NEW DRUG APPROVAL

Brand Name	Twyneo®
Generic Name	tretinoin and benzoyl peroxide
Drug Manufacturer	Sol-Gel Technologies Inc.

New Drug Approval

FDA approval date: July 26, 2021

Review designation: Standard

Type of review: Type 4 - New Combination; New Drug Application (NDA): 214902

Dispensing restriction: None

Place in Therapy

DISEASE DESCRIPTION & EPIDEMIOLOGY

Acne vulgaris is an inflammatory disorder of the pilosebaceous unit, which runs a chronic course, and it is self-limiting. Acne vulgaris is triggered by *Cutibacterium acnes* in adolescence, under the influence of normal circulating dehydroepiandrosterone (DHEA). It is a very common skin disorder which can present with inflammatory and non-inflammatory lesions chiefly on the face but can also occur on the upper arms, trunk, and back.

Acne may appear in adolescence, and it persists through the early thirties. Acne is more common in males than in females. Urban populations are more affected than rural populations. About 20% of the affected individuals develop severe acne, which results in scarring. Some races appear to be more affected than others. Asians and Africans tend to develop severe acne, but mild acne is more common in the white population. In general, populations with darker skin also tend to develop hyperpigmentation. Acne can also develop in neonates but in most cases, resolves spontaneously.

Efficacy

The safety and efficacy of Twyneo® 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® 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 non-inflammatory 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 non-inflammatory 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.

Table 1. Efficacy Results in Subjects with Acne Vulgaris at Week 12 (Trial 1 and 2)

	Trial 1		Trial 2	
	TWYNEO (N = 281)	Vehicle (N = 143)	TWYNEO (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.

Safety

ADVERSE EVENTS

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

WARNINGS & PRECAUTIONS

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

CONTRAINDICATIONS

History of serious hypersensitivity reaction to benzoyl peroxide or any component of Twyneo®.

Clinical Pharmacology

MECHANISMS 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.

Dose & Administration

ADULTS

Apply a thin layer of Twyneo® to the affected areas once daily.

PEDIATRICS

- Age 9 years and older: Apply a thin layer of Twyneo® to the affected areas once daily
- The safety and effectiveness of Twyneo® in pediatric patients below 9 years of age have not been established

GERIATRICS

Refer to adult dosing

RENAL IMPAIRMENT

N/A

HEPATIC IMPAIRMENT

N/A

Product Availability

DOSAGE FORM(S) & STRENGTH(S)

Cream: 0.1% tretinoin/3% benzoyl peroxide