Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Eskeriele 685 mg cutaneous solution

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 1.5 mL applicator contains 685 mg of hydrogen peroxide.
For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Cutaneous solution
Clear, colourless solution

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Eskeriele is indicated in adults for the treatment of seborrheic keratosis lesions that are not pedunculated, and up to a maximum diameter of 15 mm each.

4.2 Posology and method of administration

Posology
After activations of Eskeriele single-use applicator, the solution is applied directly to the targeted lesion(s) up to 4 times, approximately 1 minute apart. See "Method of administration".

Typically, up to 4 lesions (body, extremities and face) are recommended to be treated on a single occasion (see section 4.4). There are only limited data of treating more (up to 10 lesions) during one session.

In order to obtain the best efficacy results, a second treatment session is recommended if the lesion does not clear after one treatment. This should be performed no sooner than 3 weeks after the initial treatment once the skin has recovered from any clinically significant reaction caused by the previous treatment.

Patients who have a lesion(s) that have not resolved after one or more treatments with Eskeriele could have additional treatments, up to a maximum of 4 treatments in total per lesion. A minimum of 3 weeks must also be maintained between each additional treatment. Lesions which do not resolve could be considered for other treatment options.

Removal of seborrheic keratosis lesions are generally undertaken for aesthetic purposes, but can also be indicated when lesions cause discomfort.
Before further seborrheic lesions are treated in a patient, it is advised to evaluate the final long-term aesthetic results of lesions initially treated with Eskeriele.

Method of administration
For topical use of seborrhoeic keratosis lesions only.

Eskeriele should only be administered by healthcare professionals with appropriate qualifications. Target lesions should be identified in consultation with a treating physician with expertise and knowledge about pigmented skin lesions. The diagnosis of seborrhoeic keratosis should be confirmed and differentiated from other skin lesions including malignant lesions.

Wear nitrile or vinyl examination gloves during the activation of the Eskeriele applicator and during the administration of the solution to the lesion(s). The method for preparing the Eskeriele applicator for use is illustrated below.

Seborrhoeic keratosis lesion targeted for treatment should be clean and dry prior to application of Eskeriele.

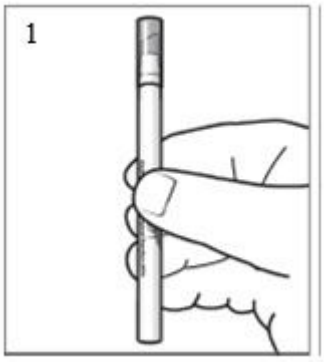
Face lesions

Avoid exposure of Eskeriele to eyes or mucous membranes as Eskeriele contains 40% hydrogen peroxide which is a strong oxidant and corrosive agent. When treating seborrheic keratosis on the face, take appropriate actions to ensure that Eskeriele will not come into contact with the eyes or within 5 mm of the orbital rim, mouth, mucous membranes or open wounds such as positioning the patient in the supine position with the head slightly elevated and angled such that any excess medication will flow away from the eye. Additionally, petrolatum jelly can be applied along the orbital rim and at the medial and lateral canthi (gently stretch the skin at time of application to distend any periorbital rhytides (e.g. "crow's feet")) to decrease the likelihood of tracking of the medication towards the eye.

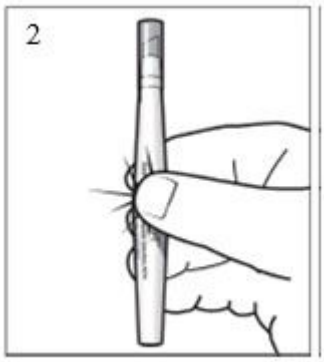
If accidental exposure occurs, flush with water for 15 to 30 minutes and initiate monitoring, and further evaluation as appropriate.

Activation of the applicator

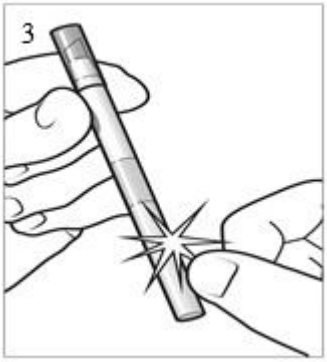
While activating the applicator, hold it away from yourself and the patient. Do not remove the cap until after completion of step 4 (below). For activation, hold the applicator with the cardboard sleeve and applicator cap pointing up (figure 1).



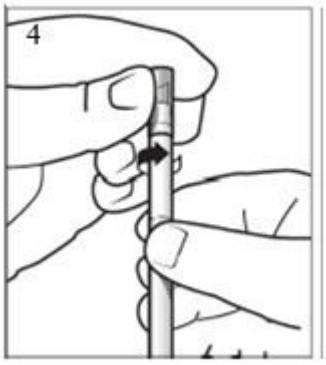
Hold the applicator by positioning the thumb and forefinger on the position marked by the diamond on the cardboard applicator sleeve and apply pressure between the thumb and forefinger, thereby crushing the ampoule containing the solution and releasing the solution into the applicator (figure 2).



Holding the applicator with cap pointing up, tap the bottom of the applicator to separate the solution from the crushed ampule (figure 3).

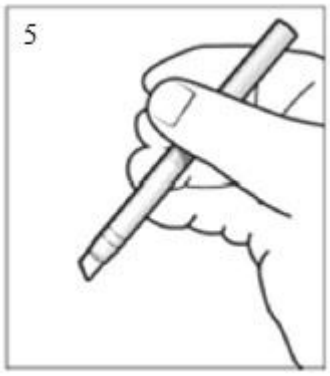


Gently remove the cap by twisting while pulling away from the applicator (figure 4).

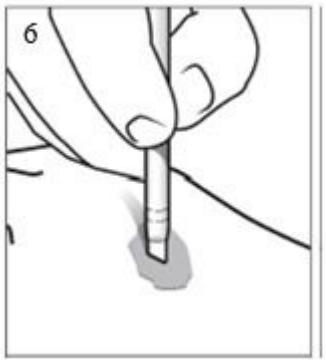


Application

After the applicator is activated, gently squeeze (away from the patient) the applicator barrel to express the solution to the applicator tip. Ensure the Eskeriele applicator tip is wet (not dripping) (figure 5).



Using firm pressure, similar to that of a pencil eraser, apply the solution directly to the seborrhoeic keratosis lesion(s), in a circular motion, for about 20 seconds and until the lesion is completely wet (figure 6).



Avoid contact with the surrounding skin. During the application, remove any excess solution from surrounding skin using a clean absorbent wipe (e.g. gauze).

Wait 1 minute and observe. Whitening of the lesion is normal. Allow the treated lesion(s) to absorb the solution then repeat the application until the lesion is fully saturated. The total number of applications can be up to 4 times one minute apart per treatment session. Do not progress to another application if erythema/oedema is severe or if pain is more than mild. Later applications may require less force.

After completing treatment of each targeted lesion, do not touch the lesion(s) until the solution has completely dried. If necessary, dab the treated lesion(s), without wiping, with an absorbent wipe (e.g. gauze) to ensure the treated lesion(s) is dry. After one use, replace the cap and discard the unit dose applicator.

The use of ice compresses can also be used to reduce swelling, should this occur.

The application of larger amounts of Eskeriele or more frequent use than recommended, will not lead to more rapid or better results and may increase the occurrence and/or intensity of local adverse effects, including irritation, erythema, vesiculation, ulceration, stinging or burning.

Paediatric population
There is no relevant use of Eskeriele in the paediatric population for the indication of seborrhoeic keratosis. Seborrhoeic keratosis is not seen in this age group.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Seborrheic keratosis lesions inside the orbital rim.

Open or infected seborrhoeic keratosis lesion(s).

4.4 Special warnings and precautions for use

Eskeriele should not be applied on seborrhoeic keratosis on eyelids or within 5 mm of the orbital rim, in intertriginous folds or areas covered with hair (see section 4.2 for information on how to avoid eyes and mucous membrane exposure).

There are limited data in patients treated with more than 4 seborrhoeic keratosis lesions each with a size of more than 15 mm in diameter.

There is limited data of hypopigmentation in individuals with dark skin.

Not all local skin reactions completely resolved 3 months post treatment and some local skin reactions, such as scarring, may never fully resolve.

Patients should be informed to contact their doctor if a new pigmented skin lesion develops, or an existing pigmented skin lesion changes in any way.

Further information
Avoid contact with hair or dyed fabrics, which may be bleached by this product.

4.5 Interaction with other medicinal products and other forms of interactions

No interaction studies have been performed.

4.6 Fertility, pregnancy and lactation

Pregnancy
There are no or limited data on the use of hydrogen peroxide in pregnant women.

In animal and human pharmacokinetic studies, the use of Eskeriele did not lead to increased serum levels of hydrogen peroxide. Therefore, harmful effects with respect to reproductive toxicity are unlikely.

As a precautionary measure, it is preferable to avoid the use of Eskeriele during pregnancy.

Breast-feeding
It is unknown whether hydrogen peroxide is excreted in human milk.

No effects on the breast-fed newborn/infant are anticipated since the use of Eskeriele did not lead to increased serum levels of hydrogen peroxide.

Fertility
Fertility studies have not been conducted. No effects on human fertility are anticipated since use of Eskeriele did not lead to increased serum levels of hydrogen peroxide.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

The most frequently observed adverse reactions are local skin reactions, such as erythema, stinging/pain, oedema, scaling/exfoliation, and crusting/scabbing. They usually occur within minutes of treatment initiation and peak in intensity within 1 week. Not all local skin reactions completely resolved 3 months post treatment and some local skin reactions, such as scarring, may never fully resolve.

Local skin reactions are directly related to the mode of action of the active substance, hydrogen peroxide. The transient reactions are expected and at least partially necessary for therapeutic efficacy of the medicinal product.

There were no treatment-related serious adverse events in clinical trials.

Tabulated list of adverse reactions

The adverse reactions are presented by frequency. Frequency categories are defined as: 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: Adverse reactions from Clinical Trials by MedDRA System Organ Classification

System Organ Class (MedDRA)	Very common	Common	Uncommon
Eye disorders			Eyelid oedema Blepharospasm
Gastrointestinal disorders			Lip swelling
Skin and subcutaneous disorders		Pruritus generalized	
General disorders and administration site conditions	At the application site: erythema pain oedema exfoliation* crusting/scabbing pruritus discolouration** vesicles erosion	At the application site: ulceration atrophy scar	
Injury, poisoning and procedural complications			Post-procedural complication

* includes scaling

** includes hyperpigmentation and hypopigmentation

Description of selected adverse reactions

Local skin reactions were very common in the first 7 days after treatment. At the visit 7 days after initial treatment, on a patient% basis, the most common local skin reactions were scaling/exfoliation (71%), crusting/scabbing (67%), erythema (64%), pruritus (18%), and site discolouration (14%), and these were mostly mild to moderate. The most common local skin reactions 15 weeks after initial treatment were site discolouration (25%), erythema (21%), exfoliation (15%), and scabbing (11%), which were predominantly mild to moderate.

On a lesion basis, severe adverse reactions to occur at any Visit time-point were erythema (6.2% immediately after first treatment), oedema (5.6% immediately after first treatment), stinging pain (4.5% immediately after first treatment), crusting (2.5% one week after first treatment), and pruritus (1.0% immediately after first treatment). By the last study day (Day 106), severe adverse reactions were limited to crusting/scabbing (0.1%), erythema (0.05%), and scaling/exfoliation (0.05%).

The majority of reported local skin reactions had resolved within 12 weeks following **up to 2 treatments; the percentage of patients with skin reactions still present 12 weeks after the last treatment were** erythema (21.1%), crusting/scabbing (11.6%), scaling (15.5%), hyperpigmentation (18.1%), hypopigmentation (6.9%), pruritus (1.9%), stinging (0.2%), atrophy (0.7%), ulceration (0.0%), scarring (1.1%); the majority of them with mild intensity.

The majority of reported local skin reactions following **up to 4 treatments** had similarly resolved within 12 weeks; **the percentage of patients with skin reactions still present 12 weeks after the last treatment were** erythema (8.1%), crusting/scabbing (13.8%), scaling (33.8%), hyperpigmentation (14.0%), hypopigmentation (6.7%), pruritus (0.9%), stinging (0.0%), atrophy (0.0%), ulceration (0.0%), scarring (0.5%); the majority of them with mild intensity.

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. Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.hpra.ie; E-mail: medsafety@hpra.ie.

4.9 Overdose

Topical overdosing of Eskeriele can increase incidence and severity of local skin reactions. Remove any excess solution using a clean absorbent wipe (e.g. gauze).

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: {group}, ATC code: D11AX25 hydrogen peroxide

Mechanism of action
Hydrogen peroxide is an oxidizing agent that removes seborrhoeic keratosis lesion tissue by inducing lipid and membrane peroxidation and protein oxidation, leading to apoptosis and necrotic cell death of the seborrhoeic keratosis cells.

Clinical efficacy and safety
In two double-blind, placebo-controlled Phase 3 clinical trials (SEBK-301 and SEBK-302) with 937 patients with four target seborrhoeic keratosis lesions on the face, trunk or extremities, 467 patients were treated with Eskeriele and 470 patients with placebo (vehicle). Each lesion received up to two treatments three weeks apart. The clearance of seborrhoeic keratosis lesions was assessed at day 106 using the validated four-point Physician Lesion Assessment (PLA) rating scale, which characterises lesions as either clear (PLA=0), near clear (PLA=1), thin (PLA=2) or thick (PLA=3).

The treatment groups in each study were well balanced with similar demographic and baseline characteristics in the safety population between treatment groups both within and between the two studies. Across the pooled studies, 389 (41.5%) patients were male and 548 (58.5%) were female. The mean age was 68.7 years (range 42 to 91 years, 41.7% were at least 71 years old) and 917 (97.9%) patients were Caucasian. Distribution of patients by Fitzpatrick skin type was 12.6% with type 1, 46.7% with type 2, 30.3% with type 3, 9.2% with type 4, 1.1% with type 5, and 0.1% with type 6.

Efficacy
In study SEBK-301, all placebo-treated and 92% of Eskeriele-treated patients received two treatments on at least three lesions. In study SEBK-302, 98% of placebo-treated and 90% of Eskeriele-treated patients received 2 treatments for at least three lesions.

In the SEBK-301 trial, 47.5% of lesions were clear or near clear (PLA ≤ 1) following treatment with Eskeriele, compared to 10.2% of placebo treated lesions ($p < 0.001$). In the SEBK-302 trial, 54.3% of lesions were clear or near clear following treatment with Eskeriele, compared to 4.7% of placebo treated lesions ($p < 0.0001$) (Table 2). Overall, results from both clinical trials showed 51.0% of lesions treated with Eskeriele were assessed as clear or near clear (PLA ≤ 1) at trial completion, versus 7.3% of lesions in the placebo group.

Table 2: Percentage of lesions achieving clear or near clear by physician lesion assessment

Mean Per-Patient Percent of Lesions Achieving Clear or Near Clear (PLA ≤ 1)			
Study	**Eskeriele**	**Vehicle**	**P-value**
SEBK-301	47.5%	10.2%	< 0.0001
SEBK-302	54.3%	4.7%	< 0.0001

Between 25.2% and 34.2% of the lesions treated per patient received full clearance (PLA=0) after application of Eskeriele, compared to 0.6% to 1.9% of lesions treated with placebo (Table 3). Overall, for 6% of the patients treated with Eskeriele all four target seborrhoeic keratosis lesions cleared. None of the patients administered placebo achieved clearance of all four lesions. These differences were highly statistically significant ($p < 0.0001$).

Table 3: Percentage of lesions achieving full clearance by physician lesion assessment

Mean Per-Patient Percent of Lesions Achieving Clear (PLA=0)			

Study	Eskeriele	Vehicle	P-value
SEBK-301	25.2%	1.9%	< 0.0001
SEBK-302	34.2%	0.6%	< 0.0001

An additional efficacy endpoint of both trials was the percentage of patients treated with Eskeriele who achieved clearance (PLA=0) of at least three of the four target seborrhoeic keratosis lesions. In the SEBK-301 trial, 13.5% of patients treated with Eskeriele achieved clearance of at least three of the four target lesions ($p < 0.0001$); in the SEBK-302 trial, 23.0% of treated patients achieved clearance of at least three of the four target lesions ($p < 0.0001$). None of the patients treated with placebo achieved this endpoint.

In the pooled patient population, the percentage of responders with at least three of the four target lesions clear was 18.4% in patients receiving Eskeriele, versus 0% in the Vehicle group ($p < 0.0001$).

Analysis by different body locations
Eskeriele achieved a more pronounced treatment effect in facial lesions as compared to all lesions: the mean percent of facial lesions cleared or nearly cleared (PLA ≤ 1) was 64.4% and 62.8% in studies SEBK-301 and -302, respectively (Table 4). The mean percent of all lesions clear (PLA=0) following Eskeriele treatment in both studies was 40.5% for the face, 25.9% for the trunk, and 14.3% for the extremities across both studies, compared to 2.8%, 1.1%, and 0.7%, respectively, with placebo treatment.

Table 4: Percentage of facial lesions achieving clear or near clear by physician lesion assessment

Mean Per-Patient Percent of Facial Lesions Achieving Clear or Near Clear (PLA ≤ 1)			
Study	**Eskeriele**	**Vehicle**	**P-value**
SEBK-301	64.4%	15.0%	< 0.0001
SEBK-302	62.8%	6.2%	< 0.0001

Analysis by number of treatments required
Between 6.8% and 10.2% of lesions were clear or near clear following one treatment with Eskeriele, between 41.9% and 43.3% were clear or near clear following two Eskeriele treatment sessions. In comparison, at most 10.0% of lesions were clear or near clear following two treatments with placebo.

Table 5: Treatments needed to achieve clear or near clear by physician lesion assessment

Percent of SKs Reaching Clear or Near-Clear (PLA ≤ 1), by Treatment Following 1 or 2 Treatments				
Study	**1× Eskeriele**	**1 × Vehicle**	**2 × Eskeriele**	**2 × Vehicle**
SEBK-301	6.8%	0.1%	41.9%	10.0%
SEBK-302	10.2%	0.0%	43.3%	4.7%

Analysis by lesion size
Lesions thickness and area size had a negligible effect on the percent of lesions clear or near clear at the end of study.
Of the lesions with sizes ≤ the median lesion size included in the SEBK studies, 54.2% were clear or near clear at day 106. Of the lesions with sizes > the median lesion size included in the SEBK studies, 48.5% were clear or near clear at day 106.

Paediatric population
The European Medicines Agency has waived the obligation to submit the results of studies with Eskeriele in all subsets of the paediatric population for the treatment of seborrhoeic keratosis (see section 4.2 for information on paediatric use).

Elderly
Of the 937 patients treated with Eskeriele in clinical trials, 70% were 65 years of age and older and 26% were 75 years of age and older. No overall differences in safety or effectiveness were observed between these patients and younger patients.

5.2 Pharmacokinetic properties

No data on systemic exposure are available following topical application.

5.3 Preclinical safety data

Repeated dose toxicity studies have indicated no special hazard in terms of systemic effects but have shown local reactions.

According to published data, hydrogen peroxide has genotoxic properties *in vitro*. However, translation of these *in vitro* genotoxicity findings into the *in vivo* situation does not generally occur, presumably due to the rapid metabolism of H_2O_2.

No significant changes in plasma hydrogen peroxide levels have been observed in animals following repeated dermal application studies. Therefore, the potential risk of systemic carcinogenicity and reproductive and developmental toxicity is negligible. There are no adequate studies to assess a risk of carcinogenicity at the application site. The risk for dermal/local carcinogenicity cannot be totally dismissed considering the genotoxic potential of H_2O_2. However, this risk is considered low due to the intermittent use and the short-lasting local action of H_2O_2.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Isopropyl alcohol
Water

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years
Use within 4 hours of applicator activation.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions. Do not freeze.

The product should be discarded after one use.

6.5 Nature and contents of container

Eskeriele is supplied in a single use Type I borosilicate glass ampoule inside of an applicator containing 1.5 mL. Each single-use applicator is packaged in a blister pack (tray and lidding) provided in a cardboard carton

Pack sizes:
-1 single-use applicator
-multipack containing 3 (3 packs of 1) single-use applicators
-multipack containing 12 (12 packs of 1) single-use applicators

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Disposal
No special requirements for disposal.
For single use only

7 MARKETING AUTHORISATION HOLDER

FGK Representative Service GmbH
Heimeranstrasse 35
80339 Munich
Germany

8 MARKETING AUTHORISATION NUMBER

PA1320/001/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 24th May 2019

10 DATE OF REVISION OF THE TEXT

June 2019