

▼ This medicinal product is subject to additional monitoring in Australia. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse events at <https://www.tga.gov.au/reporting-problems>.

AUSTRALIAN PRODUCT INFORMATION

FILSUVEZ® (birch bark dry extract (84-95% triterpenes)) gel

1 NAME OF THE MEDICINE

Birch bark dry extract (84-95% triterpenes)

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

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) quantified to 72-88% (w/w) betulin, 2.4-5.7% (w/w) lupeol, 2.6-4.2% (w/w) betulinic acid, 0.5-1.2% (w/w) erythrodiol, 0.3-0.8% (w/w) oleanolic acid.

For the full list of excipients see [section 6.1 LIST OF EXCIPIENTS](#).

3 PHARMACEUTICAL FORM

Gel

Colourless to slightly yellowish, opalescent, non-aqueous 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 DOSE AND METHOD OF ADMINISTRATION

Dosage

The gel should be applied at a thickness of approximately 1 mm to a sterile non-adhesive wound dressing that is placed directly over the wound or applied to the wound surface and covered by the dressing. The gel should be applied liberally. 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 as systemic exposure is negligible (see [section 5.2 PHARMACOKINETIC PROPERTIES](#)).

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 topical 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 LIST OF EXCIPIENTS](#).

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Identified precautions

Hypersensitivity

Hypersensitivity has occurred in patients treated with FILSUVEZ (see [section 4.8 ADVERSE EFFECTS \(UNDESIRABLE EFFECTS\)](#)). 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 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS](#)). Treatment with FILSUVEZ 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 clinical data in patients with DDEB and JEB is limited (see [section 5.1 PHARMACODYNAMIC PROPERTIES](#)). 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.

Use in the elderly

See [section 4.2 DOSE AND METHOD OF ADMINISTRATION](#).

Paediatric use

See [section 4.2 DOSE AND METHOD OF ADMINISTRATION](#).

Effects on laboratory tests

No data available.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

The major constituent of birch bark dry extract, betulin, undergoes metabolism through multiple CYP enzymes (including CYP3A4, CYP3A5, CYP2C8 and CYP2C19), with CYP3A having the greatest contribution. Non-CYP hepatic enzymes are also known to contribute to its metabolism, but they were not identified. 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.

Based on *in vitro* data, betulin directly inhibits CYP2C8 and CYP3A and slightly induces CYP3A4 expression. It is not known if betulin also interacts with other transporters.

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

Effects on fertility

No adverse effects on fertility were observed in male and female rats orally administered birch bark extract at dose levels up to 100 mg/kg/day. No effects on human fertility are anticipated, since the systemic exposure is negligible.

Use in pregnancy (Category B1)

There are no data from the use of FILSUVEZ in pregnant women. No effects during pregnancy are anticipated, since systemic exposure to FILSUVEZ is negligible. FILSUVEZ can be used during pregnancy.

In an embryofetal development study, birch triterpenes were orally administered to pregnant rats at doses of 10, 30, or 100 mg/kg/day during the period of organogenesis. Birch triterpenes did not cause maternal toxicity or fetal malformations at doses up to 100 mg/kg/day. In a prenatal and postnatal development study, birch triterpenes were orally administered to pregnant rats at doses of 10, 30, or 100 mg/kg/day from gestation day 5 through lactation day 20. Birch triterpenes did not affect development at doses up to 100 mg/kg/day. Given that the animal studies involved oral administration, systemic exposures are expected to be substantially higher than those achieved clinically via dermal application.

Use in 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.

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 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

EASE clinical trial

The safety of FILSUVEZ was evaluated in the EASE study, a randomised, double-blind, multicentre, controlled trial in 223 adult and paediatric subjects with inherited EB. During the double-blind phase of EASE, subjects received topical treatment with either FILSUVEZ or a control gel on partial-thickness wounds every 1 to 4 days for a total of 90 days.

Table 1 presents adverse events that occurred in at least 2% of subjects treated with FILSUVEZ in the EASE study.

Table 1. Adverse events which occurred in >2% FILSUVEZ-treated subjects in the EASE study

Adverse Event	FILSUVEZ (n = 109) n (%)	Control gel (n = 114) n (%)
Wound complication	67 (61.5)	61 (53.5)

Adverse Event	FILSUIVEZ (n = 109) n (%)	Control gel (n = 114) n (%)
Pyrexia	9 (8.3)	15 (13.2)
Wound infection	8 (7.3)	10 (8.8)
Pruritus	8 (7.3)	6 (5.3)
Anaemia	8 (7.3)	4 (3.5)
Fall	4 (3.7)	1 (0.9)
Wound infection staphylococcal	4 (3.7)	3 (2.6)
Upper respiratory tract infection	4 (3.7)	1 (0.9)
Application site pruritus	4 (3.7)	1 (0.9)
Cough	3 (2.8)	8 (7.0)
Nasopharyngitis	3 (2.8)	7 (6.1)
Wound infection bacterial	3 (2.8)	5 (4.4)
Administration site pain	3 (2.8)	3 (2.6)
Oropharyngeal pain	3 (2.8)	2 (1.8)
Pharyngitis	3 (2.8)	0
Toothache	3 (2.8)	0
Ulcerative keratitis	3 (2.8)	0

Tabulated list of adverse reactions

Table 2 lists all adverse reactions reported across clinical studies. 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 ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1,000$ to $< 1/100$); rare ($\geq 1/10,000$ to $< 1/1,000$); very rare ($< 1/10,000$), not known (cannot be estimated from the available data).

Table 2. Adverse reactions reported during treatment with FILSUIVEZ

System organ class	Frequency	Adverse reaction
Infections and infestations	Common	Wound infections
Immune system disorders	Common	Hypersensitivity reactions*
Skin and subcutaneous tissue disorders	Very common	Wound complication*
	Common	Pruritus
	Uncommon	Dermatitis ^a , rash pruritic ^a , purpura ^a
General disorder and administration site conditions	Common	Application site reactions* (e.g. application site pain and application site pruritus)
Injury, poisoning and procedural complications	Common	Wound complication ^{aa}
	Uncommon	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

Hypersensitivity-like reactions were common in 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 SPECIAL WARNINGS AND PRECAUTIONS FOR USE](#).

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

Of patients randomised in the pivotal study, 70% (n = 156) were under the age of 18 years 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 suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

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.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

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

Mechanism of action

The mechanism of action of FILSUVEZ in the treatment of wounds associated with EB is unknown.

In vitro cell culture assays with human primary keratinocytes and fibroblasts and *ex vivo* studies with porcine skin show that the birch bark dry extract, which includes the main component betulin, modulates inflammatory mediators and is associated with activation of intracellular pathways known to be involved in keratinocyte differentiation and migration, wound healing and closure.

Clinical trials

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 (EASE study). 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 1-4 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, (range: 6 months to 81 years), 70% were under 18 years of age, 8% of patients were below 4 years of age and 60% of patients 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%). The results including the primary endpoint, are presented in [Table 3](#).

Table 3. Efficacy results for the EASE study

Efficacy parameter	FILSUVEZ n = 109	Control gel n = 114	p-value
Primary endpoint			
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
Key secondary endpoint			
Proportion of patients with first complete closure of target wound within 90 days	50.5%	43.9%	0.296

The median duration of FILSUVEZ treatment for all patients in the DBP and OLP is 733 days with a maximum of 931 days.

5.2 PHARMACOKINETIC PROPERTIES

Absorption

Systemic exposure of betulin was assessed in the 66 evaluable subjects aged ≥ 13 months to ≤ 52 years in the EASE study using venous blood sampling and validated liquid chromatography with tandem mass spectrometry assay.

Following treatment with FILSUVEZ once daily (n=27), every 2 (n=33) or 3 days (n=4) or once weekly (n=2) for 90 days with a mean treatment area of 12% body surface area or affected wound surface area of 0.11 m² at baseline, betulin blood concentrations in 68% subjects (n=45) were below the lower limit of quantification of 10 ng/mL on Day 90. The highest concentrations of betulin in adult and pediatric subjects with a median age of 10 years (range: ≥ 13 months to <18 years) were 33 ng/mL and 207 ng/mL, respectively, which were observed on Day 90.

Distribution

The *in vitro* 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 oxygenation, 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 (74%), while the CYP mediated pathways (26%) are mainly driven by CYP3A4/5 isoenzyme.

Excretion

No *in vivo* elimination studies have been performed.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

Birch bark dry extract was not mutagenic in the Ames reverse mutation assay and was not clastogenic in the *in vitro* human lymphocyte chromosomal aberration assay. Birch bark dry extract was not clastogenic in the *in vivo* micronucleus assay in mice, however systemic exposure was not demonstrated and these results are considered inconclusive. Overall, the weight of evidence indicates that birch bark dry extract does not represent a genotoxic risk.

Carcinogenicity

No studies have been conducted to evaluate carcinogenicity.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Sunflower oil.

6.2 INCOMPATIBILITIES

See also [section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS](#).

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 30°C.

Use immediately after opening.

Single use in one patient only. Contains no antimicrobial preservative. Discard any residue.

6.5 NATURE AND CONTENTS OF CONTAINER

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

Each tube contains 23.4 g gel and are supplied in cartons of 1, 10 and 30 tubes.

Not all pack sizes may be marketed.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of in accordance with local requirements.

6.7 PHYSICOCHEMICAL PROPERTIES

Birch triterpenes are a botanical drug substance composed of a mixture of pentacyclic triterpenes extracted from birch bark from *Betula pendula* Roth, *Betula pubescens* Ehrh. The triterpenes content is calculated as the sum of betulin, betulinic acid, erythrodiol, lupeol and oleanolic acid.

CAS number

1640971-03-4

7 MEDICINE SCHEDULE (POISONS STANDARD)

Prescription Only Medicine (Schedule 4)

8 SPONSOR

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9 DATE OF FIRST APPROVAL

TBC

10 DATE OF REVISION

TBC

Summary table of changes

Section changed	Summary of new information
All	New Product Information