SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Epsolay 50 mg/g crème

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 g of cream contains 50 mg of benzoyl peroxide, hydrous (incorporated in microcapsules).

Excipient with known effect:
Cetyl alcohol: 3.0 % (30 mg/g)

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Cream
White to off-white cream

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Epsolay is indicated for topical treatment of inflammatory lesions of rosacea in adults 18 years of age and older.

4.2 Posology and method of administration

Posology
Apply a pea-sized amount of Epsolay once daily in a thin layer to each area of the face (forehead, chin, nose, each cheek) on clean and dry skin until the skin is clear or almost clear. A pea sized amount is approximately 0.2 g. The daily dose is approximately 1.2 g.

In the event of recurrence of symptoms of rosacea, once daily treatment should be re-initiated as needed.

Elderly population
No dose adjustment is necessary.

Paediatric population
The safety and efficacy of Epsolay in children aged under 18 years have not been established. No data are available.

Method of administration
Cutaneous use.

A thin layer is to be applied to each area of the face (forehead, chin, nose, each cheek) on clean and dry skin. Avoid the eyes, lips, and mouth.
Wash hands after application.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1. (See sections 4.4 and 6.1).

4.4 Special warnings and precautions for use

For external use only.

- Hypersensitivity

Hypersensitivity reactions, including anaphylaxis, angioedema, and urticaria, have been reported with the use of benzoyl peroxide products. If a serious hypersensitivity reaction occurs, Epsolay should be discontinued immediately and appropriate therapy must be initiated.

- Skin Irritation/Contact Dermatitis

Skin irritation with erythema, scaling, dryness, and stinging/burning may be experienced with use of Epsolay. A moisturiser must be applied and if symptoms do not improve, Epsolay must be discontinued. Treatment should be discontinued if pruritus, swelling or blistering of the skin occurs, indicating contact dermatitis. Epsolay should not be applied to cuts, abrasions, eczematous or sunburned skin. Epsolay should be used with caution on dry and sebostatic skin.

- Photosensitivity

Benzoyl peroxide may increase sensitivity to sunlight. Exposure to natural or artificial sunlight (tanning beds or UVA/B treatment) while using Epsolay must be minimised or avoided. Sun protection measures (e.g., sunscreen and loose-fitting clothes) should be taken when sun exposure cannot be avoided. Discontinue Epsolay at the first evidence of sunburn.

- Contact with the eyes

Epsolay must not get into the eyes. Accidental contact with the eyes will cause reddening and burning. If Epsolay accidentally comes into contact with the eyes, rinse them thoroughly with water.

Precautions for use
Epsolay must be applied in a thin layer, avoiding the eyes, lips, and mouth. Wash hands immediately after application.
Epsolay may bleach hair or coloured fabric.

<u>Excipients with known effect</u>

Cetyl alcohol
This medicinal product contains cetyl alcohol. May cause local skin reactions (e.g. contact dermatitis).

Benzoic acid
This medicinal product contains benzoic acid (as degradation product of benzoyl peroxide). May cause local irritation.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed.

Concomitant application of Epsolay with tretinoin, isotretinoin and adapalene should be avoided. If combination treatment is required, the products should be applied at different times of the day (e.g. one in the morning and the other in the evening).
Caution should be exercised when using medicinal products or cosmetics with abrasive, irritant or drying effects, including salicylic acid, as these may lead to an additive effect in terms of skin irritation when used in combination with Epsolay.

4.6 Fertility, pregnancy and lactation

Pregnancy
There are no adequate human studies on the use of benzoyl peroxide during pregnancy. Limited animal studies show no reproductive toxicity (see section 5.3). Benzoyl peroxide is only absorbed by the skin to a limited extent (see section 5.2).
Epsolay can be used topically during pregnancy.

Breastfeeding
Given the low systemic exposure, Epsolay can be used during breastfeeding except on the breast to avoid accidental transfer to the child.

Fertility
Fertility studies have not been conducted with benzoyl peroxide.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

In two randomised, double blind, vehicle-controlled trials, adult subjects with rosacea applied Epsolay (N = 488) or vehicle (N = 234) once daily for 12 weeks. The majority of subjects were Caucasian (93%) and female (73%) with a mean age of 51 years.

Adverse drug reactions are listed by MedDRA system organ class and by frequency (Table 1). Frequencies are defined as: very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1000 to < 1/100) and not known (cannot be estimated from the available data).

Table 1: Adverse drug reactions from clinical trials

MedDRA Organ Classification System	**Common** **(≥ 1/100 to < 1/10)**
General disorders and administration site conditions	Application site pain Application site erythema Application site pruritus Application site oedema*

* Application site oedema includes: application site swelling and application site oedema

Particularly at the beginning of a treatment period, skin reactions may occur at the administration site.

Adverse drug reactions from post-marketing experience with the active ingredient:

The following adverse drug reactions have been observed during the post-marketing experience with other topical formulations of benzoyl peroxide for the treatment of inflammatory skin diseases. Although these reactions may also occur with the microencapsulated formulation of benzoyl peroxide (Epsolay), their frequency cannot be estimated from the available data.

MedDRA Organ Classification System	Frequency not known
Immune system disorders	Anaphylaxis
Skin and subcutaneous tissue disorders	Angioedema Urticaria Contact dermatitis Skin burning sensation Dry skin Blistering Skin swelling
General disorders and administration site conditions	Application site skin flaking

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 the national reporting system listed in Appendix V.

4.9 Overdose

Epsolay is a preparation indicated for cutaneous treatment only. If the medication is applied excessively, no faster or better results will be obtained.

If Epsolay is applied too thickly or too frequently, the skin irritations described in section 4.8 may occur more frequently. In this case, it is sufficient to reduce the frequency of application or the amount applied by wiping off the excess with a paper towel or washing it off with water.

Accidental ingestion may cause irritation of the mucous membranes with retrosternal pain, stomach pain, nausea and vomiting. The administration of charcoal and fluids might be considered. Do not induce vomiting.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: dermatological, anti-acne preparations for cutaneous use, peroxides, benzoyl peroxide, ATC code: D10AE01.

Mechanism of action
Benzoyl peroxide is an oxidising agent with bactericidal and keratolytic effects but the precise mechanism of action in the treatment of rosacea is unknown.

Pharmacodynamic effects
A long-term open-label extension study [NCT03564145] demonstrated that Epsolay provided pharmacodynamic effects that began as early as 4 weeks after treatment initiation, with 31.9% of subjects achieving IGA success (clear or almost clear). The therapeutic effect progressively improved throughout the study duration, with 57.9% achieving success by Week 40 and 73.2% success in the Epsolay group by

Week 52. Facial erythema showed substantial improvement, with the percentage of subjects having no or mild erythema increasing from 10.1% at baseline to 76.2% at Week 40, and severe cases decreasing from 14.4% to just 1.8%. After treatment discontinuation in subjects who achieved clear/almost clear status, the median time to relapse was 58 days, indicating the durability of the pharmacodynamic effect after treatment cessation.

Clinical efficacy and safety

The safety and efficacy of Epsolay was evaluated in two multicenter, randomised, double blind, vehicle-controlled trials (Trial 1 [NCT03448939] and Trial 2 [NCT03564119]) in subjects with moderate to severe papulopustular rosacea. The trials were conducted in 733 subjects, aged 18 years and older. Subjects were treated once daily for 12 weeks with either Epsolay or vehicle cream. Of the 733 subjects in the clinical trials of Epsolay, 127 (17%) subjects were 65 and over, while 37 (3%) subjects were 75 and over.

Subjects were required to have a minimum of 15 to 70 total inflammatory lesions (papules and/or pustules) and no more than 2 nodules (where a nodule was defined as a papule or pustule greater than 5 mm in diameter) and an Investigator Global Assessment (IGA) score of 3 ("moderate") or 4 ("severe") at baseline. Overall, 93% of subjects were Caucasian, 73% were female, and the mean age was 51 years (ranged from 18 to 85 years). At baseline, subjects had a mean inflammatory lesion count of 27.5, 89% were scored as moderate (IGA=3) and 11% as severe (IGA=4).

The co-primary efficacy endpoints were the proportion of subjects with treatment success at Week 12, defined as an IGA score of 0 ("clear") or 1 ("almost clear") with at least a two-grade reduction from baseline, and the absolute change from baseline in inflammatory lesion counts at Week 12. The results at Week 12 are presented in Table 2. Epsolay was more effective than vehicle cream on the co-primary efficacy endpoints starting from 4 weeks of treatment; see Figs. 1-2.

Table 2: Efficacy Results of Epsolay in Subjects with Moderate to Severe Papulopustular Rosacea at Week 12

	Combined Results	
	Epsolay	**Vehicle**
	(N = 493)	**(N = 240)**
IGA Treatment Success* (95% CI)	48.3% (43.7%, 53.0%)	24.5% (19.4%, 30.5%)
Difference from Vehicle	23.8%	
Inflammatory Lesions		
Mean Number at Baseline (95% CI)	27.8 (27.3, 28.3)	26.9 (26.2, 27.6)
Mean Number at Week 12 (95% CI)	8.6 (8.2, 9.0)	15.9 (15.1, 16.6)
Mean† Absolute Change (95% CI)	-19.2 (19.7, -18.7)	-11.0 (-11.7, -10.4)
Difference from Vehicle	-8.2	
Mean† Percent Change (95% CI)	-69.4 (-70.6, -68.2)	-42.6 (-45.2. -40.0)
Difference from Vehicle	-26.8	

CI = Confidence Interval.

* Investigator Global Assessment (IGA) success was defined as an IGA score of 0 ("clear") or 1 ("almost clear") with at least a two-grade reduction from baseline.

† Means presented in the table are Least Square (LS) Means.

Figure 1: IGA Success Rate Over Time

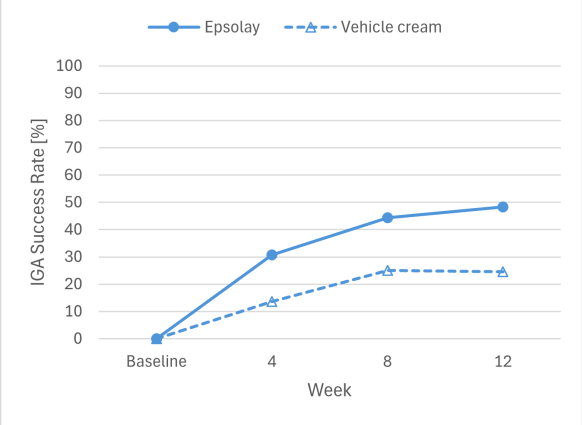
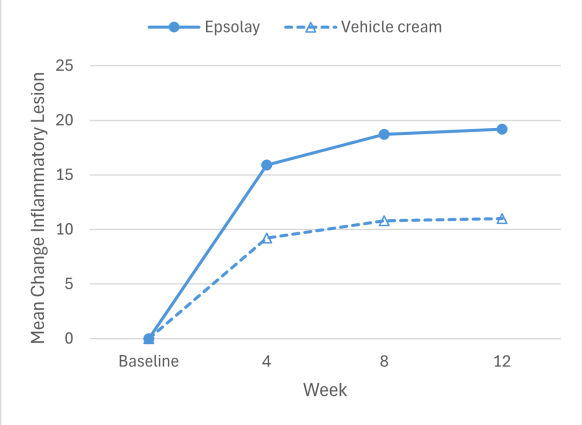


Figure 2: Mean Absolute Change in Inflammatory Lesion Counts from Baseline Over Time



Data on the use of Epsolay in patients with very severe papulopustular rosacea (>70 inflammatory lesions) are limited.

Local tolerability
During the clinical trials, local tolerability evaluations were conducted at baseline and at each study visit by assessment of dryness, itching, scaling, and stinging/burning. Table 2 presents the local tolerability assessments by severity grade at Week 12.

Table 3: Facial Cutaneous Tolerability Assessment

Sign/Symptom	**Epsolay N = 455***		
	Severity at Week 12		
	Mild	**Moderate**	**Severe**
Dryness	25%	7%	0%
Itching	24%	6%	0%
Scaling	13%	4%	0%
Stinging/ Burning	20%	3%	1%

* Of the 488 subjects treated with Epsolay, 455 subjects had local tolerability assessments at Week 12.

In a 40-week open label extension safety study (for a total of up to 52 weeks of treatment), the frequency and severity of local tolerability signs and symptoms at Week 52 were comparable to those reported at Week 12.

5.2 Pharmacokinetic properties

The percutaneous penetration of benzoyl peroxide is low. The majority of the penetrated benzoyl peroxide is converted into benzoic acid, an endogenous substance, which is eliminated in the urine. The systemic exposure of benzoyl peroxide following the application of Epsolay has not been assessed since topically applied benzoyl peroxide is known to have negligible systemic concentrations.

5.3 Preclinical safety data

Non-clinical data on benzoyl peroxide reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, and reproductive toxicity.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Citric acid (E 330)
Cetrimonium chloride
Cetyl alcohol
Cyclomethicone
Disodium edetate (E 385)
Glycerol (E 422)
Hydrochloric acid (E 507)
Lactic acid (E 270)
Macrogol stearate (Type I) (E 431)
Glycerol monostearate 40-55 (Type II)
Phenoxyethanol
Polyquaternium-7
Silica colloidal hydrated
Sodium hydroxide (E 524)
Purified water

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months.

6.4 Special precautions for storage

Do not store above 25ºC.
Do not freeze.
Discard 60 days after first opening.

6.5 Nature and contents of container

Epsolay is a white to off-white cream packaged in a 30-mL (30 g fill), Mezzo airless container closure system. The Mezzo airless pump container system consists of a polypropylene (PP) bottle with an HDPE/ thermoplastic olefin (TPO) piston, a Mezzo pump actuator assembly made of polypropylene, polyethylene (PE), TPO and a transparent polypropylene cap.

6.6 Special precautions for disposal

No special requirements for disposal.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

INFECTOPHARM Arzneimittel und Consilium GmbH
Von-Humboldt-Strasse 1
64646 Heppenheim
Duitsland

8. MARKETING AUTHORISATION NUMBER(S)

RVG 135063

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Datum van eerste verlening van de vergunning: 21 oktober 2026

10. DATE OF REVISION OF THE TEXT