EPSOLAY® (ep' soe lay)
(benzoyl peroxide) cream

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use EPSOLAY safely and effectively. See full prescribing information for EPSOLAY.

EPSOLAY® (benzoyl peroxide) cream, for topical use

Initial U.S. Approval: 1984

----------INDICATIONS AND USAGE----------

EPSOLAY is indicated for the treatment of inflammatory lesions of rosacea in adults. (1)

-------DOSAGE AND ADMINISTRATION--------

- Apply to the affected areas once daily. (2)
- Wash hands after application. (2)
- Not for oral, ophthalmic, or intravaginal use. (2)

------DOSAGE FORMS AND STRENGTHS------

Cream 5% (3)

----------CONTRAINDICATIONS----------

A history of a serious hypersensitivity reactions to benzoyl peroxide or any component of the formulation in EPSOLAY. (4)

--------WARNINGS AND PRECAUTIONS-------

- Hypersensitivity: Severe hypersensitivity reactions, including anaphylaxis and angioedema, have been reported with the use of benzoyl peroxide products. (5.1)
- Skin irritation/contact dermatitis: Erythema, scaling, dryness, stinging/burning, irritation and allergic contact dermatitis may occur with use of EPSOLAY and may necessitate discontinuation. (5.2)
- Photosensitivity: Avoid or minimize exposure to natural or artificial sunlight and use sun protection measures. (5.3)

----------ADVERSE REACTIONS----------

- Most common adverse reactions (incidence ≥ 1%) are application site reactions: pain, erythema, pruritis and edema. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Galderma Laboratories, L.P. at 1-866-735-4137 or FDA at 1800-FDA-1088 or www.fda.gov/medwatch. See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 04/2023

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

EPSOLAY is indicated for the treatment of inflammatory lesions of rosacea in adults.

2 DOSAGE AND ADMINISTRATION

- Before initial use, prime the pump until the first drop of cream is released.
- 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. Avoid the eyes, lips and mouth.
- Wash hands after application.
- EPSOLAY may bleach hair or colored fabric.
- EPSOLAY is for topical use only. Not for oral, ophthalmic, or intravaginal use.
- Discard unused EPSOLAY 60 days after first use.

3 DOSAGE FORMS AND STRENGTHS

Cream, 5%. Each gram of EPSOLAY contains 50 mg of benzoyl peroxide in a white to off-white base.

4 CONTRAINDICATIONS

EPSOLAY is contraindicated in patients with a history of hypersensitivity reactions to benzoyl peroxide or any components of the formulation in EPSOLAY *[see Warnings and Precautions (5.1)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Hypersensitivity

Hypersensitivity reactions, including anaphylaxis, angioedema, and urticaria, have been reported with the use of benzoyl peroxide products. If a serious hypersensitivity reaction occurs, discontinue EPSOLAY immediately and initiate appropriate therapy.

5.2 Skin Irritation

Erythema, scaling, dryness and stinging/burning may be experienced with use of EPSOLAY. Irritation and contact dermatitis may occur. Apply a moisturizer and discontinue EPSOLAY if symptoms do not improve. Avoid application of EPSOLAY to cuts, abrasions, eczematous or sunburned skin.

5.3 Photosensitivity

Benzoyl peroxide may increase sensitivity to sunlight. Minimize or avoid exposure to natural or artificial sunlight (tanning beds or UVA/B treatment) while using EPSOLAY. Instruct the patient to implement sun protection measures (e.g., sunscreen and loose-fitting clothes) when sun exposure cannot be avoided. Discontinue EPSOLAY at the first evidence of sunburn.

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

In two randomized, 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.

Table 1 presents the most common adverse reactions occurring in ≥ 1% of subjects treated with EPSOLAY and more frequently than in subjects treated with vehicle.

Table 1: Adverse Reactions Occurring in ≥ 1% of Subjects Treated with EPSOLAY and with Greater Frequency than Subjects Treated with Vehicle

	EPSOLAY N = 488	Vehicle N = 234
Application site pain	11 (2%)	2 (1%)
Application site erythema	11 (2%)	2 (1%)
Application site pruritus	6 (1%)	1 (<1%)
Application site edema*	4 (1%)	0 (0%)

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

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 2: 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.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

The systemic exposure of benzoyl peroxide is unknown. Based on the published literature, benzoyl peroxide is metabolized to benzoic acid (an endogenous substance), which is eliminated in the urine. Hence, maternal use is not expected to result in fetal exposure to the drug. Animal reproductive studies have not been conducted with EPSOLAY or benzoyl peroxide.

The background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

8.2 Lactation

Risk Summary

There are no data on the presence of benzoyl peroxide in human milk, its effects on the breastfed infant or its effects on milk production. The systemic exposure of benzoyl peroxide is unknown. Based on the published literature, benzoyl peroxide is metabolized to benzoic acid (an endogenous substance), which is eliminated in the urine. Any amount of benzoyl peroxide excreted into human milk by a nursing mother would be expected to be metabolized by tissue and stomach esterases. Therefore, breastfeeding is not expected to result in exposure of the infant to EPSOLAY. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for EPSOLAY and any potential adverse effects on the breastfed child from EPSOLAY or from the underlying maternal condition.

8.4 Pediatric Use

Safety and effectiveness of EPSOLAY for the treatment of inflammatory lesions of rosacea have not been established in pediatric patients.

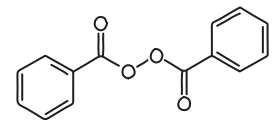
8.5 Geriatric Use

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. No overall differences in safety or effectiveness were observed between these subjects and younger subjects.

11 DESCRIPTION

EPSOLAY (benzoyl peroxide) cream is for topical use. Each gram of EPSOLAY contains 50 mg of benzoyl peroxide.

The chemical name for benzoyl peroxide is benzoyl benzenecarboperoxoate. It has the following structural formula:



Molecular Formula: $C_{14}H_{10}O_4$ Molecular Weight: 242.23

The benzoyl peroxide in EPSOLAY is in a solid form that is incorporated into a microcapsule composed of silicon dioxide, cetrimonium chloride and polyquaternium-7.

EPSOLAY contains anhydrous citric acid, cetrimonium chloride, cetyl alcohol, cyclomethicone, edetate disodium, glycerin, hydrochloric acid, lactic acid, macrogol stearate Type I, mono and di glycerides, phenoxyethanol, polyquaternium-7, purified water, silicon dioxide and sodium hydroxide as inactive ingredients.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

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

12.2 Pharmacodynamics

The pharmacodynamics of EPSOLAY in the treatment of rosacea are unknown.

12.3 Pharmacokinetics

Benzoyl peroxide is absorbed by the skin where it is converted to benzoic acid, an endogenous substance, which is eliminated in the urine. The systemic exposure of benzoyl peroxide following the application of EPSOLAY was not assessed.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity, mutagenicity, and impairment of fertility studies were not conducted with EPSOLAY.

The role of benzoyl peroxide as a tumor promoter has been well established in several animal species. However, the significance of this finding in humans is unknown.

No significant increase in tumor formation was observed in rats treated topically with a 15 to 25% benzoyl peroxide carbopol gel (3 to 5 times the concentration of benzoyl peroxide in EPSOLAY) for two years. Similar results were obtained in mice topically treated with 25% benzoyl peroxide gel for 56 weeks followed by intermittent treatment with 15% benzoyl peroxide gel for rest of the 2 years study period and in mice topically treated with 5% benzoyl peroxide gel for two years.

Bacterial mutagenicity assays (Ames test) conducted with benzoyl peroxide have provided mixed results; mutagenic potential was observed in a few studies but not in a majority of investigations. Benzoyl peroxide has been found to cause DNA strand breaks in a variety of mammalian cell types and to cause sister chromatid exchanges in Chinese hamster ovary cells.

Fertility studies were not conducted with benzoyl peroxide.

14 CLINICAL STUDIES

The safety and efficacy of EPSOLAY was evaluated in two multicenter, randomized, 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.

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% scored as severe (IGA=4).

The co primary efficacy endpoints in both trials 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 3. EPSOLAY was more effective than vehicle cream on the co primary efficacy endpoints starting from 4 weeks of treatment in both trials, see Figure 1 through Figure 4.

Table 3: Efficacy Results of EPSOLAY in Subjects with Moderate to Severe Papulopustular Rosacea at Week 12

	Trial 1		Trial 2	
	EPSOLAY (N=243)	Vehicle (N=118)	EPSOLAY (N=250)	Vehicle (N=122)
IGA Treatment Success*	47.4%	20.7%	49.2%	28.2%
Difference from Vehicle (95% CI)	26.7% (16.7%, 36.8%)		21.0% (10.7%, 31.3%)	
Inflammatory Lesions				
Mean† Absolute Change	-17.4	-9.5	-20.3	-13.3
Difference from Vehicle (95% CI)	-7.9 (-10.0, -5.9)		-6.9 (-9.0, -4.9)	
Mean† Percent Change	-68.2%	-38.3%	-69.4%	-46.0%
Difference from Vehicle (95% CI)	-29.9% (-37.8%, -22.0%)		-23.4% (-30.5%, -16.3%)	

*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 table are Least Square (LS) Means.

Figure 1: IGA Success Rate Over Time in Trial 1

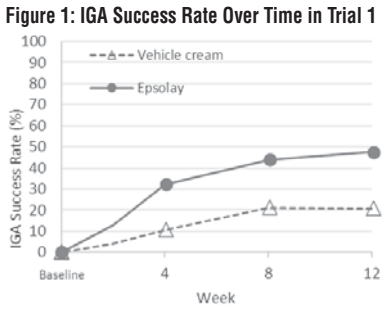


Figure 2: IGA Success Rate Over Time in Trial 2

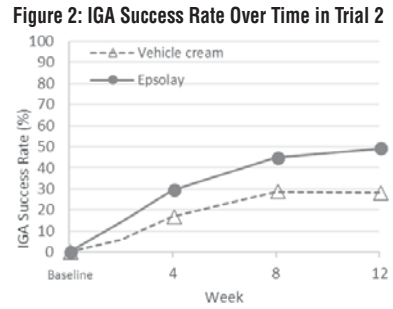


Figure 3: Mean Absolute Change in Inflammatory Lesion Counts from Baseline Over Time in Trial 1

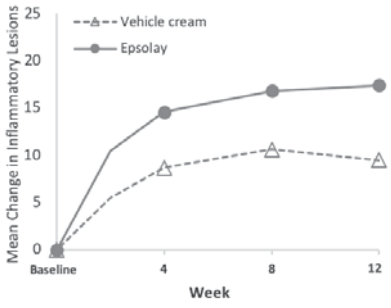
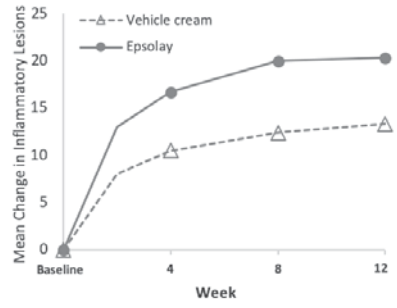


Figure 4: Mean Absolute Change in Inflammatory Lesion Counts from Baseline Over Time in Trial 2



16 HOW SUPPLIED/STORAGE AND HANDLING

How Supplied

EPSOLAY is a white to off white cream supplied in an airless pump as follows:
30 gram pump: NDC 0299-5890-30

Storage and Handling

- Store at 20°C to 25°C (68°F to 77°F) with excursions permitted to 15°C to 30ºC (59°F to 86ºF) [see USP Controlled Room Temperature].
- Keep away from heat.
- Do not freeze.
- Discard unused cream 60 days after first use.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA approved patient labeling (Patient Information).

Hypersensitivity

Inform patients that serious hypersensitivity reactions occurred with the use of benzoyl peroxide products. If a patient experiences a serious hypersensitivity reaction, instruct patient to discontinue EPSOLAY immediately and seek medical help *[see Warnings and Precautions (5.1)]*.

Skin Irritation/Contact Dermatitis

Inform patients that EPSOLAY may cause irritation such as erythema, scaling, dryness, stinging or burning. Advise the patient to use a moisturizer for irritation *[see Warnings and Precautions (5.2)]*.

Photosensitivity

Advise patients to minimize or avoid exposure to natural or artificial light (tanning beds or UVA/B treatment) and to use sun protective measures, if patients need to be outdoors while using EPSOLAY *[see Warnings and Precautions (5.3)]*.

Administration Instructions

Advise patients to apply EPSOLAY exactly as directed in a thin layer, avoiding the eyes, lips and mouth and to wash hands immediately after application. Inform patients that EPSOLAY may bleach hair or colored fabric *[see Dosage and Administration (2)]*.

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PATIENT INFORMATION
EPSOLAY® (ep' soe lay)
(benzoyl peroxide) cream

Important: EPSOLAY is for use on the skin only (topical). Do not use EPSOLAY in or on your mouth, eyes or vagina.

What is EPSOLAY?
EPSOLAY is a prescription medicine used on the skin (topical) to treat adults with pimples and bumps caused by a condition called rosacea.
It is not known if EPSOLAY is safe and effective in children.

Do not use EPSOLAY if you have had an allergic reaction to benzoyl peroxide or any of the ingredients in EPSOLAY. See the end of this leaflet for a complete list of ingredients in EPSOLAY.

Before using EPSOLAY, tell your healthcare provider about all of your medical conditions, including if you:
- have other skin problems, including eczema, cuts, or sunburn.
- are pregnant or plan to become pregnant. It is not known if EPSOLAY will harm your unborn baby.
- are breastfeeding or plan to breastfeed. It is not known if EPSOLAY passes into your breast milk. Talk to your healthcare provider about the best way to feed your baby during treatment with EPSOLAY.

Tell your healthcare provider about all the medicines you take, including prescription and over the counter medicines, vitamins, and herbal supplements.

How should I use EPSOLAY?
- Use EPSOLAY exactly as your healthcare provider tells you.
- Apply EPSOLAY to your face 1 time each day on clean and dry skin.
- Before you use EPSOLAY for the first time, prime the pump by pressing down until the first drop of cream is released.
- Use the pump to dispense a pea size amount of EPSOLAY onto your fingertip. Spread a thin layer over each area of your face (forehead, chin, nose, each cheek). Avoid contact with your eyes, lips and mouth.
- Wash your hands right away after applying EPSOLAY.

What should I avoid while using EPSOLAY?
- Avoid using EPSOLAY on skin areas with cuts, abrasions, eczema, or on sunburned skin.
- Limit your time in sunlight. Avoid sunlight or artificial sunlight such as sunlamps or tanning beds. EPSOLAY may make your skin more sensitive to the sun and the light from sunlamps and tanning beds. Use sun protection measures such as sunscreen and wear loose-fitting clothes that cover your skin while out in sunlight. Stop using EPSOLAY if you get sunburn.
- Avoid getting EPSOLAY in your hair or on colored fabric. EPSOLAY may bleach hair or colored fabric.

What are the possible side effects of EPSOLAY?
EPSOLAY may cause serious side effects, including:
- **Allergic reactions.** Stop using EPSOLAY and get medical help right away if you have any of the following symptoms during treatment with EPSOLAY:
  - hives, rash or severe itching
  - swelling of your face, eyes, lips, tongue, or throat
  - trouble breathing or throat tightness
  - feeling faint, dizzy, or lightheaded
- **Skin irritation.** EPSOLAY may cause skin irritation such as redness, scaling, dryness, stinging, or burning. You may use a moisturizer if you develop skin irritation. Tell your healthcare provider if your symptoms do not improve, you may need to stop treatment with EPSOLAY.
- **Sensitivity to sunlight.** See **"What should I avoid while using EPSOLAY?"**

The most common side effects of EPSOLAY include pain, redness, itching, and swelling at application site. These are not all the possible side effects with EPSOLAY.
Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store EPSOLAY?
- Store EPSOLAY at room temperature between 68°F to 77°F (20°C to 25°C).
- Keep EPSOLAY away from heat.
- Do not freeze EPSOLAY.
- Throw away (discard) unused EPSOLAY 60 days after first use.

Keep EPSOLAY and all medicines out of the reach of children.

General information about the safe and effective use of EPSOLAY.
Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use EPSOLAY for a condition for which it was not prescribed. Do not give EPSOLAY to other people, even if they have the same symptoms that you have. It may harm them. You can ask your pharmacist or healthcare provider for information about EPSOLAY that is written for health professionals.

What are the ingredients in EPSOLAY?
Active ingredient: benzoyl peroxide
Inactive ingredients: anhydrous citric acid, cetrimonium chloride, cetyl alcohol, cyclomethicone, edetate disodium, glycerin, hydrochloric acid, lactic acid, macrogol stearate Type I, mono and di-glycerides, phenoxyethanol, polyquaternium-7, purified water, silicon dioxide and sodium hydroxide.

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