Product Monograph

Including Patient Medication Information

^{Pr}TWYNEO®

Tretinoin and benzoyl peroxide cream

For topical use

0.1% w/w Tretinoin and 3% w/w Benzoyl Peroxide

Acne Therapy

Searchlight Pharma Inc.
1600 Notre Dame Street West, Suite 312
Montreal, Quebec
H3J 1M1

Date of Authorization:

2025-12-04

Submission Control Number: 293525

Recent Major Label Changes

None at time of the most recent authorization.

Table of Contents

Certain sections or subsections that are not applicable at the time of the preparation of the most recent authorized product monograph are not listed.

Recent Major Label Changes **2**

Table of Contents **2**

Part 1: Healthcare Professional Information **4**

1. Indications **4**

1.1. Pediatrics 4

1.2. Geriatrics 4

2. Contraindications **4**

4. Dosage and Administration **4**

4.1. Dosing Considerations 4

4.2. Recommended Dose and Dosage Adjustment 4

4.4. Administration 5

4.5. Missed Dose 5

5. Overdose **5**

6. Dosage Forms, Strengths, Composition, and Packaging **5**

7. Warnings and Precautions **6**

General 6

Carcinogenesis and Genotoxicity 6

Immune 7

Reproductive Health 7

Skin 7

7.1. Special Populations 7

7.1.1. Pregnancy 7

7.1.2. Breastfeeding 8

7.1.3. Pediatrics 8

7.1.4. Geriatrics 8

8. Adverse Reactions **9**

8.1. Adverse Reaction Overview 9

8.2. Clinical Trial Adverse Reactions 9
8.3. Less Common Clinical Trial Adverse Reactions 11
8.5. Post-Market Adverse Reactions 11
9. Drug Interactions 11
9.2. Drug Interactions Overview 11
9.3. Drug-Behaviour Interactions 11
9.4. Drug-Drug Interactions 11
9.5. Drug-Food Interactions 11
9.6. Drug-Herb Interactions 12
9.7. Drug-Laboratory Test Interactions 12
10. Clinical Pharmacology 12
10.1. Mechanism of Action 12
10.2. Pharmacodynamics 12
10.3. Pharmacokinetics 12
11. Storage, Stability and Disposal 13
12. Special Handling Instructions 13
Part 2: Scientific Information 14
13. Pharmaceutical Information 14
14. Clinical Trials 15
14.1. Clinical Trials by Indication 15
Treatment of Acne Vulgaris 15
15. Microbiology 16
16. Non-Clinical Toxicology 17
Patient Medication Information 20

Part 1: Healthcare Professional Information

1. Indications

TWYNEO (tretinoin and benzoyl peroxide cream) is indicated for:

- the topical treatment of acne vulgaris in adults and pediatric patients 9 years of age and older.

1.1. Pediatrics

Pediatrics (< 18 years of age): The safety and effectiveness of TWYNEO has been established in pediatric patients 9 to 17 years of age.

Safety and effectiveness of TWYNEO in pediatric patients below 9 years of age has not been established. Therefore, Health Canada has not authorized an indication for pediatric use in this patient population. See 4.2 Recommended Dose and Dosage Adjustment and 7.1.3 Pediatrics.

1.2. Geriatrics

Geriatrics (≥ 65 years of age): A limited number of patients aged 65 years and over have been treated with TWYNEO in clinical trials; therefore, the safety and efficacy of TWYNEO have not been established in this patient population (see 4.2 Recommended Dose and Dosage Adjustment and 7.1.4 Geriatrics).

2. Contraindications

- TWYNEO is contraindicated in patients with a history of hypersensitivity reactions to benzoyl peroxide, tretinoin or any ingredients in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see 6 Dosage Forms, Strengths, Composition, and Packaging.
- TWYNEO is contraindicated in pregnant women and women planning a pregnancy (see 7.1.1 Pregnancy).

4. Dosage and Administration

4.1. Dosing Considerations

TWYNEO is for dermatologic use only and not for oral, ophthalmic, or intravaginal use.

4.2. Recommended Dose and Dosage Adjustment

The recommended dose of TWYNEO is a small amount applied once daily as a thin layer to the affected areas on clean and dry skin, as instructed by a healthcare professional.

Pediatrics (< 18 years of age):

No dose adjustment is required in pediatric patients 9 years of age and older.

Health Canada has not authorized an indication for pediatric use below 9 years of age.

Geriatrics (≥ 65 years of age): There is limited information in patients aged 65 years and older.

4.4. Administration

- Before initial use, prime the pump until the first drop of cream is released.
- Apply a small amount of TWYNEO once daily in a thin layer to affected areas on clean and dry skin, as instructed by a healthcare professional. Avoid contact with the eyes, lips, mouth, paranasal creases, and mucus membranes.
- Avoid contact with cuts, abrasions, eczematous or sunburned skin.
- If TWYNEO gets in or near eyes, rinse thoroughly with water.
- Wash hands thoroughly after application.
- TWYNEO may bleach hair or colored fabric.
- TWYNEO is for topical use only. Not for oral, ophthalmic, or intravaginal use.
- Discard unused TWYNEO 12 weeks after date of dispensing or 60 days after first opening, whichever is sooner.

4.5. Missed Dose

In the event of a missed dose, the patient should be instructed to continue with the next scheduled application as usual. The patient should not apply an additional amount to compensate for the missed dose.

5. Overdose

Acute overdose with the topical use of TWYNEO is unlikely. If TWYNEO is applied excessively, no more rapid, or better results will be obtained and marked redness, peeling or discomfort may occur. In the event of accidental ingestion, treatment should be symptomatic.

Inadvertent oral ingestion of tretinoin may lead to the same adverse effects as those associated with excessive oral intake of Vitamin A (hypervitaminosis) or other retinoids, including teratogenesis in women of childbearing age. If accidental oral ingestion occurs, the patient should be monitored, and appropriate supportive measures should be administered as necessary, including pregnancy testing in women of childbearing age.

For the most recent information in the management of a suspected drug overdose, contact your regional poison control centre or Health Canada's toll-free number, 1-844 POISON-X (1-844-764-7669).

6. Dosage Forms, Strengths, Composition, and Packaging

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

The formulation of TWYNEO 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. The encapsulation allows the benzoyl peroxide and tretinoin to be slowly released from the microcapsules, on to the skin.

Table 1 – Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form/ Strength/Composition	Non-Medicinal Ingredients
Topical	Cream, 1 mg/g (0.1%) of tretinoin / 30 mg/g (3%) of benzoyl peroxide	anhydrous citric acid, butylated hydroxytoluene, carbomer homopolymer, cetrimonium chloride, cetyl alcohol, cyclomethicone, edetate disodium, glycerin, hydrochloric acid, imidurea, lactic acid, macrogol stearate, mono and di-glycerides, polyquaternium-7, purified water, silicon dioxide, sodium hydroxide, squalane, tetraethyl orthosilicate and white wax.

7. Warnings and Precautions

General

TWYNEO is for external use only. Not for oral, ophthalmic, or intravaginal use.

Avoid contact with the eyes, eyelids, paranasal creases, lips, mouth, mucous membranes, severely inflamed skin. The product should not be applied to cuts, open lesions, abrasions, eczematous or sunburned skin or to other areas where treatment is not intended. If contact occurs, rinse immediately and thoroughly with water.

Excessive use of TWYNEO should be avoided.

Concomitant topical acne therapy is not recommended because a possible cumulative irritancy effect may occur, especially with the use of peeling, desquamating, or abrasive agents. Avoid concomitant use of other potentially irritating topical products (medicated or abrasive soaps and cleansers, soaps and cosmetics that have strong skin-drying effect and products with high concentrations of alcohol, astringents, spices, or limes).

Use of electrolysis, “waxing” and chemical depilatories for hair removal should be avoided on skin treated with TWYNEO.

TWYNEO may bleach hair and coloured fabric**.** Use caution when applying near hairline.

Patients should be advised to use non-comedogenic cosmetics.

Carcinogenesis and Genotoxicity

Carcinogenicity and mutagenicity studies were not conducted with TWYNEO. 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. See 16 Non-Clinical Toxicology for additional information.

Immune

- 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 immediately and initiate appropriate therapy.

Reproductive Health

- Teratogenic Risk (class effect)

Topical tretinoin is contraindicated in pregnant women and women planning a pregnancy because of the possibility of an increased systemic exposure due to various factors (e.g., damaged skin barrier, excessive use). See 2 Contraindications.

Skin

- Skin Irritation

Patients using TWYNEO may experience application site dryness, pain, exfoliation, erythema, dermatitis, pruritus and irritation (see 8 Adverse Reactions). Depending upon the severity of these adverse reactions, instruct patients to use a moisturizer, reduce the frequency of the application of the TWYNEO, or discontinue use. Avoid application of TWYNEO to cuts, abrasions, eczematous or sunburned skin.

In case of sunburn, allow the skin to heal before using TWYNEO. Weather extremes, such as wind or cold, may also be irritating to patients under treatment with tretinoin.

- Photosensitivity

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

7.1. Special Populations

7.1.1. Pregnancy

TWYNEO is contraindicated in women who are or may become pregnant (see 2 Contraindications). There are no available data on TWYNEO use in pregnant women to evaluate a drug associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes.

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 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.

Animal reproductive studies have not been conducted with TWYNEO 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 16 Non-Clinical Toxicology).

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.

7.1.2. Breastfeeding

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. Precaution should be exercised because many drugs can be excreted in human milk. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for TWYNEO and any potential adverse effects on the breastfed child from TWYNEO or from the underlying maternal condition. If used during lactation, TWYNEO should not be applied to the chest region and, care should be taken to avoid accidental exposure by the infant.

7.1.3. Pediatrics

Pediatrics (< 18 years of age): The safety and effectiveness of TWYNEO 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 patients 9 years of age and older received TWYNEO in the clinical studies (see 10 Clinical Pharmacology and 14 Clinical Trials).

Safety and effectiveness of TWYNEO have not been established in pediatric patients below the age of 9 years. Therefore, Health Canada has not authorized an indication for pediatric use in this patient population (see 1.1 Pediatrics and 4.2 Recommended Dose and Dosage Adjustment).

7.1.4. Geriatrics

Geriatrics (≥ 65 years of age): Clinical trials of TWYNEO did not include sufficient number of patients 65 years of age and older to determine whether they respond differently than younger patients (see 1.2 Geriatrics and 4.2 Recommended Dose and Dosage Adjustment).

8. Adverse Reactions

8.1. Adverse Reaction Overview

Most adverse reactions were mild or moderate in severity, cutaneous and occurred at the application site.

8.2. Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. Therefore, the frequencies of adverse reactions observed in the clinical trials may not reflect frequencies observed in clinical practice and should not be compared to frequencies reported in clinical trials of another drug.

In two multicenter, randomized, double-blind, vehicle-controlled trials, 832 patients 9 years of age and older with facial acne vulgaris applied TWYNEO (N = 555) or vehicle (N = 277) once daily for 12 weeks. The majority of patients 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% of patients treated with TWYNEO (and for which the rate exceeded the rate for vehicle), as well as the corresponding rates reported in patients treated with vehicle are presented in Table 2.

Table 2 – Adverse Reactions Reported by ≥ 1% of Patients with Facial Acne Vulgaris Treated with TWYNEO and More Frequently than Vehicle

System Organ Class/ Preferred Term	TWYNEO (N = 555) n (%)	Vehicle (N = 277) n (%)
General Disorders and Administration Site Conditions		
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 trials by assessment of erythema, scaling, pigmentation, dryness, itching, burning, and stinging. Table 3 presents the active assessment of the signs and symptoms of local facial tolerability during the 12-week treatment period in patients treated with TWYNEO or vehicle. Both the assessments at week 12 and the maximum assessed incidence throughout the trial are presented.

Table 3 – Facial Cutaneous Tolerability Assessment during 12-Week Treatment Period in Patients with Acne Vulgaris Treated with TWYNEO

	TWYNEO (N = 555) %						Vehicle (N = 277) %					
	Mild		Moderate		Severe		Mild		Moderate		Severe	
	Maximum During Treatment *	Week 12 (End of Treatment) **	Maximum During Treatment *	Week 12 (End of Treatment) **	Maximum During Treatment *	Week 12 (End of Treatment) **	Maximum During Treatment *	Week 12 (End of Treatment) **	Maximum During Treatment *	Week 12 (End of Treatment) **	Maximum During Treatment *	Week 12 (End of Treatment) **
Erythema	34.9	33.0	17.5	6.9	2.2	0.2	26.9	26.9	13.4	8.0	0.7	0
Pigmentation	27.3	27.3	9.5	6.3	1.0	0.4	26.5	26.5	8.3	4.5	0.4	0
Dryness	35.8	22.3	12.7	5.3	2.6	0.4	19.9	16.7	5.5	2.3	0.4	0
Scaling	26.9	16.4	12.9	2.6	1.1	0	15.8	12.9	1.8	0.8	0.4	0
Burning	19.8	5.9	11.2	2.2	2.1	0	8.7	3.4	1.8	0.8	0	0
Itching	16.1	11.1	4.9	1.8	0.6	0	14.7	8.7	2.7	2.7	0	0
Stinging	14.2	5.3	6.4	0.2	1.5	0	7.6	1.9	1.1	1.1	0	0

* The denominators for calculating the percentages were the number of patients with at least one post-baseline cutaneous tolerability assessment.

** The denominators for calculating the percentages were the 494 of 555 patients treated with TWYNEO and 264 of 277 patients 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 generally during the first two weeks of treatment and then gradually decreased.

8.3. Less Common Clinical Trial Adverse Reactions

General Disorders and Administration Site conditions: Application site swelling, application site rash, application site acne, application site discoloration, application site erosion, application site paraesthesia

Skin and subcutaneous tissue disorders: pain of skin

8.5. Post-Market Adverse Reactions

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

9. Drug Interactions

9.2. Drug Interactions Overview

No clinical studies evaluating the drug interaction potential of TWYNEO have been conducted.

As TWYNEO has the potential for local irritation, it is possible that concomitant use of abrasive cleansers, strong drying agents, or irritant products may produce additive irritant effects.

9.3. Drug-Behaviour Interactions

TWYNEO should not come into contact with any coloured material including hair and fabrics as this may result in bleaching and discolouration.

As with other retinoids, use of electrolysis, “waxing” and chemical depilatories for hair removal should be avoided on skin treated with TWYNEO.

Patients should be advised to use non-comedogenic cosmetics. Colour cosmetics such as blushers and powders are acceptable; however, make-up cosmetics should be water based. Cosmetics must be removed by thorough cleansing before the area is treated.

9.4. Drug-Drug Interactions

Interactions with other drugs, including other topical medications, have not been established with TWYNEO.

Concomitant topical medication, medicated or abrasive soaps and cleansers, soaps and cosmetics that have a strong drying effect and products with high concentrations of alcohol, astringents, spices, or lime should be used with caution as they may produce additive irritant effects. Particular caution should be exercised in using preparations containing sulphur, resorcinol, or salicylic acid in combination with TWYNEO.

9.5. Drug-Food Interactions

Interactions with food have not been established.

9.6. Drug-Herb Interactions

Interactions with herbal products have not been established.

9.7. Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

10. Clinical Pharmacology

10.1. 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.

10.2. Pharmacodynamics

The pharmacodynamics of TWYNEO in the treatment of acne vulgaris are unknown.

10.3. Pharmacokinetics

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

Plasma concentrations of tretinoin and its major metabolites were evaluated in 35 patients in an open-label, randomized, pharmacokinetic (PK) study. Patients 9 years of age and older with acne vulgaris applied a mean daily dose of 1.9 g TWYNEO 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 for 14 days are provided in Table 4. No detectable levels of the metabolites all-trans 4-keto retinoic acid and 9-cis retinoic acid were found in patients treated with TWYNEO.

Table 4 – Pharmacokinetics of Tretinoin and its Major Metabolites When Treated with TWYNEO in Patients 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

11. Storage, Stability and Disposal

TWYNEO 0.1%/3% is a yellow cream and is supplied as a 30 g bottle with a pump.

Prior to Dispensing: Store TWYNEO between 2°C to 8°C until dispensed to the patient. Do not freeze.

After Dispensing: Store TWYNEO at room temperature between 15-30°C. Discard 12 weeks after date of dispensing or 60 days after first opening, whichever is sooner. Keep out of sight and reach of children. Do not freeze.

12. Special Handling Instructions

Cleanse and dry the area to be treated. Prime pump bottle before initial use. Apply TWYNEO as a thin layer, avoiding the eyes, lips, paranasal creases and mucus membranes. Wash hands immediately after application. TWYNEO may bleach hair or colored fabric.

Part 2: Scientific Information

13. Pharmaceutical Information

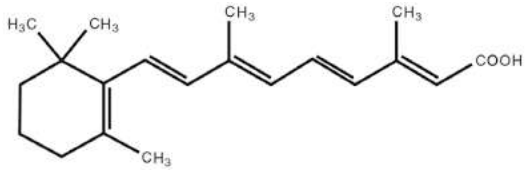
Drug Substance

Proper name: tretinoin

Chemical name: 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

Molecular formula and molecular mass: $C_{20}H_{28}O_2$ Molecular Weight: 300.44 g/mol

Structural formula:



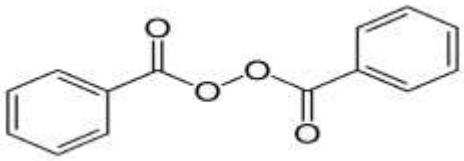
Physicochemical properties: Tretinoin is a yellow to yellow-orange, crystalline powder which is extremely light- and air- sensitive. It is practically insoluble in water, sparingly soluble in methylene chloride, slightly soluble in ethanol, alcohol and chloroform.

Proper name: benzoyl peroxide

Chemical name: benzoyl benzenecarboperoxoate

Molecular formula and molecular mass: $C_{14}H_{10}O_4$ Molecular Weight: 242.23 g/mol

Structural formula:



Physicochemical properties: Benzoyl peroxide is a white, granular powder, which is sparingly soluble in water or alcohol, soluble in benzene, chloroform and ether.

14. Clinical Trials

14.1. Clinical Trials by Indication

Treatment of Acne Vulgaris

Table 5 – Summary of Patient Demographics for Clinical Trials in Acne Vulgaris

Study #	Study design	Dosage, route of administration and duration	Study subjects (n)	Mean age (Range)	Sex M/F
Study 1 (SGT-65-04)	Multicenter, double-blind, randomized, vehicle-controlled	TWYNEO once daily Vehicle once daily Topical (facial application) 12 weeks	281 143	20.9 (11-67) 21.4 (10-57)	106/175 60/83
Study 2 (SGT-65-05)	Multicenter, double-blind, randomized, vehicle-controlled	TWYNEO once daily Vehicle once daily Topical (facial application) 12 weeks	290 144	20.1 (10-51) 20.3 (9-42)	117/173 67/77

M = Male; F = Female.

The safety and efficacy of TWYNEO was evaluated in two multicenter, randomized, double-blind, vehicle-controlled studies which were identical in design. The trials were conducted in 858 patients, aged 9 years and older with facial acne vulgaris, who were treated once daily for 12 weeks with either TWYNEO or vehicle.

Patients 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 non-inflammatory lesions (open and closed comedones) and two or fewer facial nodules.

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

Study Results

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 patients 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 6.

Table 6 – Efficacy Results of Phase 3 Trials with TWYNEO in Patients with Acne Vulgaris at Week 12 (Intent-to-Treat Population)

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

CI = Confidence Interval.

15. Microbiology

No microbiological information is required for this drug product. Microbiological activity was not specifically studied in the development of TWYNEO.

16. Non-Clinical Toxicology

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

General Toxicity

A 13 week repeat dose dermal toxicity study in Gottingen minipigs conducted with a benzoyl peroxide and tretinoin formulation containing double the benzoyl peroxide (6%) compared to the TWYNEO (3%), found only mild transient irritation due to treatment. No systemic toxicity was observed.

Genotoxicity

No studies have been performed to evaluate the genotoxic potential of the formulation of benzoyl peroxide and tretinoin in TWYNEO.

Bacterial mutagenicity assays (Ames test) with benzoyl peroxide reported mutagenic potential in a few but not in the majority of investigations. Benzoyl peroxide has been shown to produce single-strand DNA breaks in human bronchial epithelial and mouse epidermal cells, DNA-protein cross-links in the human cells, and a dose-dependent increase in sister chromatid exchanges in Chinese hamster ovary cells.

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.

Carcinogenicity

No animal carcinogenicity or photocarcinogenicity studies have been conducted with the benzoyl peroxide and tretinoin formulation in TWYNEO.

<u>Benzoyl peroxide</u>

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 (5 to 8 times the concentration of benzoyl peroxide in TWYNEO) 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-year study period and in mice treated topically with 5% benzoyl peroxide gel for two years.

In a photocarcinogenicity study conducted with 5% benzoyl peroxide in carbopol gel, no increase in UV induced tumor formation was observed in hairless mice topically treated for 40 weeks.

Bacterial mutagenicity assays (Ames test) with benzoyl peroxide were largely negative with the exception of one strain where a weakly positive response was reported.

<u>Tretinoin</u>

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).

Reproductive and Developmental Toxicology

No dedicated animal fertility studies have been conducted with the benzoyl peroxide and tretinoin formulation in TWYNEO.

Tretinoin

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.

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).

Special Toxicology

A phototoxicity study conducted with TWYNEO concluded the 3% benozyl peroxide / 0.1% tretinoin formulation showed no signs of phototoxicity.

A study in Hartley guinea pigs found that a benzoyl peroxide and tretinoin formulation with 6% benzoyl peroxide (vs. 3% in TWYNEO) was a weak sensitizer.

Patient Medication Information

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PrTWYNEO®

tretinoin and benzoyl peroxide cream

This Patient Medication Information is written for the person who will be taking **TWYNEO**. This may be you or a person you are caring for. Read this information carefully. Keep it as you may need to read it again.

This Patient Medication Information is a summary. It will not tell you everything about this medication. If you have more questions about this medication or want more information about **TWYNEO**, talk to a healthcare professional.

What TWYNEO is used for:

TWYNEO is used on the skin to treat acne in adults and children 9 years of age and older. It is not approved for use in children younger than 9 years of age.

How TWYNEO works:

TWYNEO has microcapsules that control the release of tretinoin and benzoyl peroxide on the skin. This means that tretinoin and benzoyl peroxide are gradually released onto your skin to treat acne. Tretinoin keeps skin cells from clogging pores and helps old skin come off so new skin can grow. Benzoyl peroxide is kills bacteria and helps to release dead skin cells.

The ingredients in TWYNEO are:

Medicinal ingredients: tretinoin and benzoyl peroxide

Non-medicinal ingredients: anhydrous citric acid, butylated hydroxytoluence, carbomer homopolymer, cetrimonium chloride, cetyl alcohol, cyclomethicone, edetate disodium, glycerin, hydrochloric acid, imidurea, lactic acid, macrogol stearate, mono and di-glycerides, polyquaternium-7, purified water, silicon dioxide, sodium hydroxide, squalene, tetraethyl orthosilicate and white wax.

TWYNEO comes in the following dosage forms:

Cream, 0.1 % tretinoin and 3 % benzoyl peroxide.

Do not use TWYNEO if:

- You are pregnant or planning to become pregnant
- You are allergic to tretinoin, benzoyl peroxide or to any of the other ingredients in TWYNEO.
- You are allergic to any part of the container.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take TWYNEO. Talk about any health conditions or problems you may have, including if you:

- have skin sensitivity to the sun

Other warnings you should know about:

Applying TWYNEO
TWYNEO should be used on skin only. You must not swallow TWYNEO or use it in your mouth. Do not apply it to your eyes or inside your vagina. Do not use TWYNEO on skin areas with cuts, lesions, abrasions, eczema, or on sunburned skin or any place you are not treating. If contact occurs, rinse thoroughly with plenty of water. Do not apply TWYNEO more often or in larger amounts than prescribed.
Avoid the use of TWYNEO with other acne products that have a drying effect on the skin, such products that peel or scrub the skin. Avoid the use of TWYNEO with other potentially irritating products, such as soaps or cosmetics containing drying agents (e.g. alcohol) or other irritants (astringents, spices, limes etc.).
Avoid using electrolysis, waxing, or chemical hair removal creams on skin treated with TWYNEO.
TWYNEO may bleach hair or colored fabrics. Be careful when applying near the hairline and avoid contact with clothing or bedding. Avoid getting TWYNEO in your hair or on colored fabric since TWYNEO may bleach hair or coloured fabric.
Use makeup and skin products that don't clog pores.

Skin Irritation

You may have dryness, pain, peeling, redness, rash, itching, or irritation on the skin that you applied TWYNEO to. If this happens, talk to your healthcare professional. Depending on your symptoms, they may tell you to use a moisturizer, use TWYNEO less often or stop using it.

Sensitivity to Light
TWYNEO may increase your sensitivity to light. Minimize or avoid exposure to natural or artificial sunlight such as tanning beds while using TWYNEO. Wear sunscreen or cover your skin when sunlight exposure cannot be avoided. Stop using TWYNEO if you get a sunburn. Do not apply it to sunburned skin.

Pregnancy

Tell your healthcare professional if you are pregnant or think you might be pregnant. You must not use TWYNEO if you are pregnant or planning to become pregnant. There is a risk that more of the medicine could be absorbed into the body, especially if skin is damaged or if TWYNEO is used too often. This could cause harm to an unborn baby.

Breastfeeding

Before you use TWYNEO, tell your healthcare provider if you are breastfeeding or are planning to breastfeed. If you use TWYNEO while breastfeeding, TWYNEO should not be applied to your chest region. It is not known if TWYNEO is safe to use while breastfeeding TWYNEO may pass into breastmilk. If you are breastfeeding or planning to, your healthcare professional will tell you if you can keep using TWYNEO.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

How to take TWYNEO:

- Use TWYNEO exactly as your healthcare professional tells you to.

- Before you use TWYNEO for the first time, prime the pump by pressing down until the first drop of cream is released.
- Dispense a small amount of TWYNEO onto your fingertip. Apply a thin layer of TWYNEO to the affected skin areas. Make sure these areas are clean and dry before you apply TWYNEO.
- Avoid applying TWYNEO near your eyes, lips, or the corners of your nose and mouth or inside them.
- If TWYNEO gets in your eyes, rinse thoroughly with water.
- Wash your hands right away after applying TWYNEO.
- Avoid applying TWYNEO to cuts, scrapes, areas with eczema, or sunburned skin.
- Throw away any unused TWYNEO 12 weeks after you receive it from your healthcare professional or from the pharmacy, or 60 days after first opening, whichever comes first.

Usual dose:

Apply a thin layer or TWYNEO to affected areas once a day on clean and dry skin.

Overdose:

If you think you, or a person you are caring for, have taken too much TWYNEO, contact a healthcare professional, hospital emergency department, regional poison control centre or Health Canada's toll-free number, 1-844 POISON-X (1-844-764-7669) immediately, even if there are no signs or symptoms.

Missed dose:

If you forget to apply TWYNEO skip the missed dose. Then, continue the next day with the usual dose. Never take a double dose to make up for a missed dose.

Possible side effects from using TWYNEO:

These are not all the possible side effects you may have when taking TWYNEO. If you experience any side effects not listed here, tell your healthcare professional.

Side effects may include:

- skin discolouration

Serious side effects and what to do about them

Frequency/Side Effect/Symptom	Talk to your healthcare professional		Get immediate medical help
	Only if severe	In all cases	
Very Common			
Skin irritation: pain, dryness, peeling, redness, swelling, itching, irritation, stinging or burning.		√	

Frequency/Side Effect/Symptom	Talk to your healthcare professional		Get immediate medical help
	Only if severe	In all cases	
Unknown Frequency			
Allergic reactions: hives, rash, severe itching, swelling of your face, lips, throat, tongue, trouble breathing, throat tightness, nausea, vomiting, diarrhea, feeling faint, dizzy, lightheaded.			√
Sensitivity to sunlight: itchy or burning rashes, blisters, hives, and a sensation of heat or pain on sun-exposed areas.			√

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (canada.ca/drug-device-reporting) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

Store TWYNEO at room temperature between 15-30°C. Throw away TWYNEO 12 weeks after you obtain TWYNEO from the pharmacy or 60 days after first opening, whichever is sooner. Do not freeze TWYNEO.

Keep TWYNEO out of reach and sight of children.

If you want more information about TWYNEO:

- Talk to your healthcare professional.
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada Drug Product Database website (Drug Product Database: Access the database); the manufacturer's website (http://www.searchlightpharma.com); or by calling 1-800-667-4708.

This leaflet was prepared by Searchlight Pharma Inc.

Last Revised: 2025-12-04