RISK MANAGEMENT PLAN

Filsuvez

[birck bark extract]

RMP Version Number : 2.3

Switzerland-specific Annex (SSA): Not applicable

Data lock point for this RMP: 14 Jan 2023

Date of final sign off: 14 Jun 2023

Marketing Autorisation Holder : Chiesi SA, Villars-sur-Glâne, Switzerland

The Risk Management Plan (RMP) is a comprehensive document submitted as part of the application dossier for market approval of a medicine. The RMP Summary contains information on the medicine's safety profile and explains the measures that are taken in order to further investigate and follow the risks as well as to prevent or minimise them.

The RMP summary of Filsuvez is a concise document and does not claim to be exhaustive.

As the RMP is an international document, the summary might differ from the "Arzneimittelinformation / Information sur le médicament" approved and published in Switzerland, e.g. by mentioning risks occurring in populations or indications not included in the Swiss authorization.

Please note that the reference document which is valid and relevant for the effective and safe use of Filsuvez in Switzerland is the "Arzneimittelinformation/ Information sur le médicament" (see www.swissmedic.ch) approved and authorized by Swissmedic. Chiesi SA is fully responsible for the accuracy and correctness of the content of the published summary RMP of Filsuvez.

Part VI: Summary of the EU risk management plan for Filsuvez (birch bark extract)

This is a summary of the risk management plan (RMP) for Filsuvez. The RMP details important risks of Filsuvez, and how more information will be obtained about Filsuvez's risks and uncertainties (missing information).

Filsuvez's summary of product characteristics (SmPC) and its package leaflet (PL) give essential information to healthcare professionals and patients on how Filsuvez should be used.

This summary of the RMP for Filsuvez should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new safety concerns or changes to the current ones will be included in updates of Filsuvez's RMP.

I. The medicine and what it is used for

Filsuvez is authorised for epidermolysis bullosa (see SmPC for the full indication). It contains birch bark extract as the active substance, and it is given topically.

Further information about the evaluation of Filsuvez's benefits can be found in Filsuvez's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage Filsuvez | European Medicines Agency (europa.eu).

II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of Filsuvez, together with measures to minimise such risks and the proposed studies for learning more about Filsuvez's risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimise its risks.

Together, these measures constitute *routine risk minimisation* measures.

If important information that may affect the safe use of birch bark extract is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of Filsuvez are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Filsuvez. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and

needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine);

List of important risks and missing information	
Important identified risks	• None
Important potential risks	• Squamous cell carcinoma and other skin malignancies
Missing information	• Use in patients of different race/ethnicity

II.B Summary of important risks

Important identified risk : None

Important Potential Risk : Squamous cell carcinoma and other skin malignancies	
Evidence for linking the risk to the medicine.	In the pivotal trial, a total of four patients experienced SCC of skin, one patient in the double-blind phase and three in the open label phase (based on interim safety analysis set). The wounds where the SCC was diagnosed had not been treated with Oleogel-S10 in two out of four patients, the other 2 cases occurred in patients at known high risk of developing SCC as had RDEB generalised severe and were over 45 years of age. All events were assessed as unlikely related to Oleogel-S10 by the investigator, while the MAH assessed 2 of the events of SCC as possibly related based on the temporal relationship. All of SCC events were assessed as severe under Grade 3 severity criteria. The outcome was reported as recovered (n=2), recovered with sequalae (n=1) and ongoing (n=1). Three out of 4 patients discontinued the study due to the SCC.
Risk factors and risk groups	Patients with prior of history of skin cancers; particularly in patients with RDEB especially severe.
Risk minimisation measures	Routine risk minimisation measures SmPC section 4.4; Warnings and Precautions PIL section 2 Prescription only medicine
Additional pharmacovigilance activities	Filsuvez Observational Safety Registry Based Study (FOSteR)

Missing information : Use in patients of different race/ethnicity	
Risk minimisation measures	Routine risk minimisation measures None Prescription only medicine
Additional pharmacovigilance activities	Filsuvez Observational Safety Registry Based Study (FOSteR)

II.C Post-authorisation development plan

II.C.1 Studies which are conditions of the marketing authorisation.

There are no studies which are conditions of the marketing authorisation or specific obligation of Filsuvez.

II.C.2 Other studies in post-authorisation development plan

Filsuvez Observational Safety Registry Based Study (FOSteR)

Study short name and title: A long-term non-interventional study to assess the incidence of skin malignancies in patients with dystrophic and junctional epidermolysis bullosa receiving treatment with Filsuvez (FOSteR).

Rationale and study objectives: The study is designed with a primary objective to estimate the incidence of first skin malignancy during follow-up in patients with DEB and JEB receiving treatment with Filsuvez in real-world clinical practice.

In the general population, the risk of skin cancer is inversely correlated with the amount of melanin present in skin. The correlation is weak and not linear, and there are numerous factors that influence the risk of developing skin cancer. The MAH will collect data on race/ethnicity to describe any possible related patterns between race/ethnicity and Filsuvez exposure to help understand the distribution of patient characteristics. Fitzpatrick skin types will not be collected in this study due to difficulties in collecting this information according to feasibility assessments.

Study design: This is a non-interventional, multi-country, cohort study based on primary data collection and secondary use of patient registry data. The study will have an approximately 2-year enrolment period, followed by a 5-year follow-up period. However, since EB is a rare disease and skin malignancy a rare event, the enrolment rates will be monitored, and the enrolment and study periods may be modified based on actual enrolment rates and Filsuvez uptake.

Data is collected when patients attend their standard care visits, which for most patients is expected to occur approximately annually. For EB registries, data is collected through the usual registration and collection practice of the respective registries.

The DEB and JEB patients will be assessed for exposure to Filsuvez and followed up for occurrence of skin malignancies from the date of study enrolment (index date) to the date of discontinuation (death, discontinuation from site or registry, physician's decision in sites, withdrawal of consent, emigration, lost to follow-up, or end of the study).

Study size and population:

Study size estimations were carried out for the primary outcome (first skin malignancy) by varying incidence rates (IR) between 1 and 10 per 100 person-years, with margins of error from 0.1 to 0.5 and follow-up values of 1, 2 and 3 years. With an estimated IR (based on literature reports of skin malignancy in RDEB patients) of 4 events per 100 person-years, for a target margin of error of 0.25 (6.25% of the IR), the estimated target size of 123 Filsuvez-exposed patients with a follow-up contribution of 2 years per patient across all study countries, would be appropriate. For a follow-up of 1 year and 3 years per patient, an estimated sample size of 246 and 82 Filsuvez-exposed patients are required, respectively.

Population considered for the inclusion in the study are patients with a confirmed diagnosis of DEB or JEB and alive during the enrolment period. Two types of data sources are planned for this study with a site-based primary data collection from specialised EB centres, and data collection from existing EB disease registries [such as Registro EB (Italy) and Dutch EB Registry (Netherlands)].

Study milestones:

- Registration in the EU PAS register: Within 30 days after protocol endorsement by European Medicines Agency (EMA)
- Anticipated start of data collection: Q2 2024
- Anticipated end of data collection: Q3 2031
- Interim reports will be generated every 24 months (2026, 2028, 2030)
- Final report of study results: 2032