swissmedic

Date: 29 August 2025
Swissmedic, Swiss Agency for Therapeutic Products

Swiss Public Assessment Report

Filsuvez

International non-proprietary name:	dry extract from birch bark, refined (Betula pendula Roth and Betula pubescens Ehrh. as well as hybrids of both species, cortex) containing 84-95 mg triterpenes calculated as the sum of betulin, betulinic acid, erythrodiol, lupeol and oleanolic acid, DER 5-10:1, extraction solvent n-heptane 95% (w/w)
Pharmaceutical form:	gel
Dosage strength(s):	100 mg/g
Route(s) of administration:	cutaneous use
Marketing authorisation holder:	Chiesi SA
Marketing authorisation no.:	70069
Decision and decision date:	approved on 25 July 2025

Note:

This assessment report is as adopted by Swissmedic with all information of a commercially confidential nature deleted.

SwissPARs are final documents that provide information on submissions at a particular point in time. They are not updated after publication.

Table of contents

1 Terms, Definitions, Abbreviations

ADA	Anti-drug antibody
ADME	Absorption, distribution, metabolism, elimination
AE	Adverse event
ALT	Alanine aminotransferase
API	Active pharmaceutical ingredient
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical Classification System
AUC	Area under the plasma concentration-time curve
$AUC_{0\text{-}24h}$	Area under the plasma concentration-time curve for the 24-hour dosing interval
CI	Confidence interval
C_{max}	Maximum observed plasma/serum concentration of drug
CYP	Cytochrome P450
DDI	Drug-drug interaction
EMA	European Medicines Agency
ERA	Environmental risk assessment
FDA	Food and Drug Administration (USA)
GI	Gastrointestinal
GLP	Good Laboratory Practice
HPLC	High-performance liquid chromatography
IC/EC_{50}	Half-maximal inhibitory/effective concentration
ICH	International Council for Harmonisation
Ig	Immunoglobulin
INN	International non-proprietary name
ITT	Intention-to-treat
LoQ	List of Questions
MAH	Marketing authorisation holder
Max	Maximum
Min	Minimum
MRHD	Maximum recommended human dose
N/A	Not applicable
NO(A)EL	No observed (adverse) effect level
PBPK	Physiology-based pharmacokinetics
PD	Pharmacodynamics
PIP	Paediatric investigation plan (EMA)
PK	Pharmacokinetics
PopPK	Population pharmacokinetics
PSP	Pediatric study plan (US FDA)
RMP	Risk management plan
SAE	Serious adverse event
SwissPAR	Swiss Public Assessment Report
TEAE	Treatment-emergent adverse event
TPA	Federal Act of 15 December 2000 on Medicinal Products and Medical Devices (SR 812.21)
TPO	Ordinance of 21 September 2018 on Therapeutic Products (SR 812.212.21)

2 Background information on the procedure

2.1 Applicant's request(s) and information regarding procedure

New active substance status
The applicant requested new active substance status for dry extract from birch bark in the above-mentioned medicinal product.

Orphan drug status
The applicant requested orphan drug status in accordance with Article 4 paragraph 1 letter a^{decies} no. 2 TPA.
Orphan drug status was granted on 14 November 2024.

Authorisation as human medicinal product in accordance with Article 13 TPA
The applicant requested a reduced assessment procedure in accordance with Article 13 TPA.

2.2 Indication and dosage

2.2.1 Requested indication

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

2.2.2 Approved indication

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

2.2.3 Requested dosage

Summary of the requested standard dosage:
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.
No data are available on liver or renal function disorders or for children under 6 months of age. No dose adjustments are considered necessary for the elderly or for patients with renal or hepatic impairment.

2.2.4 Approved dosage

(see appendix)

2.3 Regulatory history (milestones)

Application	17 December 2024
Formal control completed	23 December 2024
Preliminary decision	17 April 2025
Response to preliminary decision	22 May 2025
Labelling corrections and/or other aspects	02 July 2025
Response to labelling corrections and/or other aspects	08 July 2025
Final decision	25 July 2025
Decision	approval

Based on Art. 13 TPA, Swissmedic has not assessed the primary data (e.g., study reports) submitted with this application and relies for its decision on the assessment of the foreign reference authority EMA. This SwissPAR relates to the assessment report for Filsuvez, EMA/260035/2022, 22 April 2022, Procedure No. EMEA/H/C/005035/0000, first published 04 July 2022 issued by EMA.

3 Quality aspects

Swissmedic has not assessed the primary data relating to quality aspects submitted with this application and relies on the assessment of the foreign reference authority EMA (see section 2.3 Regulatory history (milestones).

4 Nonclinical aspects

Swissmedic has not assessed the primary data relating to nonclinical aspects submitted with this application and relies on the assessment of the foreign reference authority EMA (see section 2.3 Regulatory history (milestones))

5 Clinical aspects

Swissmedic has not assessed the primary data relating to clinical aspects submitted with this application and relies on the assessment of the foreign reference authority EMA (see section 2.3 Regulatory history (milestones).

6 Risk management plan summary

The RMP summaries contain information on the medicinal products′ safety profiles and explain the measures that are taken to further investigate and monitor the risks, as well as to prevent or minimise them.
The RMP summaries are published separately on the Swissmedic website. It is the responsibility of the marketing authorisation holder to ensure that the content of the published RMP summaries is accurate and correct. As the RMPs are international documents, their summaries might differ from the content in the Information for healthcare professionals / product information approved and published in Switzerland, e.g., by mentioning risks that occur in populations or indications not included in the Swiss authorisations.

7 Appendix

Approved Information for healthcare professionals

Please be aware that the following version of the Information for healthcare professionals for Filsuvez was approved with the submission described in the SwissPAR. This Information for healthcare professionals may have been updated since the SwissPAR was published.

Please note that the valid and relevant reference document for the effective and safe use of medicinal products in Switzerland is the Information for healthcare professionals currently authorised by Swissmedic (see www.swissmedicinfo.ch).

Note:
The following Information for healthcare professionals has been translated by the MAH. It is the responsibility of the authorisation holder to ensure the translation is correct. The only binding and legally valid text is the Information for healthcare professionals approved in one of the official Swiss languages.

▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected new or serious adverse reactions. See the "Undesirable effects" section for advice on the reporting of adverse reactions.

FILSUVEZ

Herbal medicine

Composition

Active substances

Refined dry extract from birch bark (Betula pendula Roth, Betula pubescens Ehrh. as well as hybrids of both species, cortex) including 84-95 mg triterpenes calculated as the sum of betulin, betulinic acid, erythrodiol, lupeol and oleanolic acid, DER 5-10:1, extraction solvent: n-Heptane 95% (m/m).

Excipients

Sunflower oil, refined.

Pharmaceutical form and active substance quantity per unit

Gel
Colourless to slightly yellowish, opalescent, non-aqueous gel. 1g of gel contains 100 mg of refined dry extract from birch bark including 84-95 mg triterpenes calculated as the sum of betulin, betulinic acid, erythrodiol, lupeol and oleanolic acid.

Indications/Uses

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

Dosage/Administration

Posology

Adults and children aged 6 months and older: 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 cm2 with a median total wound area of 735 cm2. 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 Pharmacokinetics).

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.

Contraindications

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

Warnings and precautions

Hypersensitivity
Hypersensitivity has occurred in patients treated with Filsuvez (see section Undesirable effects). 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 Interactions). 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 Properties/Effects). 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.

Interactions

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.

Pregnancy, 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 Preclinical data). No effects during pregnancy are anticipated, since systemic exposure to Filsuvez is negligible. Filsuvez can be used during pregnancy.

Lactation

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.

Effects on ability to drive and use machines

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

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 Properties/Effects) 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 very important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions online via the ElViS portal (Electronic Vigilance System). You can obtain information about this at www.swissmedic.ch.

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.

Properties/Effects

ATC code

D03AX13.

Mechanism of action

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.

Pharmacodynamics

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

Clinical efficacy

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 cm2 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

Pharmacokinetics

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 IC50 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.

Preclinical 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.

Other information

Incompatibilities

Not applicable.

Shelf life

Do not use this medicine after the expiry date ("EXP") stated on the pack.

Stability after opening

Once opened, the product should be used immediately and be discarded after use.

Special precautions for storage

Do not store over 30°C. Keep out of reach of children.

Authorisation number

70069

Packs

10 and 30 tubes of 23,4 g of gel.

Marketing authorisation holder

Chiesi SA, Villars-sur-Glâne.

Date of revision of the text

April 2025