1. NAME OF THE MEDICINAL PRODUCT

Filsuvez gel

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Birch bark extract 10 % w/w

1 g of gel contains 100 mg of birch extract extract (as dry extract, refined from *Betula pendula* Roth, *Betula pubescens* Ehrh. as well as hybrids of both species, cortex (equivalent to 0.5-1.0 g birch bark), including 84-95 mg triterpenes calculated as the sum of betulin, betulinic acid, erythrodiol, lupeol and oleanolic acid. Extraction solvent: n-Heptane.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Gel

Colourless to slightly yellowish, opalescent gel.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

4.2 Posology and method of administration

Posology

The gel should be applied to the wound surface at a thickness of approximately 1 mm and covered by a sterile non-adhesive wound dressing or applied to the dressing so that the gel is in direct contact with the wound. The gel should not be applied sparingly. It should not be rubbed in. The gel should be reapplied at each wound dressing change. The maximum total wound area treated in clinical studies was 5,300 cm^2 with a median total wound area of 735 cm^2. If symptoms persist or worsen after use, or if wound complications occur, the patient's condition should be fully clinically assessed prior to continuation of treatment, and regularly re-evaluated thereafter.

Special populations

Renal or hepatic impairment
No studies have been conducted with Filsuvez in patients with renal or hepatic impairment. No dose adjustment or special considerations are anticipated for patients with renal or hepatic impairment (see section 5.2).

Elderly
No dose adjustment is required.

Paediatric population
The posology in paediatric patients (6 months and older) is the same as in adults.
The safety and efficacy of Filsuvez in children aged less than 6 months have not been established. No data are available.

Method of administration

For cutaneous application only.
Filsuvez should be applied to cleansed wounds. This medicinal product is not for ophthalmic use and should not be applied to mucous membranes.

Each tube is for single use only. The tube should be discarded after use.

4.3 Contraindications

Hypersensitivity to the active substance or to the excipient listed in section 6.1.

4.4 Special warnings and precautions for use

Hypersensitivity

Hypersensitivity has occurred in patients treated with Filsuvez (see section 4.8). If signs and symptoms of local or systemic hypersensitivity occur, Filsuvez should be discontinued immediately and appropriate therapy should be initiated.

Wound infection

The gel is sterile. However, wound infection is an important and serious complication that can occur during wound healing. In the case of infection, it is recommended to interrupt treatment. Additional standard treatment may be required (see section 4.5). Treatment may be re-initiated once the infection has resolved.

Squamous cell carcinoma and other skin malignancies

Patients with dystrophic EB (DEB) and junctional EB (JEB) may be at increased risk of development of squamous cell carcinoma. While there has been no increased risk of skin malignancies associated with Filsuvez to date, a theoretical increased risk of skin malignancies associated with use of Filsuvez cannot be ruled out. In the case of diagnosis of squamous cell carcinoma or other skin malignancies, treatment to the affected area should be discontinued.

Use in dominant dystrophic EB (DDEB) and junctional EB (JEB)

The quantity of clinical data from use of Filsuvez in patients with DDEB and JEB is limited (see section 5.1). The patient's condition should be regularly evaluated to assess the benefit of continued treatment.

Birch pollen allergy

Filsuvez is safe to use for people who are allergic to birch pollen, as these allergens are not present in this medicinal product.

Accidental eye exposure

In the case of exposure to eyes product should be removed by eye irrigation.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed. Since the systemic exposure of the main component betulin following cutaneous application is negligible no interaction with systemic treatments is expected. Interactions with topical products have not been investigated in clinical trials. Other topical products should not be concomitantly used together with Filsuvez but rather sequentially or alternatively depending on the clinical need.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no data from the use of Filsuvez in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3). No effects during pregnancy are anticipated, since systemic exposure to Filsuvez is negligible. Filsuvez can be used during pregnancy.

Breast-feeding

It is unknown whether birch bark extract/metabolites are excreted in human milk. No effects on the breastfed newborn/infant are anticipated since the systemic exposure of the breastfeeding woman to Filsuvez is negligible. Filsuvez can be used during breast-feeding, unless the chest area is subject to treatment.

Fertility

No adverse effects on fertility were observed in male and female rats administered birch bark extract. No effects on human fertility are anticipated, since the systemic exposure is negligible.

4.7 Effects on ability to drive and use machines

Filsuvez has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile

The most frequently observed adverse reactions were wound complication (in 11.6% of EB patients and 2.9% of patients with other partial thickness wounds (PTW)), application site reaction (in 5.8% of EB patients), wound infections (in 4.0% of EB patients), pruritus (in 3.1% of EB patients and 1.3% of patients with other PTW), pain of skin (in 2.5% of patients with other PTW) and hypersensitivity reactions (in 1.3% of EB patients). There were no clinically relevant differences in the reactions reported in EB patients compared to patients with other PTW.

Tabulated list of adverse reactions

In the following table, adverse reactions are listed by MedDRA system organ class and preferred term. Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

The frequency of adverse reactions is defined as follows: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000), not known (cannot be estimated from the available data).

Table 1 lists all adverse reactions reported across clinical studies.

Table 1: Adverse reactions

System organ class	Very common	Common	Uncommon
Infections and infestations		Wound infections	
Immune system disorders		Hypersensitivity reactions*	
Skin and subcutaneous tissue disorders	Wound complication*	Pruritis	
			Dermatitis[a]
			Rash pruritic[a]
			Purpura[a]
General disorders and administration site conditions		Application site reactions* (e.g. application site pain and application site pruritis)	Pain[a]
Injury, poisoning and procedural complications		Wound complication*[a]	Wound secretion

* see Description of selected adverse reactions

[a] adverse reactions observed in studies of patients with grade 2a burn wounds or split-thickness skin grafts

Description of selected adverse reactions

Hypersensitivity
Common cases of hypersensitivity-like reactions have been observed during clinical trials in EB patients. These reactions include rash, urticaria and eczema which were mild in 1.3% of patients and severe in 0.4% of patients. For specific recommendations, see section 4.4.

Application site reactions
Mild or moderate application site reactions are common and include application site pain and application site pruritis.

Wound complication
In studies with EB patients, wound complication comprised different kinds of local complications such as increase in wound size, wound re-opening, wound pain and wound haemorrhage.

In studies in patients with burn wounds or split-thickness skin grafts, wound complications comprised different kinds of local complications such as post-procedural complications, wound necrosis, wound secretion, impaired healing, or inflammation of wound.

Paediatric population

70% (n = 156) of patients randomised in the pivotal study (see section 5.1) were under the age of 18 with a median age of 12 years. 8% (n = 17) of patients were below 4 years of age and 2 patients were under 1 year of age. The adverse reactions observed in the overall population were similar to those observed in the paediatric population.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form: https://sideeffects.health.gov.il

4.9 Overdose

Overdosing with Filsuvez is unlikely. No case of overdose has been reported when a maximum amount of 69 g was used on a daily basis for more than 90 days.

No data have been generated to establish the effect of accidental ingestion of Filsuvez. Further management should be as clinically indicated.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Preparations for treatment of wounds and ulcers, other cicatrizants; ATC code: D03AX13.

Mechanism of action and pharmacodynamic effects

Cell culture assays with human primary keratinocytes and fibroblasts and *ex vivo* studies with porcine skin show that the extract including the main component betulin modulate inflammatory mediators and are associated with activation of intracellular pathways known to be involved in keratinocyte differentiation and migration, wound healing and closure.

The precise mechanism of action of Filsuvez in wound healing is not known.

Clinical efficacy and safety

The efficacy and safety of Filsuvez in the treatment of partial thickness wounds associated with inherited EB were evaluated in a pivotal global Phase 3, randomised, double blind, controlled study in adults and children (Study BEB-13; EASE). Patients with DEB and JEB were randomised 1:1 to receive Filsuvez (n = 109) or a blinded control gel (consisting of sunflower oil, refined; beeswax, yellow and carnauba wax) (n = 114) and instructed to apply the investigational product at a thickness of approximately 1 mm to all their wounds at each dressing change (every 1 to 4 days) for 90 days. At randomisation, one wound was selected by the investigator as the target wound for the evaluation of the primary efficacy endpoint. The target wound was defined as a partial thickness wound of 10-50 cm^2 in surface area and present for 21 days to 9 months prior to screening. The primary endpoint was the proportion of patients with first complete closure of the target wound by day 45 of the 90-day double blind phase (DBP) of the study. Following completion of the DBP, patients entered a 24-month open label phase (OLP) of the study during which all wounds were treated with Filsuvez.

Of the 223 patients randomised, the median age was 12 years (range: 6 months to 81 years), 70% were under 18 years of age and 8% of patients were below 4 years of age. 60% of patients randomised were male. Of these 223 patients, 195 had DEB of which 175 patients had recessive DEB (RDEB), 20 had dominant DEB (DDEB); in addition, there were 26 patients with JEB. In the DBP the majority of patients applied the study treatment to all wounds either daily or every 2 days (between 70% and 78%). Limited data are available for Black and Asian patients.

The results, including the primary endpoint, are presented in Table 2.

Table 2: Efficacy results (study BEB-13; 90-day double-blind phase, full analysis set)

Efficacy parameter	Filsuvez n = 109	Control gel n = 114	p-value
Proportion of patients with first complete closure of target wound within 45 days	41.3%	28.9%	0.013
By EB subtype			
RDEB (n = 175)	44.0%	26.2%	0.008
DDEB (n = 20)	50.0%	50.0%	0.844
JEB (n = 26)	18.2%	26.7%	0.522
Proportion of patients with first complete closure of target wound within 90 days*	50.5%	43.9%	0.296

* key secondary endpoint

The median daily extent of exposure for all patients in DBP and OLP combined are presented in Table 3. The median duration of Filsuvez treatment for all patients in the DBP and OLP is 733 days with a maximum of 931 days.

Table 3: Median daily and cumulative extent of exposure and number of tubes used monthly for DBP and OLP combined - all patients and by age category.

	All patients	0 - < 4 years	4 - < 12 years	12 - < 18 years	≥ 18 years
Median daily extent of exposure (grams per day)	10	15	10	10	9
Median cumulative extent of exposure (grams)	6117	8240	7660	5769	3467
Median number of tubes used per month	19	24	17	20	19

5.2 Pharmacokinetic properties

Absorption

Systemic exposure to the main component betulin was assessed at baseline and periodically during BEB-13 using a dried blood spot bioanalytical method. Betulin venous blood concentrations were below quantitation limits (10 ng/mL) in the large majority of subjects. In a minority of subjects, measurable venous blood concentrations of betulin were observed, suggesting that there is minimal absorption of topically administered betulin. These venous blood concentrations, no greater than 207 ng/mL, were similar to those observed with ingestion of food sources containing betulin.

Distribution

The plasma protein binding of betulin is > 99.9%.

Metabolism

The *in vitro* metabolism of betulin was assessed in a suspension of human hepatocytes, where 99% were completely metabolised in five hours. The most abundant metabolite *in vitro* was formed through oxidation, methylation, and sulfation. Three other metabolites were formed by sulfation or glucuronidation. Non-CYP enzymatic pathways are expected to play the predominant role in the overall hepatic metabolism of betulin (75%), while the CYP mediated pathways (25%) are mainly driven by CYP3A4/5 isoenzyme.

Betulin showed a direct inhibition of CYP2C8 (test substrate amodiaquine) and CYP3A (test substrates testosterone and midazolam) with IC_{50} values of 0.60 µM (266 ng/mL), 0.17 µM (75 ng/mL) and 0.62 µM (275 ng/mL), respectively in human hepatocytes. In addition, betulin caused a very slight induction of CYP3A4 mRNA (2.7-fold). However given the negligible systemic exposure, no interaction with systemic treatments is expected.

Elimination

No *in vivo* elimination studes have been performed.

5.3 Preclinical safety data

Non clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, toxicity to reproduction and development, and phototoxicity. After a 4-week topical treatment with Filsuvez gel, several reactions are observed at the site of administration in minipigs, including inflammatory effects, lympho-histiocytic inflammatory cell infiltration and epithelial hyperplasia. Following a 9-month dermal treatment in minipigs, epidermal hyperplasia, orthokeratotic hyperkeratosis, dermal lymphocytic and/or neutrophilic infiltration, and pustules in the stratum corneum were observed in some animals.

In vitro genotoxicity studies were negative. Further studies on genotoxicity or carcinogenicity have not been performed.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sunflower oil, refined.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

The expiry date of the product is indicated on the packaging materials.
Once opened, the product should be used immediately and be discarded after use.

6.4 Special precautions for storage

Do not store above 30°C.

6.5 Nature and contents of container

White collapsible aluminium tube, interior lacquered with epoxy phenolic coating, and with a sealing compound in the fold. The tube is closed with a tamper-evident aluminium membrane and fitted with a white polypropylene screw cap. The tube is packed in a carton.

Pack size:
30 tubes of 23.4 g gel.

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

TrueMed Ltd, 10 Beni Gaon St., Poleg Industrial Park, P.O.B 8105, South Netanya 4250499

8. MANUFACTURER

Chiesi Farmaceutici S.p.A, Via Palermo 26/A,43122 Parma, Italy

9. MARKETING AUTHORISATION NUMBER

180-35-38161

Approved in September 2025