HIGHLIGHTS OF PRESCRIBING INFORMATION

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

TWYNEO® (tretinoin and benzoyl peroxide) Cream, 0.1%/3%, for topical use.

Initial U.S. Approval: 2021

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

TWYNEO Cream is a combination of tretinoin, a retinoid, and benzoyl peroxide indicated for the topical treatment of acne vulgaris in adults and pediatric patients 9 years of age and older. (1)

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

- Apply a thin layer of TWYNEO Cream to the affected areas once daily. (2)
- Avoid contact with the eyes, lips, paranasal creases, and mucous membranes. (2)
- Wash hands after application. (2)
- Not for oral, ophthalmic, or intravaginal use. (2)

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

Cream: 0.1% tretinoin/ 3% benzoyl peroxide (3)

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

History of serious hypersensitivity reaction to benzoyl peroxide or any component of TWYNEO Cream. (4)

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

- *Hypersensitivity*: Severe hypersensitivity reactions, including anaphylaxis and angioedema, have been reported with use of benzoyl peroxide products. (4, 5.1)
- *Skin Irritation*: Pain, dryness, exfoliation, erythema, and irritation may occur with use of TWYNEO Cream. Avoid application of TWYNEO Cream to cuts, abrasions, eczematous or sunburned skin. (5.2)
- *Photosensitivity*: Minimize unprotected exposure to sunlight and sunlamps. Use sunscreen and protective clothing when sun exposure cannot be avoided. (5.3)

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

The most common adverse reactions (incidence ≥ 1%) are pain, dryness, exfoliation, erythema, dermatitis, pruritus and irritation (all at the application site). (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: 7/2021

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

TWYNEO Cream is indicated for the topical treatment of acne vulgaris in adults and pediatric patients 9 years of age and older.

2 DOSAGE AND ADMINISTRATION

- Apply a thin layer of TWYNEO Cream to the affected areas once daily on clean and dry skin. Avoid contact with the eyes, lips, paranasal creases, and mucous membranes.
- Wash hands after application.
- TWYNEO Cream is for topical use only. TWYNEO Cream is not for oral, ophthalmic, or intravaginal use.

3 DOSAGE FORMS AND STRENGTHS

Cream 0.1%/3%: Each gram of TWYNEO Cream contains 1 mg (0.1%) of tretinoin and 30 mg (3%) of benzoyl peroxide in a yellow cream in a 30-gram bottle with a pump.

4 CONTRAINDICATIONS

TWYNEO Cream is contraindicated in patients with a history of hypersensitivity reaction to benzoyl peroxide or any components of TWYNEO Cream *[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 TWYNEO Cream immediately and initiate appropriate therapy.

5.2 Skin Irritation

Patients using TWYNEO Cream may experience application site dryness, pain, exfoliation, erythema, dermatitis, pruritis, and irritation *[see Adverse Reactions (6.1)]*. Depending upon the severity of these adverse reactions, instruct patients to use a moisturizer, reduce the frequency of the application of TWYNEO Cream, or discontinue use. Avoid application of TWYNEO Cream to cuts, abrasions, eczematous, or sunburned skin.

5.3 Photosensitivity

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

6 ADVERSE REACTIONS

6.1 Clinical trials experience

The following adverse reactions are discussed in greater detail elsewhere in the labeling:

- Hypersensitivity *[see Warnings and Precautions (5.1)]*
- Skin Irritation *[see Warnings and Precautions (5.2)]*

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 multicenter, randomized, double-blind, vehicle-controlled trials (Trials 1 and 2), 832 subjects 9 years of age and older with facial acne vulgaris applied TWYNEO Cream (N = 555) or vehicle (N = 277) once daily for 12 weeks. The majority of subjects were White (73%) and female (59%). Approximately 33% were Hispanic/Latino, and 46% were younger than 18 years of age. Adverse reactions reported in ≥ 1.0% of subjects treated with TWYNEO Cream (and for which the rate exceeded the rate for vehicle), as well as the corresponding rates reported in subjects treated with vehicle are presented in Table 1.

Table 1: Adverse Reactions Reported by ≥ 1% of Subjects with Facial Acne Vulgaris Treated with TWYNEO Cream and More Frequently than Vehicle in Trials 1 and 2

	TWYNEO Cream (N = 555) n (%)	Vehicle (N = 277) n (%)
Application Site Pain*	59 (10.6)	1 (0.4)
Application Site Dryness	27 (4.9)	1 (0.4)
Application Site Exfoliation	23 (4.1)	0
Application Site Erythema	22 (4.0)	0
Application Site Dermatitis	7 (1.3)	1 (0.4)
Application Site Pruritus	7 (1.3)	0
Application Site Irritation	6 (1.1)	1 (0.4)

* Application site pain defined as application site stinging, burning or pain.

Local tolerability evaluations were conducted at each study visit in the clinical trial by assessment of erythema, scaling, pigmentation, dryness, itching, burning, and stinging. Table 2 presents the active assessment of the signs and symptoms of local facial tolerability at Week 12 in subjects treated with TWYNEO Cream.

Table 2: Facial Cutaneous Tolerability Assessment at Week 12 in Subjects with Acne Vulgaris Treated with TWYNEO Cream

	TWYNEO Cream (N = 494*) (%)			Vehicle (N = 264*) (%)		
	Mild	Moderate	Severe	Mild	Moderate	Severe
Erythema	33.0	6.9	0.2	26.9	8.0	0
Pigmentation	27.3	6.3	0.4	26.5	4.5	0
Dryness	22.3	5.3	0.4	16.7	2.3	0
Scaling	16.4	2.6	0	12.9	0.8	0
Burning	5.9	2.2	0	3.4	0.8	0
Itching	11.1	1.8	0	8.7	2.7	0
Stinging	5.3	0.2	0	1.9	1.1	0

* The denominators for calculating the percentages were the 494 of 555 subjects treated with TWYNEO Cream and 264 of 277 subjects treated with vehicle in these trials who had cutaneous signs and local tolerability results reported at Week 12.

Local tolerability scores for erythema, scaling, dryness, itching, burning, and stinging rose during the first two weeks of treatment and decreased thereafter.

6.2 Postmarketing Experience

The following adverse reactions have been identified during use of benzoyl peroxide. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Immune System Disorders: Anaphylaxis, angioedema, and urticaria

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Available data from published observational studies of topical tretinoin in pregnant women have not established a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes. Studies conducted with topical benzoyl peroxide have not demonstrated systemic absorption and maternal use is not expected to result in fetal exposure to benzoyl peroxide. There are no data on TWYNEO Cream use in pregnant women.

There are reports of major birth defects reported with maternal use of topical tretinoin similar to those seen in infants exposed to oral retinoids, but these case reports do not establish a pattern or association with tretinoin-related embryopathy (*see Data*).

Animal reproductive studies have not been conducted with TWYNEO Cream or benzoyl peroxide. Topical administration of tretinoin to pregnant rats during organogenesis was associated with malformations (craniofacial abnormalities [hydrocephaly], asymmetrical thyroids, variations in ossification, and increased supernumerary ribs) at doses greater than 1 mg tretinoin/kg/day, approximately 5 times the maximum recommended human dose (MRHD) based on body surface area (BSA) comparison and assuming 100% absorption. Oral administration of tretinoin to pregnant cynomolgus monkeys during organogenesis was associated with malformations at 10 mg/kg/day (approximately 100 times the MRHD based on BSA comparison and assuming 100% absorption) (*see Data*).

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

Data

Human Data

While available studies cannot definitively establish the absence of risk, published data from multiple prospective controlled observational studies on the use of topical tretinoin products during pregnancy have not identified an association with topical tretinoin and major birth defects or miscarriage. The available studies have methodologic limitations, including small sample size and in some cases, lack of physical exam by an expert in birth defects. There are published case reports of infants exposed to topical tretinoin during the first trimester that describe major birth defects similar to those seen in infants exposed to oral retinoids; however, no pattern of malformations has been identified and no causal association has been established in these cases. The significance of these spontaneous reports in terms of risk to the fetus is not known.

Animal Data

For purposes of comparison of the animal exposure to human exposure, the MRHD is defined as 1.5 g of TWYNEO Cream (containing 0.1% tretinoin) applied daily to a 60-kg person (0.03 mg tretinoin/kg body weight).

Topical tretinoin embryofetal development studies have generated equivocal results. There is evidence for malformations (shortened or kinked tail) after topical tretinoin administration in Wistar rats at doses greater than 1 mg/kg/day (approximately 5 times the MHRD based on BSA comparison and assuming 100% absorption). Anomalies (humerus: short 13%, bent 6%, or parietal incompletely ossified 14%) have also been reported when 10 mg/kg/day (approximately 50 times the MRHD based on BSA comparison and assuming 100% absorption) was topically applied to pregnant rats during organogenesis. Increased incidence of domed head and hydrocephaly, typical of retinoid-induced fetal malformations were noted in New Zealand White rabbits administered topical doses greater than 0.2 mg/kg/day (2.2 times the MRHD based on BSA comparison and assuming 100% absorption).

Oral tretinoin induced malformations in rats, mice, hamsters, and nonhuman primates when administered during the period of organogenesis. Fetal malformations were observed when tretinoin was orally administered to pregnant Wistar rats during organogenesis. It was teratogenic and fetotoxic in Wistar rats when given orally or topically in doses greater than 1 mg/kg/day (approximately 5 times the MRHD based on BSA comparison and assuming 100% absorption). In the cynomolgus monkey, fetal malformations were reported when an oral dose of 10 mg/kg/day was administered to pregnant monkeys during organogenesis (approximately 100 times the MRHD based on BSA comparison and assuming 100% absorption). No fetal malformations were observed at an oral dose of 5 mg/kg/day (approximately 50 times the MRHD based on BSA comparison and assuming 100% absorption). Increased skeletal variations were observed at all doses, and a dose-related increase in embryo lethality and abortion was reported in this study. Similar results have also been reported in pigtail macaques.

Oral tretinoin has been shown to be fetotoxic in rats when administered at a dose of 2.5 mg/kg/day (13 times the MRHD based on BSA comparison and assuming 100% absorption). Topical tretinoin has been shown to be fetotoxic in rabbits when administered at a dose of 0.5 mg/kg/day (5 times the MRHD based on BSA comparison and assuming 100% absorption).

8.2 Lactation

Risk Summary

There are no data on the presence of benzoyl peroxide and tretinoin or its metabolites in human milk, the effects on the breastfed infant, or the effects on milk production. It is not known whether topical administration of tretinoin could result in sufficient systemic absorption to produce detectable concentrations in human milk. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for TWYNEO Cream and any potential adverse effects on the breastfed child from TWYNEO Cream or from the underlying maternal condition.

8.4 Pediatric Use

The safety and effectiveness of TWYNEO Cream for the topical treatment of acne vulgaris have been established in pediatric patients 9 years of age and older based on evidence from two multicenter, randomized, double-blind, parallel-group, vehicle-controlled, 12-week clinical trials and an open-label pharmacokinetic study. A total of 283 pediatric subjects 9 years of age and older received TWYNEO Cream in the clinical studies *[see Clinical Pharmacology (12.3) and Clinical Studies (14)]*.

The safety and effectiveness of TWYNEO Cream in pediatric patients below 9 years of age have not been established.

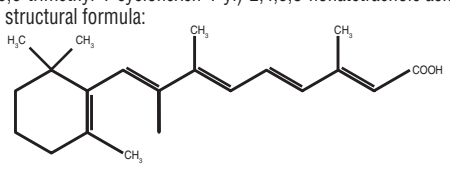
8.5 Geriatric Use

Clinical trials of TWYNEO Cream did not include sufficient numbers of subjects 65 years of age and older to determine whether they respond differently than younger subjects.

11 DESCRIPTION

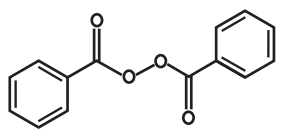
TWYNEO (tretinoin and benzoyl peroxide) Cream is a yellow cream for topical use. Each gram of TWYNEO Cream contains 1 mg (0.1%) of tretinoin and 30 mg (3%) of benzoyl peroxide. Tretinoin is a retinoid and benzoyl peroxide is an oxidizing agent.

The chemical name for tretinoin is all-trans-retinoic acid, also known as (all-E)-3,7-dimethyl-9-(2,6,6-trimethyl-1-cyclohexen-1-yl)-2,4,6,8-nonatetraenoic acid. Tretinoin has the following structural formula:



Molecular Formula: $C_{20}H_{28}O_2$ Molecular Weight: 300.44

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



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

The formulation of TWYNEO Cream uses silica (silicon dioxide) core shell structures to separately micro-encapsulate tretinoin crystals and benzoyl peroxide crystals enabling inclusion of the two active ingredients in the cream. TWYNEO Cream contains the following inactive ingredients: anhydrous citric acid, butylated hydroxytoluene, carbomer homopolymer type C, cetrimonium chloride, cetyl alcohol, cyclomethicone, edetate disodium, glycerin, hydrochloric acid, imidurea, (S)lactic acid, macrogol stearate, mono and di-glycerides, polyquaternium-7, purified water, silicon dioxide, sodium hydroxide, squalane, tetraethyl ortho silicate and white wax.

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 is unknown. Tretinoin is a metabolite of vitamin A that binds with high affinity to specific retinoic acid receptors located in both the cytosol and nucleus. Tretinoin activates three members of the retinoic acid (RAR) nuclear receptors (RARα, RARβ, and RARγ) which act to modify gene expression, subsequent protein synthesis, and epithelial cell growth and differentiation. It has not been established whether the clinical effects of tretinoin are mediated through activation of retinoic acid receptors and/or other mechanisms.

Although the exact mechanism of action of tretinoin in acne treatment is unknown, current evidence suggests that topical tretinoin decreases cohesiveness of follicular epithelial cells with decreased microcomedo formation. Additionally, tretinoin stimulates mitotic activity and increased turnover of follicular epithelial cells causing extrusion of the comedones.

12.2 Pharmacodynamics

Pharmacodynamics of TWYNEO Cream in the treatment of acne vulgaris are unknown.

12.3 Pharmacokinetics

The systemic exposure of benzoyl peroxide was not assessed. Benzoyl peroxide is absorbed by the skin where it is converted to benzoic acid and eliminated in the urine.

Plasma concentrations of tretinoin and its major metabolites were evaluated in 35 subjects in an open-label, randomized, pharmacokinetic (PK) study. Subjects 9 years of age and older with acne vulgaris applied a mean daily dose of 1.9 g TWYNEO Cream to the skin of the face, shoulders, upper back and upper chest once daily for 14 days. Steady-state PK characteristics were determined from samples drawn on Day 14. The mean baseline corrected C_{max} and AUC_{0-24} of tretinoin and its metabolites after once daily application of TWYNEO Cream for 14 days are provided in Table 3. No detectable levels of the metabolites all-trans 4-keto retinoic acid and 9-cis retinoic acid were found in subjects treated with TWYNEO Cream.

Table 3: Pharmacokinetics of Tretinoin and its Major Metabolites When Treated With TWYNEO Cream in Subjects 9 Years of Age and Older With Acne Vulgaris for 14 Days

Age Group (years)	n	Compound	Mean (± SD) C_{max} (ng/mL)	Mean (±SD) AUC_{0-24} (ng·h/mL)
≥ 18 years of age	12	tretinoin	0.15 ± 0.17	0.63 ± 0.95
		4-keto 13-cis RA	0.27 ± 0.29	2.88 ± 3.61
		13-cis RA	0.21 ± 0.19	1.99 ± 2.90
12 to 17	15	tretinoin	0.19 ± 0.18	1.56 ± 1.97
		4-keto 13-cis RA	0.32 ± 0.28	2.39 ± 3.05
		13-cis RA	0.28 ± 0.35	1.79 ± 2.79
9 to 11	8	tretinoin	0.18 ± 0.22	2.06 ± 3.96
		4-keto 13-cis RA	0.34 ± 0.36	2.89 ± 3.17
		13-cis RA	0.13 ± 0.09	0.96 ± 1.36

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

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

Benzoyl Peroxide

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 15 to 25% benzoyl peroxide carbopol gel (5 to 8 times the concentration of benzoyl peroxide in TWYNEO Cream) for two years. Similar results were obtained in mice treated topically with 25% benzoyl peroxide carbopol gel for 56 weeks followed by intermittent treatment with 15% benzoyl peroxide gel for the rest of the two-year study period, and in mice treated topically with 5% benzoyl peroxide carbopol 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.

Tretinoin

In a 91-week dermal study, in which CD-1 mice were administered 0.017% and 0.035% formulations of tretinoin, cutaneous squamous cell carcinomas and papillomas in the treatment area were observed in some female mice. A dose-related incidence of liver tumors in male mice was observed at those same doses. The maximum systemic doses associated with the administered 0.017% and 0.035% formulations are 0.5 and 1.0 mg/kg/day, respectively. These doses are 1.3 and 2.7 times the MRHD based on BSA comparison and assuming 100% absorption. The biological significance of these findings is not clear because they occurred at doses that exceeded the dermal maximally tolerated dose (MTD) of tretinoin and because they were within the background natural occurrence rate for these tumors in this strain of mice. There was no evidence of carcinogenic potential when 0.025 mg/kg/day of tretinoin was administered topically to mice (0.07 times the MRHD based on BSA comparison and assuming 100% absorption).

The genotoxic potential of tretinoin was evaluated in an in vitro bacterial reversion test and an in vivo rat micronucleus assay, both of which were negative.

In dermal fertility studies of another tretinoin formulation in rats, slight (not statistically significant) decreases in sperm count and motility were seen at 0.5 mg/kg/day (approximately 2.7 times the MRHD based on BSA comparison and assuming 100% absorption), and slight (not statistically significant) increases in the number and percent of nonviable embryos in females treated with 0.25 mg/kg/day and above (1.3 times the MRHD based on BSA comparison and assuming 100% absorption) were observed.

14 CLINICAL STUDIES

The safety and efficacy of TWYNEO Cream was evaluated in the treatment of acne vulgaris in two multicenter, randomized, double-blind, vehicle-controlled trials [Trial 1 (NCT03761784), Trial 2 (NCT03761810)], which were identical in design. The trials were conducted in 858 subjects 9 years of age and older with facial acne vulgaris, who were treated once daily for 12 weeks with either TWYNEO Cream or vehicle.

Subjects were required to have a score of moderate (3) or severe (4) on the Investigator Global Assessment (IGA), 20 to 100 inflammatory lesions (papules, pustules and nodules), 30 to 150 noninflammatory lesions (open and closed comedones) and two or fewer facial nodules.

Overall, 73 of subjects were White and 59% were female. Eighteen (18) (2%) subjects were 9 to 11 years of age, 370 (43%) subjects were 12 to 17 years of age, and 470 (55%) subjects were 18 years of age or older. At baseline, subjects had a mean inflammatory lesion count of 30.7 and a mean noninflammatory lesion count of 46.4. Additionally, 91% of subjects had an IGA score of 3 ("moderate").

The co-primary efficacy endpoints were the absolute change from baseline in non-inflammatory lesion count, and absolute change in inflammatory lesion count at Week 12 and the proportion of subjects with IGA success at Week 12, defined as an IGA score of 0 ("clear") or 1 ("almost clear"), and at least a two-grade improvement (decrease) from baseline at Week 12. The efficacy results are provided in Table 4.

Table 4: Efficacy Results in Subjects with Acne Vulgaris at Week 12 (Trials 1 and 2)

	Trial 1		Trial 2	
	TWYNEO Cream (N = 281)	Vehicle (N = 143)	TWYNEO Cream (N = 290)	Vehicle (N = 144)
IGA Success*	39.9%	14.3%	26.8%	15.1%
Difference from Vehicle	25.7%		11.6%	
(95% CI)	(17.1%, 34.2%)		(3.6%, 19.7%)	
Inflammatory Lesions				
Mean‡ Absolute Change from Baseline	-21.6	-14.8	-16.2	-14.1
Difference from Vehicle	-6.8		-2.1	
(95% CI)	(-9.1, -4.6)		(-3.9, -0.4)	
Mean‡ Percent Change from Baseline	-66.1%	-43.5%	-57.6%	-50.8%
Difference from Vehicle	-22.6%		-6.8%	
(95% CI)	(-29.2%, -16.0%)		(-13.1%, -0.5%)	
Non-Inflammatory Lesions				
Mean‡ Absolute Change from Baseline	-29.7	-19.8	-24.2	-17.4
Difference from Vehicle	-9.9		-6.8	
(95% CI)	(-13.0, -6.8)		(-9.9, -3.7)	
Mean‡ Percent Change from Baseline	-61.6%	-40.9%	-54.4%	-41.5%
Difference from Vehicle	-20.7%		-13.0%	
(95% CI)	(-27.2%, -14.2%)		(-19.6%, -6.4%)	

* 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.

16 How Supplied/Storage and Handling

How Supplied

TWYNEO (tretinoin and benzoyl peroxide) Cream, 0.1%/3%, is a yellow cream and is supplied as:

- 30-gram bottle with a pump, NDC 0299-5945-30

Storage and Handling

- *Prior to Dispensing*: Store TWYNEO Cream between 2ºC to 8ºC (36ºF to 46ºF) until dispensed to the patient.
- *After Dispensing*: Store TWYNEO Cream at room temperature 20ºC to 25ºC (68ºF to 77ºF). Discard 12 weeks after date of dispensing or 30 days after first opening, whichever is sooner.
- Do not freeze.

17 Patient Counseling Information

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

Hypersensitivity

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

Skin Irritation

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

Photosensitivity

Advise patients to minimize unprotected exposure to sunlight and sunlamps; recommend the use of sunscreen products and protective apparel (e.g., hat) over treated areas when sun exposure cannot be avoided *[see Warnings and Precautions (5.3)]*.

Administration Instructions

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

Discard Instructions

Instruct patients to store TWYNEO Cream at room temperature and to discard 12 weeks after date of dispensing or 30 days after first opening, whichever is sooner *[see How Supplied/Storage and Handling (16)]*.

Marketed by
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PATIENT INFORMATION
TWYNEO® (Twye'nee oh)
(tretinoin and benzoyl peroxide)
cream, for topical use

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

What is TWYNEO Cream?

TWYNEO Cream is a prescription medicine used on the skin (topical) to treat acne vulgaris in adults and children 9 years of age and older.

It is not known if TWYNEO Cream is safe and effective in children below 9 years of age.

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

Before using TWYNEO Cream, tell your healthcare provider about all of your medical conditions, including if you:

- have other skin problems, including eczema, cuts, or sunburn
- have skin sensitivity to the sun
- are pregnant or plan to become pregnant. It is not known if TWYNEO Cream will harm your unborn baby.
- are breastfeeding or plan to breastfeed. It is not known if TWYNEO Cream passes into your breast milk. Talk to your healthcare provider about the best way to feed your baby during treatment with TWYNEO Cream.

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 TWYNEO Cream?

- Use TWYNEO Cream exactly as your healthcare provider tells you to use it.
- Apply TWYNEO Cream to the affected areas 1 time a day.
- Apply TWYNEO Cream on clean and dry skin.
- TWYNEO Cream comes in a bottle with a pump. Press down on (depress) the pump to dispense a small amount of TWYNEO Cream on your fingertip. Apply a thin layer of TWYNEO Cream to the affected skin areas. Avoid contact with your eyes, lips, corners of your nose, and mouth.
- Wash your hands right away after applying TWYNEO Cream.

What should I avoid while using TWYNEO Cream?

- Avoid using TWYNEO Cream on skin areas with cuts, abrasions, eczema, or sunburns.
- Limit your time in sunlight. You should avoid using sunlamps, tanning beds, and ultraviolet light during treatment with TWYNEO Cream. If you have to be in the sunlight or are sensitive to sunlight, use sunscreen and wear protective clothing or a wide-brimmed hat to cover the treated areas.
- Avoid getting TWYNEO Cream in your hair or on colored fabric. TWYNEO Cream may bleach hair or colored fabric.

What are the possible side effects of TWYNEO Cream?

TWYNEO Cream may cause serious side effects including:

- **Allergic reactions.** Stop using TWYNEO Cream and get medical help right away if you have any of the following symptoms during treatment with TWYNEO Cream:
  - 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.** TWYNEO Cream may cause skin irritation such as redness, scaling, peeling, dryness, pain, stinging or burning. If you develop these symptoms, your healthcare provider may tell you to use a moisturizer, decrease the number of times you apply TWYNEO Cream, or completely stop treatment with TWYNEO Cream.

The most common side effects of TWYNEO Cream include pain, dryness, peeling, redness, swelling, itching, and irritation at the application site.

These are not all the possible side effects of TWYNEO Cream.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

You may also report side effects to Galderma Laboratories, L.P. at 1-866-735-4137.

How should I store TWYNEO Cream ?

- Store TWYNEO Cream at room temperature between 68°F to 77°F (20°C to 25°C).
- Throw away (discard) TWYNEO Cream 12 weeks after the date you receive it or 30 days after first opening, whichever is sooner.
- Do not freeze.

Keep TWYNEO Cream and all medicines out of reach of children.

General information about the safe and effective use of TWYNEO Cream.

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use TWYNEO Cream for a condition for which it was not prescribed. Do not give TWYNEO Cream 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 TWYNEO Cream that is written for health professionals.

What are the ingredients in TWYNEO Cream?

Active ingredients: tretinoin and benzoyl peroxide

Inactive ingredients: anhydrous citric acid, butylated hydroxytoluene, carbomer homopolymer type C, cetrimonium chloride, cetyl alcohol, cyclomethicone, edetate disodium, glycerin, hydrochloric acid, imidurea, (S)-lactic acid, macrogol stearate, mono and di-glycerides, polyquaternium-7, purified water, silicon dioxide, sodium hydroxide, squalane, tetraethyl ortho silicate and white wax.

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This Patient Information has been approved by the U.S. Food and Drug Administration.
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