Prevalence	DEB: 10.7 cases per million persons. JEB: 1.0 cases per million persons. Based on minimum point prevalence estimates in April 2021 from a UK-based EB registry database (Petrof 2022).	Minimum point prevalence is a conservative estimate of prevalence that reflects the lowest plausible prevalence at a specific point in time, based on identified or confirmed cases. Petrof 2022 noted that while patients with severe types of EB would be included, some milder cases of EBS and dominant DEB may not be captured in the study, and that 4% of the cohort could not be classified into EB subtype. Petrof 2022 noted an increase in the prevalence of all EB subtypes over the 19-year study period, which is likely due to better case ascertainment with time but may reflect increased life expectancy resulting from improved care in severe EB types. However, prevalence estimates over time were not reported.
Birth incidence of DEB and JEB	DEB: 26.1 per million live births. JEB: 8.9 per million live births. Based on birth incidence estimates between 2002 and 2021 from a UK-based EB registry database (Petrof 2022). The submission assumed that the birth incidence would remain constant over the first 6 years of listing.	Birth incidence estimates appear to be overestimated. Petrof 2022 noted a reduction in birth incidence over the 19-year study period for all EB subtypes. Estimates based on the average birth incidence over the last 5 years (2016 to 2021) were 14.4 for DEB and 3.7 for JEB. The paper noted that this may be explained by increasing uptake of genetic counselling advice following the birth of a first child with EB. The Pre-PBAC Response presented revised estimates based on an incidence of 18.1 per million births.
Proportion of patients eligible for treatment	100%. Assumption, based on Australian clinical expert opinion (not provided).	This assumption is inconsistent with the proposed restriction, which requires patients to have a partial thickness wound age ≥21 days, and a chronic wound field of ≥10 cm² or a discrete wound

Parameter	Value applied and source	Comment
		≥10 cm². The proportion of patients eligible for treatment is likely to be less than 100% in clinical practice, depending on clinical discretion.
Treatment utilisation		
Uptake in the prevalent population	Year 1: [redacted]%; Year 2: [redacted]% ([redacted]% uptake in Year 2×70% of remaining untreated patients); Year 3-6: [redacted]%. Assumption, based on estimates from launches in other markets (not provided).	The assumed pattern of uptake, with prevalent patients only initiating treatment with birch triterpenes gel in the first 2 years of listing (resulting in [redacted]% of the eligible prevalent population never initiating treatment), appears inconsistent with the submission's claim that uptake is expected to be high. It is unclear whether uptake will be the same among different EB subtypes and age groups. The Pre-PBAC Response presented revised assumptions regarding uptake (the results are shown in Table 15).
Uptake in the incident population	Year 1: [redacted]%; Year 2: [redacted]%; Year 3: [redacted]%; Year 4: [redacted]%; Year 5: [redacted]%; Year 6: [redacted]%. Assumption, based on estimates from launches in other markets (not provided).	The assumed uptake rates are uncertain. The submission's approach assumes that incident patients can only initiate birch triterpenes gel treatment in their incident year (resulting in [redacted]% of incident patients never initiating treatment). This appears inconsistent with the submission's claim that uptake is expected to be high. It is unclear whether uptake will be the same among different EB subtypes and age groups. The Pre-PBAC Response presented revised assumptions regarding uptake (the results are shown in Table 15).
Treatment response	100%; assumption.	The proposed restriction requires that patients demonstrate a treatment response after 45-60 days for continued treatment (defined as complete closure, ≥50% reduction in wound area, or at least 2 supportive improvements). In the EASE trial, only 41.3% of patients treated with birch triterpenes gel achieved complete wound closure within 45 days.
Treatment persistence	99%; based on an annual discontinuation rate of 1% derived from UK expert clinical opinion (not provided).	Treatment persistence appears to be overestimated. Discontinuations during the EASE study were 8.3% over the 90-day double blind phase; and 31.2% over the 24-month open label phase (7.8% due to adverse events).
Utilisation of birch triterpenes gel	25.7 tubes per 30 days; based on a post hoc analysis of birch triterpenes gel and control gel use in the EASE trial and open label extension.	The average use of birch triterpenes gel in clinical practice is uncertain. There was large variation in utilisation of birch triterpenes gel based on data from the double blind phase of the EASE trial and extension study (median 18.59; IQR 14.01-27.54). The mean number of tubes per 30 days in patients treated with birch triterpenes during the double blind and open label extension was 26.23 and not 25.7.

Source: Section 4, pp157-167of the submission; Section 4 financial implications Excel workbook
Abbreviations: DEB, dystrophic epidermolysis bullosa; IQR, interquartile range; JEB, junctional epidermolysis bullosa.

6.76 Table 15 presents the estimated use and financial implications of listing birch triterpenes gel on the PBS.

Table 15: Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
As presented in the submission (corrected during evaluation)[a]						
Estimated extent of use						
Total patients (initiating and continuing)	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]
Total number of scripts [b]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]
Estimated financial implications of birch triterpenes gel						
Net cost to the PBS/RPBS	$[redacted][3]	$[redacted][4]	$[redacted][4]	$[redacted][4]	$[redacted][4]	$[redacted][4]
As presented in the Pre-PBAC Response						
Estimated extent of use						
Total patients (initiating and continuing) [c]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]
Total number of scripts [b]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][5]	[redacted][5]
Estimated financial implications of birch triterpenes gel						
Net cost to the PBS/RPBS	$[redacted][3]	$[redacted][4]	$[redacted][6]	$[redacted][7]	$[redacted][7]	$[redacted][7]

Source: Section 4, pp157-167of the submission; Section 4 financial implications Excel workbook.

[a] There was an error in the budget impact model that resulted in population estimates for 45- to 65-year-olds in 2026 being based on 2022 data. This was corrected during the evaluation. The estimates of initiating patients were estimated based on corrected ABS population.

[b] Based on an average of 25.7 tubes of birch triterpenes gel per 30 days from the EASE trial and open label extension, equivalent to 312.9 tubes per year, requiring 31.29 scripts of birch triterpenes gel 10 tube pack (=25.7/30×365.25/10) or 10.43 scripts of birch triterpenes gel 30 tube pack (=25.7/30×365.25/30); and assuming a 30%/70% split. May be underestimated as based on an average of 25.7 tubes per 30 days from the EASE trial and open label phase (rather than 26.23 tubes) as described in Table 11.

[c] Based on birth incidence of 18.1 per million live births and adjustment to carry forward untreated patients in a preceding year.

The redacted values correspond to the following ranges:

[1] *< 500*

[2] *500 to < 5,000*

[3] *$10 million to < $20 million*

[4] *$30 million to < $40 million*

[5] *5,000 to < 10,000*

[6] *$40 million to < $50 million*

[7] *$50 million to < $60 million*

6.77 The submission estimated the cost of birch triterpenes gel to the PBS/RPBS to be $10 million to < $20 million in Year 1, increasing to $30 million to < $40 million in Year 6, with a total cost of $100 million to < $200 million over the first 6 years of listing. This estimate was increased significantly in the pre-PBAC response (see paragraph 6.80).

6.78 The estimated cost to the PBS/RPBS was considered uncertain for the following reasons:

- The birth incidence of DEB and JEB (31.0 per million births), based on data from a UK epidermolysis bullosa registry database (Petrof 2022), appears overestimated. Petrof 2022 noted a reduction in birth incidence over the 19-year study period for all epidermolysis bullosa subtypes, with a birth incidence of DEB and JEB of 18.1 per million births between 2016 and 2021. The Response considered an estimate of 18.1 per million births to be reasonable and provided revised estimates using this rate.
- The assumed patterns of treatment uptake, with prevalent patients only able to initiate treatment in the first 2 years of listing and incident patients only able to

initiate treatment in their incident year, did not appear plausible. The PSCR stated that "the uptake assumptions were intended to reflect expected clinical practice in a rare disease setting, whereby most clinically appropriate prevalent patients would be identified and considered for treatment relatively early following listing (from Year 2026), with subsequent growth driven mainly by incident cases (Year 2027 onwards). This approach avoids double-counting and provides a reasonable, pragmatic representation of treatment uptake in clinical practice for a rare disease". The resulting proportions of untreated patients over the first 6 years of listing (45.5% of prevalent patients; 53.4% of incident patients) appear inconsistent with the submission's claim that uptake of birch triterpenes gel is anticipated to be high due to the rarity of disease and lack of pharmacologic treatment options for epidermolysis bullosa. In their PSCR, the sponsor agreed that initial uptake of birch triterpenes gel may be higher than originally estimated. The Pre-PBAC Response presented revised estimates, carrying forward untreated patients each year so they could commence treatment in subsequent years.

- The proposed restriction requires that patients demonstrate a treatment response after 45 to 60 days for continued treatment (defined as complete closure, ≥50% reduction in wound area, or at least 2 supportive improvements). The assumption that all patients would demonstrate a response to birch triterpenes gel and continue treatment was not adequately justified. In the EASE trial, only 41.3% of patients treated with birch triterpenes gel achieved the primary outcome of complete wound closure within 45 days.
- Treatment persistence, based on an annual discontinuation rate of 1%, appears to be overestimated. Treatment discontinuation was 8.3% over the 90-day period of the EASE double blind phase, and 31.2% over the 24-month open label phase. The PSCR noted that many of the discontinuations in the EASE trial were protocol related, with some discontinuations related to logistical challenges in complying with the trial follow-up requirements. The Pre-PBAC Response stated that due to the nature of the disease that treatment would be more likely to be intermittent or temporarily interrupted for individual wounds rather than permanently discontinued and that uncertainty with respect to annual discontinuation rates could be managed through a Risk Sharing Arrangement if required.
- Average monthly utilisation of birch triterpenes gel in clinical practice is uncertain, due to dynamic nature of partial thickness wounds, with fluctuations in body surface area affected by partial thickness wounds.
- There is the potential for use of birch triterpenes gel beyond the proposed restriction in patients with other subtypes of epidermolysis bullosa, given the lack of requirements for documentation of diagnosis in the proposed restriction.

6.79 The financial estimates were sensitive to the incidence and prevalence of DEB and JEB, estimated uptake and the average monthly utilisation of birch triterpenes gel. Sensitivity analyses are presented in Table 16.

Table 16: Sensitivity analyses presented in the submission and conducted during the evaluation

Analysis	Cumulative net PBS/RPBS cost over 6 years	% change from base case
Base case	$[redacted][1]	-
DEB/JEB prevalence (base case: 11.7 per million)		
Decrease by 10% (10.5 per million)	$[redacted][1]	-[redacted]%
Increase by 10% (12.8 per million)	$[redacted][1]	+[redacted]%
10.1 per million (Kho 2010; NSW population: DEB 8.0; JEB 2.1)	$[redacted][1]	-[redacted]%
4.6 per million (Kho 2010; Australian population: DEB 3.9; JEB 0.7)	$[redacted][2]	-[redacted]%
5.3 per million (Harris 2016; Australian population: DEB 4.6; JEB 0.7)	$[redacted][3]	-[redacted]%
DEB/JEB incidence (base case: 35.0 per million based on estimates from 2002 to 2021 from Petrof 2022)		
Decrease by 10% (31.5 per million)	$[redacted][1]	-[redacted]%
Increase by 10% (38.5 per million)	$[redacted][1]	+[redacted]%
DEB/JEB incidence 18.1 per million (based on estimates from 2016 to 2021 from Petrof 2022)	$[redacted][1]	-[redacted]%
Uptake (base case: prevalent patients 30% in Year 1; 35% in Year 2; 0% in Years 3-6; incident patients 30% in Year 1, increasing to 65% in Year 6)		
Decrease by 10% (27% in Year 1; 31.5% in Year 2; increasing to 58.5% in Year 6)	$[redacted][1]	-[redacted]%
Increase by 10% (33% in Year 1; 38.5% in Year 2; increasing to 71.5% in Year 6)	$[redacted][1]	+[redacted]%
Increase by 20% (36% in Year 1; 42% in Year 2; increasing to 78% in Year 6)	$[redacted][4]	+[redacted]%
Use of birch triterpenes gel tubes (base case: 25.70 tubes/30 days based on average utilisation in the EASE trial (birch triterpenes gel arm only) and open label extension (patients previously randomised to birch triterpenes gel or control gel)		
Median utilisation in the EASE trial and open label extension (birch triterpenes gel and control gel arms; 18.59[b] tubes)	$[redacted][1]	-[redacted]%
1st quartile utilisation in the EASE trial and open label extension (birch triterpenes gel and control gel arms; 14.01 tubes)	$[redacted][3]	-[redacted]%
3rd quartile utilisation in the EASE trial and open label extension (birch triterpenes gel and control gel arms; 27.54 tubes)	$[redacted][1]	+[redacted]%
Average utilisation in the EASE trial and open label extension (birch triterpenes gel arm only; 26.23 tubes)	$[redacted][1]	+[redacted]%

Source: Tables 4.6 2 and 4.6 3, p165 of submission; Section 4 financial implications Excel workbook

Abbreviations: DEB, dystrophic epidermolysis bullosa; JEB, junctional epidermolysis bullosa; PBS, Pharmaceutical Benefits Scheme; RPBS, Repatriation Pharmaceutical Benefits Scheme.

[b] This was reported as 19.00 tubes in the submission and was corrected during the evaluation.

The redacted values correspond to the following ranges:

[1] *$100 million to < $200 million*

[2] *$80 million to < $90 million*

[3] *$90 million to < $100 million*

[4] *$200 million to < $300 million*

6.80 The Pre-PBAC Response presented updated financial estimates that incorporated revised treatment uptake assumptions and a new incidence estimate. The revised estimates assumed that eligible patients untreated in a given year would be carried forward and that they could start birch triterpenes gel in any later year within the 6-year horizon. The revised estimates assumed the birth incidence of DEB and JEB would

be 18.1 per million live births, reflecting the latest published estimate. These revisions increased the estimated cumulative net PBS/RPBS cost over 6 years from approximately $100 million to < $200 million (Table 16) to approximately $200 million to < $300 million.

6.81 The Pre-PBAC Response also presented sensitivity analyses that included different assumption regarding average monthly gel use. The Response stated that by applying the mean number of gel tubes used per 30-day cycle for patients treated with birch triterpenes gel in the EASE trial (26.23 tubes), the estimated cumulative net PBS/RPBS cost over 6 years would increase to approximately $200 million to < $300 million.

For more detail on PBAC's view, see section 7 PBAC outcome.

7 PBAC Outcome

7.1 The PBAC did not recommend the listing of birch triterpenes gel for the treatment of patients with partial thickness skin wounds caused by dystrophic epidermolysis bullosa (DEB) or junctional epidermolysis bullosa (JEB). The PBAC recognised there is a high clinical need for both earlier and complete wound closure for patients with this debilitating condition. The PBAC noted that results from the EASE trial showed treatment with birch triterpenes gel was associated with a statistically significantly higher proportion of patients achieving first complete closure of the target wound within 45 days compared to control gel, however, there was no significant difference in time to wound closure within 90 days. It was also noted that the EASE trial specified a limited number of permitted dressings in the control group, which was not representative of Australian clinical practice. Overall, the PBAC considered the incremental benefit of birch triterpenes gel to be modest. The PBAC noted that the economic model had attempted to estimate long-term benefits of birch triterpenes gel but considered that it was not possible to determine to what extent the short-term benefits observed in the EASE trial would translate to longer term benefits from the data presented. Despite being a rare condition, the financial impact was estimated to be more than $200 million to < $300 million over 6 years reflecting the high proposed price of birch triterpenes gel, which the PBAC considered was not justified by the clinical evidence presented.

7.2 The PBAC considered that the primary reason for this outcome was the comparative clinical evidence.

7.3 The PBAC noted that the Australian Government's National Epidermolysis Bullosa Dressing Scheme (NEBDS) provides a broad range of wound care products including primary layer dressings for direct wound contact (silicone/non-silicone dressings, hydrogels, honey/medicated/silver dressings), secondary layer dressings for absorption and protection (exudate transfer dressings, foam, gauze, absorbent padding), enzymatic/antimicrobial products, barrier films and creams, bandages and securement dressings, debriding solutions and other accessories (needles and

lancets). The NEBDS scheme supports people with EB by providing affordable access to specialised bandages and dressings.

7.4 The PBAC noted and welcomed the input from health professionals and organisations supporting the PBS listing of birch triterpenes gel. The PBAC noted that the input highlighted the high unmet need and the substantial burden in terms of quality of life, pain, risk of infection, functional limitations and dressing changes that partial thickness wounds have on patients, families and carers. The PBAC noted the clinician's advice at the sponsor hearing that patients with severe DEB and JEB are at risk of serious and potentially fatal complications from chronic wounds, including squamous cell carcinoma, septicaemia, and systemic complications from blood or protein loss. The PBAC also noted the clinician's view that accelerated wound closure lowers the risk of a wound becoming chronic. The consumer input indicated that benefits of birch triterpenes gel include improved wound healing and reduced complications, and potential to improve quality of life by reducing pain, itch, inflammation and wound burden, resulting in fewer and less painful dressing changes and reduced analgesic use. The PBAC noted that the input indicated a range of responses to the treatment, including positive results reported for some patients and no benefit reported for others.

7.5 The PBAC noted that the proposed restriction would allow up to 30 tubes of birch triterpenes gel to be supplied per month, with 5 repeats, which the submission expected would be sufficient for 6 months of treatment. The PBAC considered that the proposed maximum quantity may be too high and that it may be appropriate to restrict the maximum number of tubes based on more stringent criteria so that treatment would be limited to wounds or wound fields in specific places for which patients would obtain the most benefit. The PBAC further noted that as not all patients would benefit from treatment, clinician assessment of response was needed within the first 3 months.

7.6 The PBAC noted that the submission proposed that use should be in addition to best supportive care (BSC) and that BSC was nominated as the comparator. The PBAC noted that current management is supportive and includes wound dressings, blister care, infection prevention, pain and itch management, nutrition support, surgery for complications, and multidisciplinary specialist care. The PBAC considered that BSC was the appropriate comparator, noting there are no PBS-listed medicines for the treatment of partial thickness wounds associated with DEB or JEB, and noting that birch triterpenes gel would be used as an adjunct to, rather than as a replacement for, existing wound care. The PBAC noted that BSC in Australian clinical practice includes a broad range of wound care products available through the NEBDS, including primary and secondary dressings, enzymatic and antimicrobial products, barrier films and creams, bandages, securement dressings, debriding solutions and other accessories. The PBAC considered that the control gel used in the EASE trial was a reasonable proxy for BSC, but noted that concomitant wound care in the trial was likely to have been more restrictive than in Australian clinical practice, given that the trial restricted use

of some dressing materials, topical skin products, systemic steroids and systemic antibiotics.

7.7 The PBAC noted that birch triterpenes gel was associated with a statistically significant increase in the proportion of patients achieving first complete closure of the target wound (a single epidermolysis bullosa partial thickness wound of 10 cm^2 to 50 cm^2 in size and ≥21 days to <9 months in age) within 45 days (41.3%) compared with control gel (28.9%) in the EASE trial (Table 4). The PBAC acknowledged the value to patients of faster wound closure, and in the context that an additional 12.4% of patients achieved first complete closure of the target wound within 45 days, the PBAC considered the clinical benefit to be modest.

7.8 The PBAC noted that Day 90 results from the EASE trial suggested no apparent difference in wound closure rates between treatment arms, and that this was also reflected in the patient reported outcomes from the trial, which indicated a small or no improvement in itching, pain, and impact on sleep and work/school attendance for patients treated with birch triterpenes gel.

7.9 The PBAC noted the sponsor's argument in the Pre-PBAC Response that accelerated wound closure may reduce the risk of malignancy, since chronic wounds can lead to the development of squamous cell carcinoma. However, the PBAC noted that the submission had not presented data that allowed the Committee to assess whether that claim was supported.

7.10 Overall, the PBAC considered that the claim of superior comparative efficacy of birch triterpenes gel (plus BSC) versus BSC alone was supported for the outcome of wound closure at 45 days but was not adequately supported for wound closure rates over longer than 45 days, infection, broader wound burden outcomes, or patient-reported outcomes.

7.11 The PBAC noted that there were higher wound complication-related adverse events in patient treated with birch triterpenes gel compared to control gel during the double-blind phase of the EASE trial (Table 6). The PBAC noted the sponsor's arguments in the Pre-PBAC Response that wound re-opening can only occur after wound closure, and that earlier and more frequent wound closure in the birch triterpenes gel arm increased the opportunity for patients to move more frequently and for wound re-opening events to be observed. The PBAC also noted the sponsor's view that although wound re-opening events were higher in the trial, that the events that would indicate the wound was worsening overall were not increased in patients treated with birch triterpenes gel. The PBAC noted that wound complication rates declined in the open-label phase of the EASE trial compared with the double-blind phase. Overall, the PBAC considered that the claim of non-inferior safety of birch triterpenes gel (plus BSC) compared to BSC alone was not adequately supported by the results from the double-blind phase of the EASE trial.

7.12 The PBAC considered that the modelled cost-utility analysis presented by the submission was not reliable for decision making.

- The PBAC noted and agreed with the ESC's concerns that the model translated modest short-term trial benefits into long-term quality-adjusted life years (QALY) gained using assumptions that were highly uncertain, including the assumed equal baseline distribution across body surface area percentage health states, transition matrices derived from sparse individual patient data, the use of open-label extension data for the birch triterpenes gel arm without comparable long-term data for BSC, and steady-state assumptions that were inconsistent with clinical advice that severe JEB and severe recessive DEB may progress over time.
- The PBAC noted that the submission had estimated utility values based on the proportion of BSA affected and considered the utility values to be highly uncertain.
- The PBAC noted that the submission had incorporated carer disutility values in the base case. The PBAC considered that health outcomes accruing to carers were a relevant contextual consideration; however, consistent with the PBAC Guidelines, these outcomes should not be included in the base case economic evaluation. The PBAC noted that, after removing carer utilities from the base case, the revised ICER was > $1,055,000 per QALY gained.
- The PBAC noted that sensitivity analyses showed results ranging from > $1,055,000 per QALY gained when carer utilities were included to > $1,055,000 per QALY gained when the inputs for the birch triterpenes gel arm were based on the EASE double-blind phase only.
- The PBAC considered the submission's estimate of the incremental cost-effectiveness ration (ICER) of birch triterpenes gel (plus BSC) compared to BSC alone based on the model to be both highly uncertain and unacceptably high.

7.13 The PBAC considered that the trial-based economic analysis presented in the submission, which focused on short-term wound closure outcomes, was more informative for decision making, and noted that based on the requested price, the incremental cost per additional patient with first complete wound closure by day 45 was $155,000 to < $255,000. While the PBAC considered this to be a more reliable estimate of cost-effectiveness than the modelled cost-utility analysis, the PBAC also considered this ICER to be unacceptably high. The PBAC further considered both the durability of wound closure and the amount of gel required to be uncertain, and overall that the proposed price was not justified by the evidence presented.

7.14 The PBAC considered the financial estimates to be high and uncertain.

- The PBAC noted that the Pre-PBAC Response presented revised estimates that assumed a lower birth incidence of 18.1 per million live births, which was in line with the evaluation's view that birth incidence estimate of 35.0 per million live births appeared to be overestimated. The PBAC considered the incidence of JEB and DEB in Australia to be uncertain.
- The PBAC noted that the Pre-PBAC Response presented revised financial estimates that allowed for eligible patients who were untreated in a given year to be carried forward so untreated patients could commence treatment in any later year within

the 6-year horizon. While the PBAC considered that this addressed the ESC's concern that the original uptake pattern that was used to form the estimates in the submission was not clinically plausible, the Committee considered the population of DEB and JEB patients likely to be treated with birch triterpenes gel in Australia to be uncertain.

- The PBAC noted that the revised financial estimates as presented in the Pre-PBAC Response based on changes to the birth incidence and the carrying forward of eligible patients (described above) estimated that the cumulative net cost to the PBS/RPBS over 6 years would be approximately $200 million to < $300 million (based on an assumption of 25.7 tubes of birch triterpenes gel per 30-day cycle). This was increased to approximately $200 million to < $300 million, after a correction was made to reflect the average utilisation from the birch triterpenes arm in the EASE trial (26.23 tubes of gel per 30-day cycle).
- The PBAC further noted that a key driver of the estimated total cost to the PBS/RPBS was the number of tubes of gel that would be required per patient. The PBAC considered the estimate of gel use per 30-day cycle to be a key source of uncertainty, given the dynamic nature of partial thickness wounds, inter- and intra-patient fluctuations with respect to the proportion of body surface area affected, and potential wastage associated with single-use tubes.

7.15 The PBAC considered there was potential for birch triterpenes gel to be used beyond the restriction for wounds that didn't meet the proposed clinical criteria and a significant risk that the number of tubes used per patient would be higher than estimated.

7.16 The PBAC noted that the proposed listing allowed flexibility for prescribers to request individualised quantities, and did not specify criteria in relation to when use of birch triterpenes gel would be appropriate as compared with other treatment options that might be provided at a much lower cost. The PBAC considered this was not appropriate given the modest clinical benefit as described in paragraph 7.7. Overall, the PBAC considered that birch triterpenes gel was not suitable for listing on the PBS as requested. The PBAC suggested that rather than the PBS, it may be more appropriate for birch triterpenes gel to be supplied by EB specialist clinics with its use restricted to individual patients and used when all other treatment options have been exhausted, or when its use is limited to certain body areas that are most difficult to manage or carry the highest risk of complications.

7.17 The PBAC noted that this submission is eligible for an Independent Review.

Outcome:
Not recommended

8 Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised through the Pharmaceutical Benefits Scheme (PBS) in Australia. It considers applications regarding the listing of medicines on the PBS and provides advice about other matters relating to the operation of the PBS in this context. A PBAC decision in relation to PBS listings does not necessarily represent a final PBAC view about the merits of the medicine or the circumstances in which it should be made available through the PBS. The PBAC welcomes applications containing new information at any time.

9 Sponsor's Comment

Chiesi is disappointed by this outcome and respectfully disagrees with the PBAC's conclusion that birch triterpenes gel is unsuitable for PBS reimbursement. While acknowledging the Committee's feedback, Chiesi is concerned that the alternative access model suggested by the PBAC, whereby treatment is supplied through individual Epidermolysis Bullosa (EB) specialist clinics and hospital funding arrangements, would create substantial inequities for patients living with EB.

Chiesi remains committed to working constructively with the Department of Health to identify a sustainable and equitable pathway to improve access for Australians living with EB. Chiesi thanks the patients, caregivers, healthcare professionals, and advocacy organisations who have provided invaluable input into the submission.