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## FULL PRESCRIBING INFORMATION

### 1 NAME OF THE MEDICINAL PRODUCT

TWYNEO

### 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each gram of TWYNEO contains 1 mg (0.1%) of tretinoin and 30 mg (3%) of benzoyl peroxide.

### 3 PHARMACEUTICAL FORM

Yellow cream in a bottle with a pump.

### 4 INDICATIONS AND USAGE

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

### 5 DOSAGE AND ADMINISTRATION

- Apply a thin layer of TWYNEO 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 is for topical use only. TWYNEO is not for oral, ophthalmic, or intravaginal use.

### 6 CONTRAINDICATIONS

- TWYNEO is contraindicated in patients with a hypersensitivity to the active substances or to any of the excipients listed in section 10.
- TWYNEO is contraindicated during pregnancy.

### 7 WARNINGS AND PRECAUTIONS

#### 7.1 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 immediately and initiate appropriate therapy.

#### 7.2 Skin Irritation

Patients using TWYNEO may experience application site dryness, pain, exfoliation, erythema, dermatitis, pruritus, and irritation [*see Adverse Reactions (8.1)*]. Depending upon the severity of these adverse reactions, instruct patients to use a moisturizer, reduce the frequency of the application of TWYNEO, or discontinue use. Avoid application of TWYNEO to cuts, abrasions, eczematous, or sunburned skin.

#### 7.3 Photosensitivity

TWYNEO may increase sensitivity to ultraviolet light. 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 and loose-fitting clothes) when sun exposure cannot be avoided.

Discontinue TWYNEO at the first evidence of sunburn.

#### 7.4 This medicine contains:

Cetyl alcohol that may cause local skin reactions (e.g. contact dermatitis).

Butylated hydroxytoluene that may cause local skin reactions (e.g. contact dermatitis), or irritation to the eyes and mucous membranes.

#### 7.5 Driving and using machines.

There is no data regarding the effect of the medication on the ability to drive or operate machinery.

## 8 ADVERSE REACTIONS

### 8.1 Clinical Trials Experience

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

- Hypersensitivity [see *Warnings and Precautions (7.1)*]
- Skin Irritation [see *Warnings and Precautions (7.2)*]

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 (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  $\geq 1.0\%$  of subjects treated with TWYNEO (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  $\geq 1\%$  of Subjects with Facial Acne Vulgaris Treated with TWYNEO and More Frequently than Vehicle in Trials 1 and 2**

	<b>TWYNEO (N = 555) n (%)</b>	<b>Vehicle (N = 277) n (%)</b>
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.

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

	TWYNEO (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 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.

## 8.2 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

### Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions to the Ministry of Health, according to the National Regulation by using an online form:

<https://sideeffects.health.gov.il>

## 9 USE IN SPECIFIC POPULATIONS

### 9.1 Pregnancy

TWYNEO is contraindicated during 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 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 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 (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).

## 9.2 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 and any potential adverse effects on the breastfed child from TWYNEO or from the underlying maternal condition.

## 9.3 Pediatric Use

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 subjects 9 years of age and older received TWYNEO in the clinical studies [*see Clinical Pharmacology (11.3) and Clinical Studies (13)*].

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

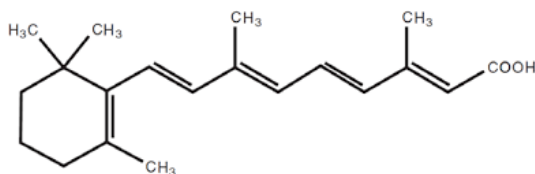
## 9.4 Geriatric Use

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

## 10 DESCRIPTION

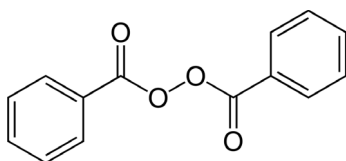
TWYNEO (tretinoin and benzoyl peroxide) cream is a yellow cream for topical use. Each gram of TWYNEO contains 1 mg (0.1%) of tretinoin and 30 mg (3%) of benzoyl peroxide. Tretinoin is a retinoid and benzoyl peroxide is an oxidizing agent.

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 benzenecarboxylate. Benzoyl peroxide has the following structural formula:



Molecular Formula: C<sub>14</sub>H<sub>10</sub>O<sub>4</sub>

Molecular Weight: 242.23

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. TWYNEO contains the following inactive ingredients: glycerin, cyclomethicone, cetyl alcohol, mono and di-glycerides, macrogol stearate type I, silicon dioxide, carbomer homopolymer type C, sodium hydroxide, anhydrous citric acid, imidurea, squalane, TEOS, hydrochloric acid, lactic acid, edetate disodium, polyquaternium-7, cetrimonium chloride, white wax, butylated hydroxytoluene and purified water.

## 11 CLINICAL PHARMACOLOGY

### 11.1 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 (RAR $\alpha$ , RAR $\beta$ , and RAR $\gamma$ ) 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.

### 11.2 Pharmacodynamics

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

### 11.3 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 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<sub>max</sub> and AUC<sub>0-24</sub> of tretinoin and its metabolites after once daily application of TWYNEO 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.

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

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

## 12 NONCLINICAL TOXICOLOGY

### 12.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

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

#### 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) 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.

### 13 CLINICAL STUDIES

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. 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 (N = 281)	Vehicle (N = 143)	TWYNEO (N = 290)	Vehicle (N = 144)
<b>IGA Success*</b>	33.9%	14.3%	26.8%	15.1%
<i>Difference from Vehicle</i>	25.7%		11.6%	
(95% CI)	(17.1%, 34.2%)		(3.6%, 19.7%)	
<b>Inflammatory Lesions</b>				
Mean‡ Absolute Change from Baseline	-21.6	-14.8	-16.2	-14.1
<i>Difference from Vehicle</i>	-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%
<i>Difference from Vehicle</i>	-22.6%		-6.8%	
(95% CI)	(-29.2%, -16.0%)		(-13.1%, -0.5%)	
<b>Non-Inflammatory Lesions</b>				
Mean‡ Absolute Change from Baseline	-29.7	-19.8	-24.2	-17.4
<i>Difference from Vehicle</i>	-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%
<i>Difference from Vehicle</i>	-20.7%		-13.0%	
<i>(95% CI)</i>	(-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.

## 14 HOW SUPPLIED/STORAGE AND HANDLING

### How Supplied

TWYNEO (tretinoin and benzoyl peroxide) cream, 0.1%/3%, is a yellow cream and is supplied as a 30-gram/50-gram bottle with a pump.

Not all package sizes may be marketed.

Shelf life: The expiry date is indicated on the packaging materials.

### Storage and Handling

- *Prior to Dispensing:* Store TWYNEO between 2°C to 8°C until dispensed to the patient.
- *After Dispensing:* Store TWYNEO below 25°C. Discard 12 weeks after date of dispensing or 60 days after first opening, whichever is sooner.
- Do not freeze.

## 15 MANUFACTURER

Sol-Gel Technologies Ltd., 7 Golda Meir St. Weizmann Science Park, Ness Ziona, 5074036, Israel

## 16 REGISTRATION HOLDER

Sol-Gel Technologies Ltd., 7 Golda Meir St. Weizmann Science Park , Ness Ziona, 5074036, Israel

### **Marketing Authorisation Number:**

178-65-37889-99

**Approved in May 2025**