# NCPE Technical Summary

## Birch bark extract (Filsuvez®)

## HTA ID: 23069

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Applicant: Chiesi Farmaceutici S.p.A

The cost-effectiveness of birch bark extract for the treatment of partial-thickness wounds associated with dystrophic and junctional epidermolysis bullosa (EB) in patients six months and older.

NCPE
National Centre for Pharmacoeconomics, Ireland

The National Centre for Pharmacoeconomics (NCPE) has issued a recommendation regarding the cost-effectiveness of birch bark extract (Filsuvez®). Following assessment of the Applicant's submission, the NCPE recommends that birch bark extract (Filsuvez®) be considered for reimbursement if cost-effectiveness can be improved.

The Health Service Executive (HSE) asked the NCPE to carry out an evaluation of the Applicant's (Chiesi Farmaceutici S.p.A) Health Technology Assessment (HTA) of birch bark extract (Filsuvez®). The NCPE uses a decision framework to systematically assess whether a technology is cost-effective. This includes clinical effectiveness and health related quality of life benefits, which the new treatment may provide and whether the cost requested by the pharmaceutical company is justified.

Following the recommendation from the NCPE, the HSE examines all the evidence which may be relevant for the decision; the final decision on reimbursement is made by the HSE. In the case of cancer drugs, the NCPE recommendation is also considered by the National Cancer Control Programme (NCCP) Technology Review Group.

## About the National Centre for Pharmacoeconomics

The NCPE are a team of clinicians, pharmacists, pharmacologists and statisticians who evaluate the benefit and costs of medical technologies and provide advice to the HSE. We also obtain valuable support from clinicians with expertise in the specific clinical area under consideration. Our aim is to provide impartial advice to help decision makers provide the most effective, safe and value for money treatments for patients. Our advice is for consideration by anyone who has a responsibility for commissioning or providing healthcare, public health or social care services.

## Summary

In October 2024, Chiesi Farmaceutici S.p.A submitted a dossier which investigated the clinical effectiveness, cost-effectiveness and budget impact of birch bark extract for the treatment of partial-thickness wounds associated with dystrophic and junctional epidermolysis bullosa (EB) in patients 6 months of age and older. Reimbursement is for the High Tech Arrangement.

Epidermolysis bullosa (EB) is a condition caused by gene mutations that result in disruption or incorrect expression of certain skin anchoring proteins leading to fragile skin that blisters and breaks, particularly in response to minor trauma or friction. There are four major classical EB types including EB simplex (EBS), junctional EB (JEB), dystrophic EB (DEB) and Kindler EB (KEB). Birch bark extract (Filsuvez) is indicated for dystrophic and junctional epidermolysis bullosa. Junctional epidermolysis bullosa (JEB) is an autosomal recessive disorder characterized by skin blistering with a plane of cleavage through the lamina lucida of the cutaneous basement membrane zone. The severity varies considerably across the two major subtypes, intermediate and severe, with the latter associated with early lethality in the first 6–24 months of life. Epidemiological data indicates that JEB is less common than simplex or dystrophic types of EB. Dystrophic epidermolysis bullosa (DEB) is characterized by a plane of skin cleavage just beneath the lamina densa in the most superficial portion of the dermis which corresponds to the level of the anchoring fibrils, reflecting the underlying molecular pathology in the gene coding for the main component of these structures, type VII collagen. It may be inherited as a dominant or recessive trait with recessive DEB being more severe, however, there is considerable phenotypic overlap between types. The hallmark of dystrophic EB is that of scarring following blistering, both in the skin and in a variety of mucosae.

Many wounds in EB are classified as partial-thickness wounds which extend through the epidermis, basement membrane and into the upper part of the dermis. In dystrophic and junctional EB there is often a high total body partial-thickness wound burden. In addition to the regular formation of new blisters and wounds patients with dystrophic and junctional EB experience an altered wound healing process with limited epithelialisation, keratinocyte migration and epithelial barrier remodelling. As a result of this dysregulation and the inability to restore the epithelial barrier epidermolysis bullosa manifests with recurrent partial-thickness wounds and blisters. Patients with epidermolysis must endure time-consuming and painful dressing changes (particularly children) at least three times per week. In addition there is an increased risk of osteoporosis and aggressive squamous cell carcinoma. Life expectancy is dependent on the severity of the disease.

Birch bark extract gel (Filsuvez) is indicated for the treatment of partial-thickness wounds associated with dystrophic and junctional epidermolysis bullosa in patients 6 months and older. Filsuvez received a positive opinion from the Committee for Medicinal Products for Human Use (CHMP) on the 22nd of April 2022 and marketing authorisation was granted by the European Medicines Agency (EMA) on the 21st of June 2022. Birch bark extract was designated an 'orphan medicine' on the 23rd February 2011. Birch bark extract gel (Filsuvez) is a non-aqueous gel with anti-inflammatory and wound healing properties in the form of a refined birch bark (triterpene) extract which includes betulin, betulinic acid, erythrodiol, lupeol and oleanolic acid. The precise mechanism of action of Filsuvez in wound healing is unknown. Cell culture assays with human primary keratinocytes and fibroblasts and ex vivo studies with porcine skin show that the birch triterpenes modulate inflammatory mediators and are associated with activation of intracellular pathways known to be involved in keratinocyte differentiation and migration, wound healing and closure.

## 1. Comparative effectiveness of birch bark extract (Filsuvez®)

The EASE study was a pivotal phase III randomised controlled trial which investigated the efficacy and safety of Oleogel – S10 (birch triterpenes) for the treatment of epidermolysis bullosa and was the primary source of evidence used in this economic submission. Filsuvez and Oleogel-S10 refer to the same product of birch bark extract. The EASE trial objective was to compare the efficacy of Oleogel-S10 with a vehicle control gel in patients aged 21 days or older with dystrophic EB, junctional EB or Kindler EB to accelerate healing of EB wounds. The EASE trial consisted of a 90 day double-blind phase followed by a 24 month open-label extension study. The primary efficacy endpoint of the study was the proportion of patients with first complete closure of the EB target wound, determined by clinical assessment within 45 days (± 7 days) of treatment. Key secondary endpoints included (i) time to first complete closure of the EB target wound (ii) the proportion of patients with first target wound closure within day 90 ± 7 days (iii) incidence and maximum severity of target wound infection between baseline and day 90 ± 7 days (iv) total body wound burden using the skin activity component of the EB Disease Activity and Scarring Index (EBDASI) (v) pain and itch and (vi) body surface area percentage (BSAP) affected by EB partial-thickness wound. Additional patient reported outcomes included background pain, wound quality of life, sleep, work days/school days missed, and treatment satisfaction questionnaire for medication safety.

The EASE study enrolled 223 patients (n=109 patients in the Oleogel-S10 arm and n=114 in the control gel arm). The median age was 12 years and 60% were male. One hundred and seventy five patients (78.5%) had a diagnosis of recessive dystrophic EB, 20 patients (9%) had dominant

dystrophic EB and 25 patients (11.7%) had junctional EB. A total of 199 patients completed the double-blind phase of the study to day 90 ± 7days. The primary endpoint in relation to the proportion of patients with first complete closure of the EB target wound by day 45 was met. Complete target wound closure was achieved in 41.3% of target wounds treated with Oleogel-S10 and 28.9% of target wounds treated with the control gel (relative risk (RR) 1.44, 95% confidence interval (CI) 1.01 – 2.05; P=0.013).

In relation to secondary endpoints the difference in the time to first target wound closure over the 90 day double-blind period was not significantly different between the treatment arms (P=0.302). By day 90 the cumulative proportion of patients with first target wound closure was 50.5% for Oleogel-S10 versus 43.9% for the control gel (P=0.296). There were six patients with target wound infections during the double-blind phase, one patient in the Oleogel-S10 arm (0.9%) compared to five patients (4.4%) in the control gel arm. Difference in total wound burden measured by the EB Disease Activity and Scarring Index (EBDASI) and the body surface area percentage (BSAP) did not reach statistical significance. Improvements in the Itch Man Scale (patients aged 4 – 13 years) were observed with both treatments, with a significant improvement observed only at day 60 with the control gel (P=0.016). A significant reduction in pain associated with dressing changes (procedural pain) in patients 4 years of age and older was noted in the Oleogel-S10 arm on day 90 however differences at other time points did not differ significantly. Analysis of dressing change frequency showed that throughout the double-blind phase patients treated with Oleogel-S10 had a reduced requirement for daily dressing changes compared with those who received the control gel. At day 90 the change with Oleogel-S10 equated to one less dressing change every 2 weeks (P=0.001). There was no significant difference in other secondary endpoints including wound quality of life, sleep quality and the number of days missed from school or work until day 90.

A total 141 patients completed the open-label phase of the EASE trial and wound treatment adherence was greater than 99%. The mean treatment duration for all patients was 584.7 days. Some 71.7% of patients in the open-label phase were aged less than 18 years and 86.8% had dystrophic EB. The mean body surface area percentage (BSAP) changes from the double-blind baseline at 3, 12 and 24 months were -4.3%, -5.9% and -3.7% for patients treated with Oleogel-S10. All these changes were statistically significant. Similarly, the mean EB Disease Activity and Scarring Index (EBDASI) score in the Oleogel-S10 group improved significantly i.e -3.9, -5.1 and -3.0 at 3, 12 and 24 months respectively.

## 2. Safety of birch bark extract (Filsuvez®)

In the double-blind phase of the EASE study a similar percentage of patients in the Oleogel-S10 and the control gel group reported adverse events which were mainly mild to moderate intensity. The most frequently reported adverse events related to wound complications and occurred at a similar frequency in both treatment arms. Serious adverse events were reported in 6.4% of patients treated with Oleogel-S10 as compared with 5.3% in those treated with the control gel. Only one serious adverse event, a wound haemorrhage in a patient treated with Oleogel-S10 was considered to be related to study treatment and resulted in withdrawal from the study.

In the open-label extension study adverse events were reported in 77.1% of patients and were typically mild-to-moderate. Severe and serious adverse events were observed in 18% and 24.4% of patients respectively. Adverse events resulted in the withdrawal of 7.8% of patients (n=16) including three with treatment-related adverse events. Nine deaths were reported but none were attributable to Oleogel-S10 treatment. The incidence of target would infections was low (n=7) with five reported as mild-to-moderate and two being severe.

## 3. Cost effectiveness of birch bark extract (Filsuvez®)

### Methods

A cohort–level state transition model was developed to estimate lifetime costs and quality adjusted life years (QALYs) associated with Filsuvez for the treatment of partial-thickness wounds in epidermolysis bullosa patients over a lifetime horizon. The Markov model includes seven distinct health states with six representing different levels of EB total wound burden, defined by discrete ranges of body surface area percentage (BSAP) covered by partial-thickness wounds e.g health state 1 was a BSAP from 0% to ≤ 4% wound coverage, health state 2 was a BSAP > 4% to ≤ 7% wound coverage increasing to health state 6 which was a BSAP > 25% wound coverage. The remaining state was the death state. Transition probabilities between health states were derived from individual patient data from the EASE clinical trial. The increased rate of wound healing and the reduction in overall wound burden with Filsuvez treatment is considered in this cost-effectiveness analysis over a lifetime horizon of 80 years. To allow for transitions to be estimated where no patients are observed transitioning from a particular health state, a continuity correction is applied to distribute transitions across states. The discontinuation rate for Filsuvez for the initial 90 days was set at 8.3% (based on the EASE trial) and was assumed to be 0% per annum thereafter. Mortality rates were applied using parametric survival curves fitted to digitisations of Kaplan-Meier curves derived from Petrof et al 2022 and Irish general population data.

Patient outcomes were quantified as quality-adjusted life years (QALYs). Utility data was obtained from a number of sources including the EASE open-label extension study, a Time Trade-Off study conducted in the general UK population, a cross-sectional study and existing health related quality of life data from the literature. The sources of these data were considered transferable to the Irish healthcare setting. The economic dossier highlights that relevant cost and healthcare resource use data, suitable for incorporation into the model, were sourced from the following: (a) the PEBLES registry (b) costing studies by Angelis et al (2016, 2022) (c) a cross-sectional survey of EB burden (d) a publication by Flannery et al (2020) and a structured expert elicitation to support resource use estimates. The PEBLES study specifically obtained cost estimates for patients with recessive dystrophic EB and along with the structured expert elicitation was used in the base case analysis. The studies by Angelis et al (2022) and Flannery et al (2020) were used in a scenario analysis. Costs and quality adjusted life-years (QALYs) were discounted at a rate of 4% over the lifetime horizon. Results in the base case represented the perspective of the Health Service Executive (HSE).

### Results

Over a lifetime horizon the total discounted costs associated with Filsuvez amounted to €2,688,115 per patient as compared with €1,096,539 for current clinical management, resulting in an incremental cost of €1,591,577. Filsuvez provided a mean quality adjusted life year (QALY) gain of 1.41 resulting in an incremental cost-effectiveness ratio (ICER) of €1,128,726 per QALY gained for both dystrophic EB and junctional EB groups (Table 1).

Table 1. Cost-effectiveness of birch bark extract (Filsuvez) versus current clinical management.

| Treatment | Total costs | Total QALYs | Incremental costs | Incremental QALYs | ICER (€/QALY) |
|---|---|---|---|---|---|
| Current clinical management | €1,096,539 | 9.80 | | | |
| Birch bark extract Filsuvez) | €2,688,115 | 11.21 | €1,591,577 | 1.41 | €1,128,726 |

ICER: Incremental cost-effectiveness ratio QALY: quality adjusted life year

A scenario analysis from a societal perspective (including carers QALYs and informal care) resulted in an ICER of €648,447/QALY. A price-ICER analysis indicated a price reduction of 80.23% would be required to reduce the base case ICER to the €45,000/QALY threshold. If the societal perspective was adopted a price reduction of 75.76% would be required to reach the cost-effectiveness threshold.

### Sensitivity analysis

A probabilistic sensitivity analysis (PSA) was conducted and resulted in an ICER of €1,122,137/QALY. The probability of Filsuvez being cost-effective at the €45,000/QALY threshold was 0%. A deterministic sensitivity analysis was also presented. The parameters that impacted the ICER included utility values for patients in individual health states, the monthly Filsuvex tube usage and health-state specific healthcare resource usage.

## 4. Budget impact of birch bark extract (Filsuvez®)

A budget impact analysis was submitted to estimate the 5 year budget impact of Filsuvez. The total drug cost per pack of Filsuvez (excluding pharmacy fees, including VAT) was €10,521.90. The average cost of Filsuvez per patient per year was estimated at €110,438. The eligible population was considered to increase from 62 patients in year 1 to 66 patients in year 5. When treatment discontinuations were taken into account the number of patients treated with Filsuvez was estimated to increase from 57 in year 1 to 66 patients in year 5. The estimated 5 year gross drug budget impact for Filsuvez was €35,101,383 inclusive of VAT. The 5 year net drug budget impact was assumed to be equal to the 5 year gross budget impact.

## 5. Patient Organisation Submission

A patient organisation submission was received for this Health Technology Assessment.

## 6. Conclusion

Having considered the cost-effectiveness of birch bark extract (Filsuvez) for the treatment of partial-thickness wounds associated with dystrophic and junctional epidermolysis bullosa in patients 6 months and older the NCPE recommends that Filsuvez be considered for reimbursement if cost-effectiveness is improved*.

*This recommendation should be considered while also having regards to the criteria specified in the Health (Pricing and Supply of Medical Goods) Act 2013.