

A SUPPLEMENT TO

# DermatologyTimes®

CLINICAL INSIGHTS THAT EXPAND EXPERTISE AND ADVANCE PRACTICE

SEPTEMBER 2018 | Vol. 39, Supp. 3

# ASPECTS *of* ACNE SCADDING

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# ASPECTS *of* ACNE SCARRING



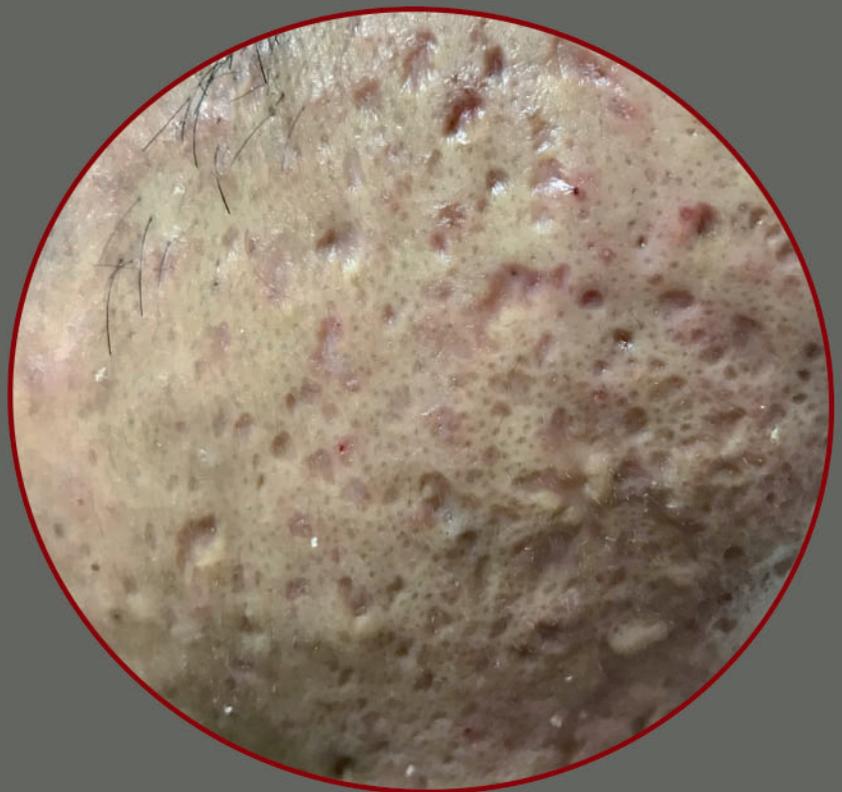
**Emerging  
treatments**

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**Why you should  
be ready to ID  
depression**

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**Antibiotic  
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### INDICATION

RETIN-A MICRO (tretinoin gel) microsphere is indicated for topical application in the treatment of acne vulgaris.

### IMPORTANT SAFETY INFORMATION

- The skin of certain individuals may become excessively dry, red, swollen or blistered during the use of RETIN-A MICRO.
- Tretinoin has been reported to cause severe irritation on eczematous skin and should be used with utmost caution in patients with this condition.
- If warranted, patients should temporarily reduce the amount or frequency of application, or discontinue use temporarily or altogether. If a reaction suggesting sensitivity occurs, use should be discontinued.
- Unprotected exposure to sunlight, including sunlamps, should be minimized during the use of RETIN-A MICRO, and patients with sunburn should be advised not to use the product until fully recovered because of heightened susceptibility to sunlight with the use of tretinoin.

- Patients should be encouraged to use a sunscreen with a SPF of 15 or higher and protective clothing over treated areas when exposure cannot be avoided.
- Weather extremes, such as wind or cold, also may be irritating to patients under treatment with tretinoin.
- The most common adverse events are mild to moderate irritation (erythema, peeling, dryness, burning/stinging, or itching of the skin).
- RETIN-A MICRO should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus, and caution should be exercised in prescribing for nursing mothers. Safety and efficacy in patients under 12 have not been established.

To report SUSPECTED ADVERSE REACTIONS, contact Ortho Dermatologics at 1-800-321-4576 or FDA at 1-800-FDA-1088 or visit [www.fda.gov/medwatch](http://www.fda.gov/medwatch).

**Please see Brief Summary of full Prescribing Information on the following page.**

**Reference: 1.** Retin-A Micro Gel Package Insert. Bridgewater, NJ: Valeant Pharmaceuticals North America LLC.

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**RETIN-A MICRO®**  
(tretinoin) Gel microsphere  
**0.06% / 0.08%**

## BRIEF SUMMARY OF PRESCRIBING INFORMATION

This Brief Summary does not include all the information needed to use RETIN-A MICRO safely and effectively. See full prescribing information for RETIN-A MICRO.

**RETIN-A MICRO® (tretinoin) gel microsphere, 0.1%, 0.08%, 0.06% and 0.04%, for topical use Initial U.S. Approval: 1971**

## INDICATIONS AND USAGE

Retin-A Micro® is a retinoid indicated for topical application in the treatment of acne vulgaris.

## CONTRAINDICATIONS

None.

## WARNINGS AND PRECAUTIONS

### Local Irritation

The skin of certain individuals may become excessively dry, red, swollen, or blistered.

Tretinoin has been reported to cause severe irritation on eczematous skin and should be used with utmost caution in patients with this condition.

If the degree of irritation warrants, patients should be directed to temporarily reduce the amount or frequency of application of the medication, discontinue use temporarily, or discontinue use all together. Efficacy at reduced frequencies of application has not been established. If a reaction suggesting sensitivity occurs, use of the medication should be discontinued.

To help limit skin irritation, patients must

- wash the treated skin gently, using a mild, non-medicated soap, and pat it dry, and
- avoid washing the treated skin too often or scrubbing it hard when washing.

Patients should apply a topical moisturizer if dryness is bothersome.

### Exposure to Ultraviolet Light or Weather Extremes

Unprotected exposure to sunlight, including sunlamps (UV light) should be avoided or minimized during the use of Retin-A Micro and patients with sunburn should be advised not to use the product until fully recovered because of heightened susceptibility to sunlight as a result of the use of tretinoin. Patients who may be required to have extended periods of UV exposure (e.g., due to occupation or sports), or those with inherent sensitivity to the sun, or those using medications that cause photosensitivity, should exercise particular caution. Use of sunscreen products (SPF 15 or higher) and protective clothing over treated areas are recommended when exposure cannot be avoided [see *Nonclinical Toxicology*].

Weather extremes, such as wind or cold, also may be irritating to tretinoin-treated skin.

## ADVERSE REACTIONS

### Clinical Trials Experience

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

#### Clinical Trials in Subjects with Acne

In separate clinical trials at each concentration, acne subjects treated with Retin-A Micro (tretinoin) Gel microsphere, 0.1% or 0.04%, over the twelve-week period showed that cutaneous irritation scores for erythema, peeling, dryness, burning/stinging, or itching peaked during the initial two weeks of therapy, decreasing thereafter.

Approximately half of the subjects treated with Retin-A Micro, 0.04%, had cutaneous irritation at Week 2. Of those subjects who did experience cutaneous side effects, most had signs or symptoms that were mild in severity (severity was ranked on a 4-point ordinal scale: 0=none, 1=mild, 2=moderate, and 3=severe). Less than 10% of patients experienced moderate cutaneous irritation and there was no severe irritation at Week 2.

In trials of Retin-A Micro (tretinoin) Gel microsphere, 0.04%, throughout the treatment period the majority of subjects experienced some degree of irritation (mild, moderate, or severe) with 1% (2/225) of subjects having scores indicative of a severe irritation; 1.3% (3/225) of subjects treated with Retin-A Micro (tretinoin) Gel microsphere, 0.04%, discontinued treatment due to irritation, which included dryness in one patient and peeling and urticaria in another.

In trials of Retin-A Micro (tretinoin) Gel microsphere, 0.1%, no more than 3% of subjects had cutaneous irritation scores indicative of severe irritation; 6% (14/224) of subjects treated with Retin-A Micro (tretinoin) Gel microsphere, 0.1%, discontinued treatment due to irritation. Of these 14 subjects, four had severe irritation after 3 to 5 days of treatment, with blistering in one subject.

In a double-blind trial with 156 acne subjects comparing 12 weeks of treatment with Retin-A Micro (tretinoin) Gel, 0.04% or 0.1%, (78 subjects each group), the most frequently reported adverse events affected the skin and subcutaneous tissue (15.4% in the 0.04% group, and 20.5% in the 0.1% group). The most prevalent of the dermatologic adverse events in the 0.04% group was skin irritation (6.4%); and in the 0.1% group skin burning (7.7%), erythema (5.1%), skin irritation (3.8%), and dermatitis (3.8%). Most adverse events were of mild intensity (63.4%), and 34.4% were moderate. One subject in each group had adverse events characterized as severe, neither were dermatologic findings and neither was characterized as related to drug by the investigator.

#### Trials in Subjects without Acne

In a half-face comparison trial conducted for up to 14 days in women with sensitive skin, but without acne, Retin-A Micro (tretinoin) Gel microsphere, 0.1%, was statistically less irritating than tretinoin cream, 0.1%. In addition, a cumulative 21-day irritation evaluation in subjects with normal skin showed that Retin-A Micro (tretinoin) Gel microsphere, 0.1%, had a lower irritation profile than tretinoin cream, 0.1%. The clinical significance of these irritation studies for patients with acne is not established. Comparable effectiveness of Retin-A Micro (tretinoin) Gel microsphere, 0.1%, and tretinoin cream, 0.1%, has not been established. The lower irritancy of Retin-A Micro (tretinoin) Gel microsphere, 0.1%, in subjects without acne may be attributable to the properties of its vehicle. The contribution of decreased irritancy by the MICROSPPONGE System has not been established. No irritation trials have been performed to compare Retin-A Micro (tretinoin) Gel microsphere, 0.04%, with either Retin-A Micro (tretinoin) Gel microsphere, 0.1%, or tretinoin cream, 0.1%.

### Postmarketing Experience

The following adverse reactions have been identified during post-approval use of Retin-A Micro Gel. 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. Temporary hyper- or hypopigmentation has been reported with repeated application of tretinoin.

## USE IN SPECIFIC POPULATIONS

### Pregnancy

#### Pregnancy Category C

There are no adequate and well-controlled studies in pregnant women. Retin-A Micro should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Thirty human cases of temporally associated congenital malformations have been reported during two decades of clinical use of tretinoin products. Although no definite pattern of teratogenicity and no causal association has been established from these cases, five of the reports describe the rare birth defect category holoprosencephaly (defects associated with incomplete midline development of the forebrain).

The significance of these spontaneous reports in terms of risk to the fetus is not known.

For purposes of comparison of the animal exposure to systemic human exposure, the MRHD applied topically is defined as 1 gram of Retin-A Micro (tretinoin) Gel microsphere, 0.1%, applied daily to a 60 kg person (0.017 mg tretinoin/kg body weight).

Pregnant rats were treated with Retin-A Micro (tretinoin) Gel microsphere, 0.1%, at daily dermal doses of 0.5 to 1.0 mg/kg/day tretinoin on gestation days 6-15. Alterations were seen in vertebrae and ribs of offspring at 5 to 10 times the MRHD based on the body surface area (BSA) comparison.

Pregnant New Zealand White rabbits were treated with Retin-A Micro (tretinoin) Gel microsphere, 0.1%, at daily dermal doses of 0.2, 0.5, and 1.0 mg/kg/day tretinoin on gestation days 7-19. Doses were administered topically for 24 hours a day while wearing Elizabethan collars to prevent ingestion of the drug. Increased incidences of certain alterations, including domed head and hydrocephaly, typical of retinoid-induced fetal malformations in this species, were observed at 0.5 and 1.0 mg/kg/day. Similar malformations were not observed at 0.2 mg/kg/day, 4 times the MRHD based on BSA comparison. Other pregnant rabbits exposed topically for six hours per day to 0.5 or 1.0 mg/kg/day tretinoin while restrained in stocks to prevent ingestion, did not show any malformations at doses up to 19 times (1.0 mg/kg/day) the MRHD based on BSA comparison, but fetal resorptions were increased at 0.5 mg/kg (10 times the MRHD based on BSA comparison).

Oral tretinoin has been shown to cause malformations in rats, mice, rabbits, hamsters, and nonhuman primates.

Tretinoin induced fetal malformations in Wistar rats when given orally at doses greater than 1 mg/kg/day (10 times the MRHD based on BSA comparison). In the cynomolgus monkey, fetal malformations were reported for doses of 10 mg/kg/day but none were observed at 5 mg/kg/day (95 times the MRHD based on BSA comparison), although increased skeletal variations were observed at all doses. Dose-related increases in embryolethality and abortion also were reported. Similar results have also been reported in pigtail macaques.

In oral peri- and postnatal development studies in rats with tretinoin, decreased survival of neonates and growth retardation were observed at doses in excess of 2 mg/kg/day (19 times the MRHD based on BSA comparison).

### Nonteratogenic effects on fetus

Oral tretinoin has been shown to be fetotoxic in rats when administered at doses 24 times the MRHD based on BSA comparison.

Topical tretinoin has been shown to be fetotoxic in rabbits when administered at doses 10 times the MRHD based on BSA comparison.

### Nursing Mothers

It is not known whether tretinoin and/or its metabolites are excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Retin-A Micro is administered to a nursing woman.

### Pediatric Use

Safety and effectiveness in children below the age of 12 have not been established.

### Geriatric Use

Safety and effectiveness in a geriatric population have not been established. Clinical trials of Retin-A Micro (tretinoin) Gel microsphere, 0.1% and 0.04%, did not include sufficient numbers of subjects aged 65 and over to determine whether they responded differently from younger subjects.

## OVERDOSAGE

Oral ingestion of large amounts of the drug may lead to the same side effects as those associated with excessive oral intake of Vitamin A.

## NONCLINICAL TOXICOLOGY

### Carcinogenesis, Mutagenesis, Impairment of Fertility

Dermal carcinogenicity testing has not been performed with Retin-A Micro (tretinoin) Gel microsphere, 0.1%, 0.08%, 0.06% or 0.04%.

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. These concentrations are near the tretinoin concentration of the 0.04% and 0.1% clinical formulations. 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 tretinoin, respectively. These doses are two and four times the MRHD based on BSA comparison.

The biological significance of these findings is not clear because they occurred at doses that exceeded the dermal maximally tolerated dose 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 (0.1 times the MRHD based on BSA comparison). Studies in hairless albino mice suggest that concurrent exposure to tretinoin may enhance the tumorigenic potential of carcinogenic doses of UVB and UVA light from a solar simulator. This effect has been confirmed in a later study in pigmented mice, and dark pigmentation did not overcome the enhancement of photocarcinogenesis by 0.05% tretinoin. Although the significance of these studies to humans is not clear, patients should minimize exposure to sunlight or artificial ultraviolet irradiation sources [see *Warnings and Precautions*].

The genotoxic potential of tretinoin was evaluated in the Ames assay and in the in vivo mouse micronucleus assay, both of which were negative.

The components of the microspheres have shown potential for genetic toxicity and fetal malformation. EGDMA, a component of the excipient acrylates copolymer, was positive for induction of structural chromosomal aberrations in the in vitro chromosomal aberration assay in mammalian cells in the absence of metabolic activation, and negative for genetic toxicity in the Ames assay, and the in vivo mouse micronucleus assay.

In oral fertility studies in rats with tretinoin, the no-observable effect level was 2 mg/kg/day (19 times the MRHD based on BSA comparison).

## PATIENT COUNSELING INFORMATION

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

### Manufactured for:

Valeant Pharmaceuticals North America LLC  
Bridgewater, NJ 08807 USA

### By:

Valeant Pharmaceuticals International, Inc.  
Laval, Quebec H7L 4A8, Canada

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Based on 9612500

October 2017 RAM.0025.USA.17

# Topical therapy reduces scar formation in acne

## COMBINATION GEL MAY OFFER AN ALTERNATIVE TO RETINOID TREATMENT

by Ingrid Torjesen | Staff Correspondent

**T**he topical gel adapalene 0.3%/benzoyl peroxide 2.5% gel (A0.3/BPO2.5) has been found to prevent and reduce atrophic scar formation in acne, according to a 24-week study published in the *American Journal of Clinical Dermatology*.<sup>1</sup>

Facial scarring is frequent in patients with acne, especially if acne is not treated early and effectively. Atrophic scars, involving loss of tissue, are the most frequent type. Treatment for scarring often involves invasive procedures, such as laser resurfacing, volumizing fillers, dermabrasion, and excisional techniques, such as punch excision, punch elevation and punch replacement, so reducing the occurrence and severity of scars is preferable.

Adapalene 0.3%/benzoyl peroxide 2.5% fixed-dose combination gel (A0.1/BPO2.5 gel) combines a retinoid with benzoyl peroxide, which exhibits potent and

90.1%

Patients were satisfied/very satisfied with the A0.3/BPO2.5 treatment compared to 59 treated with vehicle gel.

rapid bactericidal effect on *Cutibacterium* (formerly *Propionibacterium*) acnes. Topical retinoids target multiple aspects of acne pathophysiology,

including normalizing infundibular hyperkeratinization and reducing inflammation, and have a unique class action in reducing the formation of acne precursor lesions and limiting the development of new lesions. However, although there is considerable evidence supporting the efficacy of topical retinoid treatments for primary acne lesions, few previous studies have looked at their impact on reducing acne scars, so researchers set out to look at the impact of A0.1/BPO2.5 gel.

The study included 67 patients aged 16–35 years with Fitzpatrick skin phototype I–IV who had moderate-to-severe facial acne, and distribution of inflammatory and non-inflammatory lesions. Atrophic acne scarring on their faces was roughly symmetrical.

At the start of the study patients had an average of approximately 40 acne lesions and 12 scars per half face. All patients had an Investigator's Global Assessment (IGA) score of three or four on both sides of their face, at least 25 inflammatory lesions with ten or more on each side of their face (excluding the nose); and ten or more atrophic acne scars greater than 2 mm (for whole face excluding the nose).

The patients, were enrolled at five centers in Canada

### Take AWAYS

The study included 67 patients between 16–35 years.

By week 24, half of treated patients had 3.8 fewer scars.

Further studies are needed in patients with severe acne.

and one in France, and were randomized to apply A0.3/BPO2.5 on half of their face and the vehicle gel on the other half of their face every evening for 24 weeks. They were asked to apply two pea-sized amounts per half face. None of the patients were using systemic therapy. Fifty four (80.6%) of the 67 patients completed the study between May 2016 and November 2017.

The results showed that by week 24, half faces treated with A0.3/BPO2.5 had 3.8 fewer scars than half faces treated with the vehicle gel – a mean of 9.5 scars versus 13.3 respectively. The scar count had fallen by 15.5% for half faces treated with A0.3/BPO2.5 while it had increased by 14.4% for half faces to which the vehicle gel was applied, meaning there was an approximate 30% difference in scar count between the two treatments.

There was also a 16.5% difference between the proportion of half faces treated with A0.3/BPO2.5 and the proportion treated with vehicle deemed clear/almost clear using Scar Global Assessment (SGA) at 24

and week 24 on the A0.3/BPO2.5 side,” said Brigitte Dréno, of the University of Nantes, Nantes in France. “The progressive incremental increase in efficacy and effect on scars observed with A0.3/BPO2.5 over 24 weeks highlights the importance of a longer duration of treatment. In fact, three months may be sufficient to observe resolution of the primary acne lesions, but the remodeling processes occur slowly, and six months may be required to induce significant stimulation of the dermal fibroblasts and collagen and clinically observe an effect on scars.”

No serious or severe adverse events were reported. Treatment-related adverse events were reported by 20.9% of patients for A0.3/BPO2.5 gel use and 9% for vehicle gel, and the most frequent problem was skin irritation, particularly during the first few weeks. However, by week 24, 44.3% of patients were not bothered at all by side effects from A0.3/BPO2.5 and 77.0% were not bothered by them with vehicle gel. Only two patients dropped out because of adverse events.

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## **“ALTHOUGH THERE IS CONSIDERABLE EVIDENCE SUPPORTING THE EFFICACY OF TOPICAL RETINOID TREATMENTS FOR PRIMARY LESIONS OF ACNE, FEW PREVIOUS STUDIES HAVE LOOKED AT THEIR IMPACT ON REDUCING ACNE SCARS SO RESEARCHERS SET OUT TO LOOK AT THE IMPACT OF A0.1/BPO2.5 GEL.”**

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weeks; 32.9% of half faces treated with A0.3/BPO2.5 were considered clear/almost clear compared with 16.4% of those treated with vehicle gel ( $p < 0.01$ ).

Reductions in acne lesions were observed for both gels, but were far greater for A0.3/BPO2.5. The reduction in inflammatory lesions with use of A0.3/BPO2.5 was 86.7% compared with 57.9% for vehicle gel, and for non-inflammatory lesions it was 86.7% for A0.3/BPO2.5 versus 57.9% for vehicle gel. Global improvement of acne occurred with both gels, but significantly more subjects were IGA clear/almost clear with A0.3/BPO2.5 than with vehicle gel at 24 weeks — 64.2% compared with 19.4%, a difference of 45%. Improvements in skin roughness and texture were also greater with the A0.3/BPO2.5 gel.

Reduction in inflammatory lesion counts and percentage IGA clear/almost clear skin at week 12 in this study were very similar to reductions observed in a previous 12-week phase 3 study,<sup>2</sup> the researchers said.

“By continuing up to 24 weeks in our study, the percentage of subjects with clear/almost clear skin continued to increase and doubled between week 12

The majority of patients (90.1%) said they were satisfied or very satisfied with the A0.3/BPO2.5 treatment compared with 59.0% for vehicle gel.

Most patients included in the study had moderate acne (92.5% IGA 3 at the start), so further studies are needed, especially in patients with severe acne “to confirm these promising results and evaluate the best treatment regimen to further reduce atrophic acne scars”, she said. ◀

### REFERENCES

- 1 Dréno, B., Bissonnette, R., Gagné-Henley, A. et al. Prevention and Reduction of Atrophic Acne Scars with Adapalene 0.3%/Benzoyl Peroxide 2.5% Gel in Subjects with Moderate or Severe Facial Acne: Results of a 6-Month Randomized, Vehicle-Controlled Trial Using Intra-Individual Comparison. *Am J Clin Dermatol* (2018) 19: 275. <https://doi.org/10.1007/s40257-018-0352-y>
- 2 Stein Gold L, Weiss J, Rueda MJ, et al. Moderate and severe inflammatory acne vulgaris effectively treated with single-agent therapy by a new fixed-dose combination adapalene 0.3%/benzoyl peroxide 2.5% gel: a randomized, double-blind, parallel-group, controlled study. *Am J Clin Dermatol*. 2016;17(3):293–303. CrossRefPubMedPubMedCentral-Google Scholar
- 3 Dréno, B., Bissonnette, R., et al., *American Journal of Clinical Dermatology*.

# Study examines current, emerging acne treatments

by Whitney J. Palmer | Staff Correspondent

**F**or the 80% of patients treated for acne vulgaris, scarring can be problematic. Atrophic scars are most common, but treatment options are available.

According to research published in the *Journal of Clinical and Aesthetic Dermatology*, including patients in approaches that evaluate scarring types and their desired outcomes can yield high patient satisfaction.

Ensure that treatment plans include in-depth conversations about patients' treatment goals, their concerns and thoughts about protocols, the authors wrote. It's also critical they understand any possible therapy limitations.

"Expectation management is important in approaching the discussion of treatment options," they wrote. "Complete resolution of acne scarring is the exception rather than the rule. Patients should be well

patients will be enhanced with a better understanding of risk factors for severe acne and acne scar formation."

For example, data shows autologous platelet rich plasma (PRP) accelerates wound healing, the authors wrote. It improves tissue repair by releasing growth factors, cytokines, and chemokines. It works well when paired with microneedling due to the pathway for wounds to absorb PRP. When used as an intradermal injection and a topical application after fractional ablative CO2 therapy, laser-damaged

## Take AWAYS

80% of patients suffer from acne scarring.

Treatment options should consider the stages of acne scarring.

If possible, identify patients who are at-risk for scarring before treatment.

**"A PATIENT-CENTERED, MULTI-STEP APPROACH THAT TAKES INTO ACCOUNT THE TYPE OF ACNE SCARRING AND PATIENT GOALS WILL YIELD THE BEST COSMETIC RESULTS AND HIGHEST PATIENT SATISFACTION."**

Connolly D, et al.

Journal of Clinical and Aesthetic Dermatology

informed about the potential risks, including post-procedure erythema, infection, poor wound healing, hyperpigmentation, and paradoxically, scarring."

Recent studies indicate there are new therapies to reduce the risk and impact of acne scarring. Diligently employing these protocols will produce the best effects.

"Therapy should be maintained until resolution of persistent inflammation and control of new lesion emergence," the authors wrote. "Determining at-risk

skin recovers better and acne scars are less obvious.

Additionally, human-derived cells show promise in affecting acne scars. Multipotential mesenchymal stem cells (MSC) from umbilical cord blood and from adipose cells can promote wound healing and are currently being evaluated for safety. ◀

## REFERENCES

Connolly D, Linh Vu H, Mariwalla K, Saedi N, Acne Scarring — Pathogenesis, Evaluation, and Treatment Options, The Journal of Clinical and Aesthetic Dermatology (2017).

## TREATMENT OPTIONS FOR ACNE SCARRING

To be effective, therapeutic protocols should consider multiple aspects of scarring. First, consider any erythema, or skin redness, and then determine if generalized or individual scars are present. Then, focus on the atrophic scars.

After evaluating your patient, consider these treatment options:

- 1.** By using light converted to heat, pulsed dye laser destroys blood vessels near the skin's surface to reduce redness. Research shows a 585 nm flashlamp-pumped PDL decreases redness and scarring by 68 percent after one or two treatments compared to untreated skin after six weeks. It also induces collagen remodeling, improving scar appearances.
- 2.** Lasers for acne scarring treatment use monochromatic light to deliver heat, stimulating dermal fibroblasts to replace lost collagen and elastin. Lasers fall into two categories: ablative and non-ablative.
- 3.** Traditional ablative lasers are effective in treating scar appearance, but they also cause significant discomfort, and increased risk of dyspigmentation, scarring, and infections with prolonged healing.
- 4.** The traditional 10,600 nm carbon dioxide laser emits infrared light, creating immediate improvement in skin tone, texture, and appearance after one treatment. Clinical tests show a 69 percent improvement after one month and 75 percent after 18 months. Additionally, the traditional 2,940 nm Er:YAG laser is less aggressive and is more easily absorbed by the water in the skin. It's comparably to the carbon dioxide laser and shows good results in patients with pitted facial scars and dark skin types — 36 percent excellent improvement and 57 percent good improvement.
- 5.** Non-ablative lasers target water in the skin and deliver photothermal energy without ablating the overlying epidermis. Consequently, patients may experience less skin damage and a shorter recovery. For example, the 1,064 nm Nd:YAG laser prompts collagen remodeling in the papillary and reticular dermis. So far, it's been shown to be effective and introduce minimal pigment alterations in patients with dark skin types. Atrophic scar improvement ranges from 20-30 percent after eight sessions.
- 6.** New therapies, such as picosecond lasers, deliver shorter duration, lower energy pulses, leading to fewer side effects. One option, Picosure® has FDA & drug administration approval to treat tattoos and pigmented lesions and improves the appearance and texture of atrophic rolling scars.
- 7.** Another treatment option, dermabrasion to remove the epidermis with or without the dermis and significantly define scar edges. It's effective for well-defined scars with distinct borders and broad-based scars with indistinct borders, but not for icepick or deep boxcar scars.
- 8.** Chemical peels can treat small depressed scars. Medium-depth peels result in moderate clinical improvement of 51-75 percent clearance, but controlling peel depth is difficult.
- 9.** Microneedling skin pricks eventually lead to collagen production, making skin smoother and improving rolling acne scars. It's also advantageous because it keeps the epidermis in tact. Full results appear within 8-12 months. This treatment option also enables the skin to absorb topical agents to improve cosmetic results.
- 10.** Injectable fillers can bolster soft tissue in soft atrophic scars, but they can lead to infection, pain, redness, lumps, swelling, and abscesses. Temporary fillers last a few months, requiring multiple treatments. Semi-permanent fillers last up to two years, showing significant scar improvement. And, permanent fillers can last several years. However, no evidence exists on scar improvement impact.

## Are you equipped to identify depression in your acne patient?

by Whitney J. Palmer | Staff Correspondent

**O**f all dermatological conditions, acne vulgaris is the most common. While its outward affects are easily noticeable, the internal ones — reduced self-esteem, decreased self-image, and increased anxiety — often go undiagnosed. As a dermatologist, though, you can help reverse those effects.

In the United States, approximately 85 percent of adolescents and two-thirds of adults over age 18 struggle with acne vulgaris. It's presence, according to a literature review published in the *International Journal of Women's Dermatology*, is associated with higher rates of depression, anxiety, social isolation, suicidal ideation, and suicide attempts. While women and individuals with severe acne vulgaris are most commonly affected, it can have significant negative impacts on anyone.

Of the affected group, 70-80 percent use self-prescribed topical treatments, but only between 5-28 percent seek care from a dermatologist. Patients with moderate-to-severe acne vulgaris (approximately 61 percent of them) are more likely to pursue medical intervention. Overall, individuals with AV take an average of 22.2 months to see a professional.

**"EFFECTIVE TREATMENT IMPROVES PATIENTS' SELF-ESTEEM, AND, AS DERMATOLOGISTS, WE HAVE AN ARMAMENTARIUM OF TREATMENT OPTIONS TO IMPROVE ACE VULGARIS."**

Gallitano SM, et al.

International Journal of Women's Dermatology

You can alleviate the stress for patient who come to see you, the study authors wrote.

"As dermatologists, we are trained in managing acne. We can provide early and effective treatment that improves the physical and psychological effects," the authors wrote. "It is up to us to bridge the gap between those suffering from acne and their access to medical treatment."

Still, be prepared for up to half being unable to follow treatment plans due to financial reasons, the authors wrote.

### ASSESSING ACNE VULGARIS

According to the literature review of 13 studies on acne vulgaris and self-esteem from 11 countries, nearly 90 percent of patients report feeling embarrassed by the condition. The earlier acne vulgaris shows up, the younger the age at which a patient will begin to report self-esteem and self-image problems. However, older adults aren't immune to the societal implications of acne.

Middle school children are among the hardest hit with decreased self-esteem. Not only are they already dealing with changing hormones, but this age group is also prone to finding and latching on to reasons to socially isolate and reject someone. In fact, the authors report, moderate-to-severe acne vulgaris in this age group is linked to higher incidences of bullying and

### Take AWAYS

Acne vulgaris is associated with higher rates of depression, anxiety, social isolation, suicidal ideation, and suicide attempts.

90 percent of patients report feeling embarrassed by the condition.

Early onset of acne vulgaris is associated with longer lasting low self-esteem.

**RETIN-A MICRO 0.06%**

## HOW MANY MORE FACES CAN YOU REACH?

**MORE PATIENTS THAN EVER.** RETIN-A MICRO 0.06% gives you more treatment options for your patients, with microsphere technology and pump-controlled dosing.<sup>1</sup>

**LOWER  
STRENGTH**

**HIGHER  
STRENGTH**

SEE TOLERABILITY AND EFFICACY RESULTS AT [RETINAMICRO.COM](http://RETINAMICRO.COM)

### INDICATION

RETIN-A MICRO (tretinoin gel) microsphere is indicated for topical application in the treatment of acne vulgaris.

### IMPORTANT SAFETY INFORMATION

- The skin of certain individuals may become excessively dry, red, swollen or blistered during the use of RETIN-A MICRO.
- Tretinoin has been reported to cause severe irritation on eczematous skin and should be used with utmost caution in patients with this condition.
- If warranted, patients should temporarily reduce the amount or frequency of application, or discontinue use temporarily or altogether. If a reaction suggesting sensitivity occurs, use should be discontinued.
- Unprotected exposure to sunlight, including sunlamps, should be minimized during the use of RETIN-A MICRO, and patients with sunburn should be advised not to use the product until fully recovered because of heightened susceptibility to sunlight with the use of tretinoin.

**Reference: 1.** Retin-A Micro Gel Package Insert. Bridgewater, NJ: Valeant Pharmaceuticals North America LLC.

- Patients should be encouraged to use a sunscreen with a SPF of 15 or higher and protective clothing over treated areas when exposure cannot be avoided.
- Weather extremes, such as wind or cold, also may be irritating to patients under treatment with tretinoin.
- The most common adverse events are mild to moderate irritation (erythema, peeling, dryness, burning/stinging, or itching of the skin).
- RETIN-A MICRO should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus, and caution should be exercised in prescribing for nursing mothers. Safety and efficacy in patients under 12 have not been established.

To report SUSPECTED ADVERSE REACTIONS, contact Ortho Dermatologics at 1-800-321-4576 or FDA at 1-800-FDA-1088 or visit [www.fda.gov/medwatch](http://www.fda.gov/medwatch).

**Please see Brief Summary of full Prescribing Information on the following page.**

Ortho | Dermatologics

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**RETIN-A MICRO<sup>®</sup>**  
(tretinoin) Gel microsphere  
**0.06% / 0.08%**

## BRIEF SUMMARY OF PRESCRIBING INFORMATION

This Brief Summary does not include all the information needed to use RETIN-A MICRO safely and effectively. See full prescribing information for RETIN-A MICRO.

RETIN-A MICRO® (tretinoin) gel microsphere, 0.1%, 0.08%, 0.06% and 0.04%, for topical use  
Initial U.S. Approval: 1971

## INDICATIONS AND USAGE

Retin-A Micro® is a retinoid indicated for topical application in the treatment of acne vulgaris.

## CONTRAINDICATIONS

None.

## WARNINGS AND PRECAUTIONS

### Local Irritation

The skin of certain individuals may become excessively dry, red, swollen, or blistered.

Tretinoin has been reported to cause severe irritation on eczematous skin and should be used with utmost caution in patients with this condition.

If the degree of irritation warrants, patients should be directed to temporarily reduce the amount or frequency of application of the medication, discontinue use temporarily, or discontinue use all together. Efficacy at reduced frequencies of application has not been established. If a reaction suggesting sensitivity occurs, use of the medication should be discontinued.

To help limit skin irritation, patients must

- wash the treated skin gently, using a mild, non-medicated soap, and pat it dry, and
- avoid washing the treated skin too often or scrubbing it hard when washing.

Patients should apply a topical moisturizer if dryness is bothersome.

### Exposure to Ultraviolet Light or Weather Extremes

Unprotected exposure to sunlight, including sunlamps (UV light) should be avoided or minimized during the use of Retin-A Micro and patients with sunburn should be advised not to use the product until fully recovered because of heightened susceptibility to sunlight as a result of the use of tretinoin. Patients who may be required to have extended periods of UV exposure (e.g., due to occupation or sports), or those with inherent sensitivity to the sun, or those using medications that cause photosensitivity, should exercise particular caution. Use of sunscreen products (SPF 15 or higher) and protective clothing over treated areas are recommended when exposure cannot be avoided [see *Nonclinical Toxicology*].

Weather extremes, such as wind or cold, also may be irritating to tretinoin-treated skin.

## ADVERSE REACTIONS

### Clinical Trials Experience

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

#### Clinical Trials in Subjects with Acne

In separate clinical trials for each concentration, acne subjects treated with Retin-A Micro (tretinoin) Gel microsphere, 0.1% or 0.04%, over the twelve-week period showed that cutaneous irritation scores for erythema, peeling, dryness, burning/stinging, or itching peaked during the initial two weeks of therapy, decreasing thereafter.

Approximately half of the subjects treated with Retin-A Micro, 0.04%, had cutaneous irritation at Week 2. Of those subjects who did experience cutaneous side effects, most had signs or symptoms that were mild in severity (severity was ranked on a 4-point ordinal scale: 0=none, 1=mild, 2=moderate, and 3=severe). Less than 10% of patients experienced moderate cutaneous irritation and there was no severe irritation at Week 2.

In trials of Retin-A Micro (tretinoin) Gel microsphere, 0.04%, throughout the treatment period the majority of subjects experienced some degree of irritation (mild, moderate, or severe) with 1% (2/225) of subjects having scores indicative of a severe irritation; 1.3% (3/225) of subjects treated with Retin-A Micro (tretinoin) Gel microsphere, 0.04%, discontinued treatment due to irritation, which included dryness in one patient and peeling and urticaria in another.

In trials of Retin-A Micro (tretinoin) Gel microsphere, 0.1%, no more than 3% of subjects had cutaneous irritation scores indicative of severe irritation; 6% (14/224) of subjects treated with Retin-A Micro (tretinoin) Gel microsphere, 0.1%, discontinued treatment due to irritation. Of these 14 subjects, four had severe irritation after 3 to 5 days of treatment, with blistering in one subject.

In a double-blind trial with 156 acne subjects comparing 12 weeks of treatment with Retin-A Micro (tretinoin) Gel, 0.04% or 0.1%, (78 subjects each group), the most frequently reported adverse events affected the skin and subcutaneous tissue (15.4% in the 0.04% group, and 20.5% in the 0.1% group). The most prevalent of the dermatologic adverse events in the 0.04% group was skin irritation (6.4%); and in the 0.1% group skin burning (7.7%), erythema (5.1%), skin irritation (3.8%), and dermatitis (3.8%). Most adverse events were of mild intensity (63.4%), and 34.4% were moderate. One subject in each group had adverse events characterized as severe, neither were dermatologic findings and neither was characterized as related to drug by the investigator.

#### Trials in Subjects without Acne

In a half-face comparison trial conducted for up to 14 days in women with sensitive skin, but without acne, Retin-A Micro (tretinoin) Gel microsphere, 0.1%, was statistically less irritating than tretinoin cream, 0.1%. In addition, a cumulative 21-day irritation evaluation in subjects with normal skin showed that Retin-A Micro (tretinoin) Gel microsphere, 0.1%, had a lower irritation profile than tretinoin cream, 0.1%. The clinical significance of these irritation studies for patients with acne is not established. Comparable effectiveness of Retin-A Micro (tretinoin) Gel microsphere, 0.1%, and tretinoin cream, 0.1%, has not been established. The lower irritancy of Retin-A Micro (tretinoin) Gel microsphere, 0.1%, in subjects without acne may be attributable to the properties of its vehicle. The contribution of decreased irritancy by the MICROSPONGE System has not been established. No irritation trials have been performed to compare Retin-A Micro (tretinoin) Gel microsphere, 0.04%, with either Retin-A Micro (tretinoin) Gel microsphere, 0.1%, or tretinoin cream, 0.1%.

### Postmarketing Experience

The following adverse reactions have been identified during post-approval use of Retin-A Micro Gel. 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.

Temporary hyper- or hypopigmentation has been reported with repeated application of tretinoin.

## USE IN SPECIFIC POPULATIONS

### Pregnancy

#### Pregnancy Category C

There are no adequate and well-controlled studies in pregnant women. Retin-A Micro should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Thirty human cases of temporally associated congenital malformations have been reported during two decades of clinical use of tretinoin products. Although no definite pattern of teratogenicity and no causal association has been established from these cases, five of the reports describe the rare birth defect category holoprosencephaly (defects associated with incomplete midline development of the forebrain).

The significance of these spontaneous reports in terms of risk to the fetus is not known.

For purposes of comparison of the animal exposure to systemic human exposure, the MRHD applied topically is defined as 1 gram of Retin-A Micro (tretinoin) Gel microsphere, 0.1%, applied daily to a 60 kg person (0.017 mg tretinoin/kg body weight).

Pregnant rats were treated with Retin-A Micro (tretinoin) Gel microsphere, 0.1%, at daily dermal doses of 0.5 to 1.0 mg/kg/day tretinoin on gestation days 6-15. Alterations were seen in vertebrae and ribs of offspring at 5 to 10 times the MRHD based on the body surface area (BSA) comparison.

Pregnant New Zealand White rabbits were treated with Retin-A Micro (tretinoin) Gel microsphere, 0.1%, at daily dermal doses of 0.2, 0.5, and 1.0 mg/kg/day tretinoin on gestation days 7-19. Doses were administered topically for 24 hours a day while wearing Elizabethan collars to prevent ingestion of the drug. Increased incidences of certain alterations, including domed head and hydrocephaly, typical of retinoid-induced fetal malformations in this species, were observed at 0.5 and 1.0 mg/kg/day. Similar malformations were not observed at 0.2 mg/kg/day, 4 times the MRHD based on BSA comparison. Other pregnant rabbits exposed topically for six hours per day to 0.5 or 1.0 mg/kg/day tretinoin while restrained in stocks to prevent ingestion, did not show any malformations at doses up to 19 times (1.0 mg/kg/day) the MRHD based on BSA comparison, but fetal resorptions were increased at 0.5 mg/kg (10 times the MRHD based on BSA comparison).

Oral tretinoin has been shown to cause malformations in rats, mice, rabbits, hamsters, and nonhuman primates.

Tretinoin induced fetal malformations in Wistar rats when given orally at doses greater than 1 mg/kg/day (10 times the MRHD based on BSA comparison). In the cynomolgus monkey, fetal malformations were reported for doses of 10 mg/kg/day but none were observed at 5 mg/kg/day (95 times the MRHD based on BSA comparison), although increased skeletal variations were observed at all doses. Dose-related increases in embryolethality and abortion also were reported. Similar results have also been reported in pigtail macaques.

In oral peri- and postnatal development studies in rats with tretinoin, decreased survival of neonates and growth retardation were observed at doses in excess of 2 mg/kg/day (19 times the MRHD based on BSA comparison).

#### Nonteratogenic effects on fetus

Oral tretinoin has been shown to be fetotoxic in rats when administered at doses 24 times the MRHD based on BSA comparison.

Topical tretinoin has been shown to be fetotoxic in rabbits when administered at doses 10 times the MRHD based on BSA comparison.

### Nursing Mothers

It is not known whether tretinoin and/or its metabolites are excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Retin-A Micro is administered to a nursing woman.

### Pediatric Use

Safety and effectiveness in children below the age of 12 have not been established.

### Geriatric Use

Safety and effectiveness in a geriatric population have not been established. Clinical trials of Retin-A Micro (tretinoin) Gel microsphere, 0.1% and 0.04%, did not include sufficient numbers of subjects aged 65 and over to determine whether they responded differently from younger subjects.

## OVERDOSAGE

Oral ingestion of large amounts of the drug may lead to the same side effects as those associated with excessive oral intake of Vitamin A.

## NONCLINICAL TOXICOLOGY

### Carcinogenesis, Mutagenesis, Impairment of Fertility

Dermal carcinogenicity testing has not been performed with Retin-A Micro (tretinoin) Gel microsphere, 0.1%, 0.08%, 0.06% or 0.04%.

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. These concentrations are near the tretinoin concentration of the 0.04% and 0.1% clinical formulations. 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 tretinoin, respectively. These doses are two and four times the MRHD based on BSA comparison.

The biological significance of these findings is not clear because they occurred at doses that exceeded the dermal maximally tolerated dose 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 (0.1 times the MRHD based on BSA comparison). Studies in hairless albino mice suggest that concurrent exposure to tretinoin may enhance the tumorigenic potential of carcinogenic doses of UVB and UVA light from a solar simulator. This effect has been confirmed in a later study in pigmented mice, and dark pigmentation did not overcome the enhancement of photocarcinogenesis by 0.05% tretinoin. Although the significance of these studies to humans is not clear, patients should minimize exposure to sunlight or artificial ultraviolet irradiation sources [see *Warnings and Precautions*].

The genotoxic potential of tretinoin was evaluated in the Ames assay and in the in vivo mouse micronucleus assay, both of which were negative.

The components of the microspheres have shown potential for genetic toxicity and fetal malformation. EGDMA, a component of the excipient acrylates copolymer, was positive for induction of structural chromosomal aberrations in the in vitro chromosomal aberration assay in mammalian cells in the absence of metabolic activation, and negative for genetic toxicity in the Ames assay, and the in vivo mouse micronucleus assay.

In oral fertility studies in rats with tretinoin, the no-observable effect level was 2 mg/kg/day (19 times the MRHD based on BSA comparison).

## PATIENT COUNSELING INFORMATION

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

### Manufactured for:

Valeant Pharmaceuticals North America LLC  
Bridgewater, NJ 08807 USA

### By:

Valeant Pharmaceuticals International, Inc.  
Laval, Quebec H7L 4A8, Canada

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Based on 9612500 October 2017 RAM.0025.USA.17

**Depression** CONTINUED FROM PAGE 8

taunting, such as verbal and physical aggression, as well as social exclusion.

The authors also report nearly 62 percent of adults over age 18 experience increased embarrassment and greater self-consciousness if they develop acne vulgaris.

**WHAT YOU CAN DO**

According to the American Academy of Dermatology (AAD), one of the most important steps you can take is strengthening your relationships with primary care providers, encouraging them to refer their acne vulgaris patients to you as early as possible. To see satisfactory results, the AAD recommends these

linked to reduced anxiety and depression, as well as augmented self-esteem. Be sure, though, to manage patient expectations about how long the medication will take to work and what differences he or she will be able to see in their skin's appearance.

In addition, discuss camouflage techniques that can cover their acne vulgaris as a strategy to help reduce how noticeable the condition is.

**SUICIDE**

Patients suffering from moderate-to-severe acne vulgaris also face a two to three times greater risk of suicidal thoughts, the authors wrote.

While treating patients for these thoughts or suicide

**“A DERMATOLOGIST WHO PRESCRIBES APPROPRIATE MEDICAL THERAPY, MANAGES PATIENT EXPECTATIONS, AND EDUCATES PATIENTS ON THE RESULTS AND TIMING WILL BEST HELP MEET PATIENTS’ MEDICAL AND PSYCHOLOGICAL NEEDS.”**

Gallitano SM, et al.

International Journal of Women's Dermatology

patients seek care in a medical setting.

In many cases, patients perceive their acne vulgaris to be far worse than it is, so you can answer their questions, allay their frustrations and fears, such as being afraid their acne vulgaris is contagious, and establish a therapeutic protocol. At their first appointment, have patients fill out forms that outline their self-care so you know what steps they're already taking to address their acne vulgaris and where to go from there.

“Because both objective and subjective severity can influence a patient's self-image, we recommend that patients evaluate their own acne vulgaris,” the authors wrote. “If they perceive their acne as being more severe than an objective examination suggests, a more aggressive approach in stepping up therapies to help them achieve their goals may be warranted.”

Even individuals with mild acne can benefit from an isotretinoin prescription, the authors wrote, because it not only improves the condition, but it has also been

attempts is outside your medical purview, the authors did offer guidance on how to identify patients with these struggles. If you encounter patients exhibiting these behaviors, notify their primary care providers:

- ▶ Poor eye contact
- ▶ Angry or negative verbalization
- ▶ Poor self-care
- ▶ Poor hygiene
- ▶ Compulsive behaviors
- ▶ Self-mutilating behaviors

Ultimately, the authors wrote, the goal of treating acne vulgaris isn't simply improving the skin's outward appearance. It's also addressing the emotional and psychological implications the condition can prompt with dermatologists being in a unique position to do so successfully.

“Perhaps most importantly, a dermatologist who prescribes appropriate medical therapy, manages patient expectations, and educates patients on the results and timing will best help meet patients' medical and psychological needs,” the authors wrote. “Effective treatment improves patients' self-esteem, and, as dermatologists, we have an armamentarium of treatment options to improve acne vulgaris.” ◀

**CITATION**

Gallitano SM, Berson DS, How Acne Bumps Cause the Blues: The Influence of Acne Vulgaris on Self-Esteem, International Journal of Women's Dermatology (2018). DOI:10.1016/j.ijwd.2017.10.004

**DEPRESSIVE SIGNS TO LOOK FOR IN YOUR ACNE PATIENTS**

- ▶ Poor eye contact
- ▶ Angry or negative verbalization
- ▶ Poor self-care
- ▶ Poor hygiene
- ▶ Compulsive behaviors
- ▶ Self-mutilating behaviors

# Spironolactone as effective as antibiotics

## STUDY FINDS WOMEN WITH ACNE MAY BENEFIT

by Ingrid Torjesen | Staff Correspondent

**D**ermatologists should consider using the diuretic drug spironolactone to treat acne in women instead of antibiotics, researchers at the University of Pennsylvania School of Medicine have said after their study found it to be similarly effective.<sup>1</sup>

They found that rates of prescription switching over a year were similar for women originally prescribed spironolactone and those originally prescribed antibiotics for their acne. Switching prescriptions is a proxy for ineffectiveness, since a change of drug is often the result of treatment failure due to lack of efficacy, side effects, cost, or other factors.

Despite antibiotics being associated with a range of adverse outcomes and efforts to curb their use because of growing antimicrobial resistance, oral antibiotics remain the most common systemic agent prescribed for the treatment of acne in the United States, according to the Centers for Disease Control, and dermatologists are the specialty that prescribes the highest level of antibiotics per provider.

Spironolactone, which blocks the effects of male hormones, meaning it's not a treatment option for men, is increasingly used to treat women with moderate-to-severe acne, despite not having been approved by the Food and Drug Administration for this indication. However, the clinical evidence to support its use is limited to small studies, so the researchers sought to compare the outcomes for spironolactone and oral tetracycline-class antibiotics among a larger population of women with acne.

They conducted a retrospective analysis of the frequency of switching to a different systemic agent within the first year of therapy among 6,684 women and girls prescribed spironolactone and 31,614 prescribed an oral tetracycline-class antibiotic between 2010-2016.

Their results, published in *Journal of Drugs and Dermatology*, revealed that 14.4% of women with acne who were started on spironolactone were prescribed a different systemic agent within one year, compared with 13.4% who started on an oral tetracycline-class antibiotic. After adjusting for age, topical retinoid, and oral contraceptive use, the odds ratio for being prescribed a different systemic agent within one year was 1.07 (95% confidence interval [CI] 0.99-1.16) for those prescribed spironolactone when compared with oral tetracycline-class antibiotics.

The researchers concluded that, based on the observation of similar switching between the two groups, spironolactone may have similar clinical effectiveness to that of oral tetracycline-class antibiotics.

Spironolactone could provide a safe and effective alternative to antibiotics for women, the study's lead author John S. Barbieri, MD, MBA, Dermatology chief resident at Penn, told *Dermatology Times*.

"Our results highlight that in this population of women being treated for acne, the rate of switching to another treatment was similar among those started on spironolactone and those started on an oral antibiotic for their acne. These results suggest that spironolactone may have similar effectiveness to oral antibiotics for women with acne," he said. "Guidelines currently recommend oral antibiotics as one of the first-line treatments for moderate to severe acne. However, given the emerging evidence regarding the effectiveness of

### Take AWAYS

Spironolactone may be as effective as oral antibiotics in women

Female patients should be given the option of spironolactone treatment first.

Future studies are needed to demonstrate safety and efficacy of spironolactone as treatment in women.

# Study: Psychological stress may increase acne severity

by Ingrid Torjesen | Staff Correspondent

Increased stress is strongly correlated with greater acne severity a study of medical students published in *Clinical, Cosmetic and Investigational Dermatology*<sup>1</sup> has found.

Although it is widely accepted that there is a relationship between stress and acne, few studies have assessed this relationship, so researchers at the medical faculty of King Abdulaziz University in Jeddah, Saudi Arabia looked at the relationship in 144 of the university's sixth year female medical students, who were aged 22 to 24 years.

Students were asked to complete the Perceived Stress Scale (PSS). This 14-item self-questionnaire is widely used in stress research, and includes some confounding factors in acne severity, such as,

## COMMON ACNE TRIGGERS

- ▶ Psychological stress
- ▶ Excessive heat
- ▶ Increased humidity

menstruation, heat and humidity, sweating, use of makeup and cosmetic products, oily hair products, use of topical steroids, and squeezing pimples.

Once the students had completed the questionnaire they were examined by an intern, who had been trained by a consultant dermatologist, for the presence of acne lesions. Acne severity was graded according to the global acne grading system (GAGS), and the type of acne lesions present (comedones, papules, pustules, and nodules) and their location were noted.

Three students (2.1%) had no acne, 104 students (72.2%) had mild acne, 33 students (22.9%) had moderate acne, and 4 students (2.8%) had severe acne.

Increased stress severity was found to strongly correlated with increased acne severity, and this

relationship was statistically significant ( $r=0.23$ ;  $p<0.01$ ). Of the eight acne aggravators included in the Perceived Stress Scale questionnaire, only excessive heat and humidity was found to have a statistically significant impact ( $p<0.05\%$ ).

The researchers said that heat and humidity may make it more favourable for *Propionibacterium acnes* to colonize the ductal hyperplasia.

While the study showed that there is an association between acne and stress levels, it did not prove a causative role for stress, commented Aryan Maleki, a medical student at Barts and The London School of Medicine and Dentistry, London, UK.<sup>ii</sup>

Acne is known to negatively affect quality of life and mood, so it is possible acne can lead to stress and not vice versa, he said. One way to establish a stronger causal relationship would be by evaluating whether stress-reduction techniques can significantly reduce acne severity.

"It would also aid in distinguishing whether the stress leading to acne originates from extrinsic factors or whether it is due to an individual's 'intrinsic' predisposition to produce stress responses," he said.

Shadi Zari, from the Faculty of Medicine at the University of Jeddah, in Saudi Arabia said that a number of mechanisms have been proposed mechanisms for how stress could aggravate acne.

In adult women with acne, chronic stress increases the secretion of adrenal androgens and results in sebaceous hyperplasia.

Activation of the hypothalamic-pituitary-adrenal

## Take AWAYS

Study finds association between stress and acne

Psychological stress can delay wound healing.

Delayed wound healing leads to deeper scars.

Stress CONTINUED ON PAGE 14

**“GUIDELINES CURRENTLY RECOMMEND ORAL ANTIBIOTICS AS ONE OF THE FIRST-LINE TREATMENTS FOR MODERATE TO SEVERE ACNE. HOWEVER, GIVEN THE EMERGING EVIDENCE REGARDING THE EFFECTIVENESS OF SPIRONOLACTONE COUPLED WITH THE POTENTIAL RISKS OF ANTIBIOTIC RESISTANCE AND OTHER COMPLICATIONS ASSOCIATED WITH ANTIBIOTIC USE, SPIRONOLACTONE SHOULD BE DISCUSSED AS AN ALTERNATIVE OPTION FOR WOMEN WITH ACNE.”**

Barbieri JS, et al.

Journal of Drugs and Dermatology

## **Spironolactone** CONTINUED FROM PAGE 12

spironolactone coupled with the potential risks of antibiotic resistance and other complications associated with antibiotic use, spironolactone should be discussed as an alternative option for women with acne.”

In addition to the importance of antibiotic stewardship, long-term oral antibiotic use may be associated with lupus, inflammatory bowel disease, and even colon and breast cancer. Spironolactone is generally well tolerated, with the most common side effect being irregular menstrual periods, which typically improve by using a lower dose or starting an oral contraceptive pill. However, it should be prescribed with caution to those with a history of kidney, heart, or liver disease and not taken by women who are pregnant.

Despite expert opinion supporting the use of spirono-

lactone for the treatment of acne in women, more clinical evidence on its safety and efficacy is needed, Barbieri acknowledged. “Ultimately, there would be significant benefit from a large clinical trial comparing spironolactone to oral antibiotics to provide definitive evidence regarding the safety and efficacy of spironolactone in the treatment of acne,” he said.

“If future studies continue to demonstrate the effectiveness and safety of spironolactone, then potentially it should replace oral antibiotics as the most common treatment of women with moderate to severe acne.” ◀

## **REFERENCE**

- <sup>1</sup> Barbieri JS, Choi JK, Mitra N, Margolis DJ. Frequency of Treatment Switching for Spironolactone Compared to Oral Tetracycline-Class Antibiotics for Women With Acne: A Retrospective Cohort Study 2010-2016. *Journal of Drugs and Dermatology* 2018; 17 (6): 611-617.

## **Stress** CONTINUED FROM PAGE 13

(HPA) axis is the main adaptive response to systemic stress. In response to emotional stress, the HPA axis activates increased levels of cortisol release.

Corticotropin-releasing hormone (CRH) is the most proximal element of the HPA axis. CRH acts as a central coordinator for neuroendocrine and behavioural responses to stress. CRH stimulates sebaceous gland lipid production and steroidogenesis, which contributes to acne.

“Studies have also shown an increase of CRH expression in the sebaceous glands of acne-involved skin, compared to a low expression in normal skin. This upregulation of CRH expression in acne-involved skin may influence the inflammatory processes that lead to stress-induced acne lesions,” Zari said. “CRH also induces cytokines IL-6 and IL-11 production in keratinocytes, contributing to inflammation, which

is regarded as a key component in the pathogenesis of acne.”

Furthermore, peripheral nerves release the neuropeptide substance P or vasointestinal peptide in response to stress. Substance P stimulates the proliferation and differentiation of sebaceous glands and upregulates lipid synthesis in sebaceous cells.

For people with acne, psychological stress could delay wound healing, which could affect the repair of acne lesions, Zari added. ◀

## **REFERENCES**

- <sup>1</sup> Zari S, Alrahmani D. The association between stress and acne among female medical students in Jeddah, Saudi Arabia. *Clinical, Cosmetic and Investigational Dermatology* 2017;10: 503–506
- <sup>2</sup> Maleki A, Khalid N. Exploring the relationship between stress and acne: a medical student’s perspective. *Clinical, Cosmetic and Investigational Dermatology* 2018;11: 173–174.

## BRIEF SUMMARY OF FULL PRESCRIBING INFORMATION

This Brief Summary does not include all the information needed to use ONEXTON Gel safely and effectively. See full prescribing information for ONEXTON Gel.

**ONEXTON® (clindamycin phosphate and benzoyl peroxide) Gel, 1.2%/3.75%, for topical use**

Initial U.S. Approval: 2000

## CONTRAINDICATIONS

### Hypersensitivity

ONEXTON Gel is contraindicated in those individuals who have shown hypersensitivity to clindamycin, benzoyl peroxide, any components of the formulation, or lincomycin. Anaphylaxis, as well as allergic reactions leading to hospitalization, has been reported in postmarketing use with ONEXTON Gel [see *Adverse Reactions*].

### Colitis/Enteritis

ONEXTON Gel is contraindicated in patients with a history of regional enteritis, ulcerative colitis, or antibiotic-associated colitis [see *Warnings and Precautions*].

## WARNINGS AND PRECAUTIONS

### Colitis

Systemic absorption of clindamycin has been demonstrated following topical use of clindamycin. Diarrhea, bloody diarrhea, and colitis (including pseudomembranous colitis) have been reported with the use of topical and systemic clindamycin. If significant diarrhea occurs, ONEXTON Gel should be discontinued.

Severe colitis has occurred following oral and parenteral administration of clindamycin with an onset of up to several weeks following cessation of therapy. Antiperistaltic agents such as opiates and diphenoxylate with atropine may prolong and/or worsen severe colitis. Severe colitis may result in death.

Studies indicate toxin(s) produced by Clostridia is one primary cause of antibiotic-associated colitis. The colitis is usually characterized by severe persistent diarrhea and severe abdominal cramps and may be associated with the passage of blood and mucus. Stool cultures for *Clostridium difficile* and stool assay for *C. difficile* toxin may be helpful diagnostically.

### Ultraviolet Light and Environmental Exposure

Minimize sun exposure (including use of tanning beds or sun lamps) following drug application [see *Nonclinical Toxicology*].

## ADVERSE REACTIONS

The following adverse reaction is described in more detail in the Warnings and Precautions section of the label:

Colitis [see *Warnings and Precautions*].

### Clinical Trials Experience

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

These adverse reactions occurred in less than 0.5% of subjects treated with ONEXTON Gel: burning sensation (0.4%); contact dermatitis (0.4%); pruritus (0.4%); and rash (0.4%).

During the clinical trial, subjects were assessed for local cutaneous signs and symptoms of erythema, scaling, itching, burning and stinging. Most local skin reactions either were the same as baseline or increased and peaked around week 4 and were near or improved from baseline levels by week 12. The percentage of subjects that had symptoms present before treatment (at baseline), during treatment, and the percent with symptoms present at week 12 are shown in Table 1.

**Table 1: Local Skin Reactions - Percent of Subjects with Symptoms Present. Results from the Phase 3 Trial of ONEXTON Gel 1.2%/3.75% (N = 243)**

	Before Treatment (Baseline)			Maximum During Treatment			End of Treatment (Week 12)		
	Mild	Mod.*	Severe	Mild	Mod.*	Severe	Mild	Mod.*	Severe
Erythema	20	6	0	28	5	<1	15	2	0
Scaling	10	1	0	19	3	0	10	<1	0
Itching	14	3	<1	15	3	0	7	2	0
Burning	5	<1	<1	7	1	<1	3	<1	0
Stinging	5	<1	0	7	0	<1	3	0	<1

\*Mod. = Moderate

### Postmarketing Experience

Because postmarketing adverse 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.

Anaphylaxis, as well as allergic reactions leading to hospitalizations, has been reported in postmarketing use of products containing clindamycin phosphate/benzoyl peroxide.

## DRUG INTERACTIONS

### Erythromycin

Avoid using ONEXTON Gel in combination with topical or oral erythromycin-containing products due to its clindamycin component. In vitro studies have shown antagonism between erythromycin and clindamycin. The clinical significance of this in vitro antagonism is not known.

### Concomitant Topical Medications

Concomitant topical acne therapy should be used with caution since a possible cumulative irritancy effect may occur, especially with the use of peeling, desquamating, or abrasive agents. If irritancy or dermatitis occurs, reduce frequency of application or temporarily interrupt treatment and resume once the irritation subsides. Treatment should be discontinued if the irritation persists.

## Neuromuscular Blocking Agents

Clindamycin has been shown to have neuromuscular blocking properties that may enhance the action of other neuromuscular blocking agents. ONEXTON Gel should be used with caution in patients receiving such agents.

## USE IN SPECIFIC POPULATIONS

### Pregnancy

Pregnancy Category C.

There are no adequate and well-controlled studies in pregnant women treated with ONEXTON Gel. ONEXTON Gel should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Animal reproductive/developmental toxicity studies have not been conducted with ONEXTON Gel or benzoyl peroxide. Developmental toxicity studies of clindamycin performed in rats and mice using oral doses of up to 600 mg/kg/day (240 and 120 times amount of clindamycin in the highest recommended adult human dose based on mg/m<sup>2</sup>, respectively) or subcutaneous doses of up to 200 mg/kg/day (80 and 40 times the amount of clindamycin in the highest recommended adult human dose based on mg/m<sup>2</sup>, respectively) revealed no evidence of teratogenicity.

### Nursing Mothers

It is not known whether clindamycin is excreted in human milk after topical application of ONEXTON Gel. However, orally and parenterally administered clindamycin has been reported to appear in breast milk. Because of the potential for serious adverse reactions in nursing infants, a decision should be made whether to use ONEXTON Gel while nursing, taking into account the importance of the drug to the mother.

### Pediatric Use

Safety and effectiveness of ONEXTON Gel in pediatric patients under the age of 12 have not been evaluated.

### Geriatric Use

Clinical trials of ONEXTON Gel did not include sufficient numbers of subjects aged 65 and older to determine whether they respond differently from younger subjects.

## NONCLINICAL TOXICOLOGY

### Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity, mutagenicity and impairment of fertility testing of ONEXTON Gel have not been performed.

Benzoyl peroxide has been shown to be a tumor promoter and progression agent in a number of animal studies. Benzoyl peroxide in acetone at doses of 5 and 10 mg administered topically twice per week for 20 weeks induced skin tumors in transgenic Tg.AC mice. The clinical significance of this is unknown.

Carcinogenicity studies have been conducted with a gel formulation containing 1% clindamycin and 5% benzoyl peroxide. In a 2-year dermal carcinogenicity study in mice, treatment with the gel formulation at doses of 900, 2700, and 15000 mg/kg/day (1.8, 5.4, and 30 times amount of clindamycin and 2.4, 7.2, and 40 times amount of benzoyl peroxide in the highest recommended adult human dose of 2.5 g ONEXTON Gel based on mg/m<sup>2</sup>, respectively) did not cause any increase in tumors. However, topical treatment with a different gel formulation containing 1% clindamycin and 5% benzoyl peroxide at doses of 100, 500, and 2000 mg/kg/day caused a dose-dependent increase in the incidence of keratoacanthoma at the treated skin site of male rats in a 2-year dermal carcinogenicity study in rats. In an oral (gavage) carcinogenicity study in rats, treatment with the gel formulation at doses of 300, 900 and 3000 mg/kg/day (1.2, 3.6, and 12 times amount of clindamycin and 1.6, 4.8, and 16 times amount of benzoyl peroxide in the highest recommended adult human dose of 2.5 g ONEXTON Gel based on mg/m<sup>2</sup>, respectively) for up to 97 weeks did not cause any increase in tumors. In a 52-week dermal photocarcinogenicity study in hairless mice, (40 weeks of treatment followed by 12 weeks of observation), the median time to onset of skin tumor formation decreased and the number of tumors per mouse increased relative to controls following chronic concurrent topical administration of the higher concentration benzoyl peroxide formulation (5000 and 10000 mg/kg/day, 5 days/week) and exposure to ultraviolet radiation.

Clindamycin phosphate was not genotoxic in the human lymphocyte chromosome aberration assay. Benzoyl peroxide has been found to cause DNA strand breaks in a variety of mammalian cell types, to be mutagenic in *S. typhimurium* tests by some but not all investigators, and to cause sister chromatid exchanges in Chinese hamster ovary cells.

Fertility studies have not been performed with ONEXTON Gel or benzoyl peroxide, but fertility and mating ability have been studied with clindamycin. Fertility studies in rats treated orally with up to 300 mg/kg/day of clindamycin (approximately 120 times the amount of clindamycin in the highest recommended adult human dose of 2.5 g ONEXTON Gel, based on mg/m<sup>2</sup>) revealed no effects on fertility or mating ability.

## PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (*Patient Information*).

Manufactured for:

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By:

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U.S. Patent 8,288,434

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# ALL ABOARD ONEXTON GEL

**Efficacy and tolerability matter** when it comes to treating acne. In the pivotal trial, ONEXTON GEL was shown to treat both inflammatory and noninflammatory acne, and no patients discontinued due to an adverse event.<sup>1,2</sup>



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TERMS AND CONDITIONS APPLY

## INDICATION

ONEXTON (clindamycin phosphate and benzoyl peroxide) Gel, 1.2%/3.75% is indicated for the topical treatment of acne vulgaris in patients 12 years of age or older.

## IMPORTANT SAFETY INFORMATION

- ONEXTON Gel is contraindicated in patients with a known hypersensitivity to clindamycin, benzoyl peroxide, any component of the formulation, or lincomycin.
- ONEXTON Gel is contraindicated in patients with a history of regional enteritis, ulcerative colitis, or antibiotic-associated colitis.
- Diarrhea, bloody diarrhea, and colitis (including pseudomembranous colitis) have been reported with the use of topical and systemic clindamycin. ONEXTON Gel should be discontinued if significant diarrhea occurs.
- Orally and parenterally administered clindamycin has been associated with severe colitis, which may result in death.
- Anaphylaxis, as well as other allergic reactions leading to hospitalizations, has been reported in postmarketing use of products containing clindamycin/benzoyl peroxide. If a patient develops symptoms of an allergic reaction such as swelling and shortness of breath, they should be instructed to discontinue use and contact a physician immediately.
- The most common local adverse reactions experienced by patients in clinical trials were mild and moderate erythema, scaling, itching, burning and stinging.

- ONEXTON Gel should not be used in combination with erythromycin-containing products because of its clindamycin component.
- ONEXTON Gel should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. A decision should be made whether to use ONEXTON Gel while nursing, taking into account the importance of the drug to the mother.
- Patients should be advised to avoid contact with the eyes or mucous membranes.
- Patients should minimize exposure to natural and avoid artificial sunlight (tanning beds or UVA/B treatment) while using ONEXTON Gel. To minimize exposure to sunlight, protective clothing should be worn and a sunscreen with SPF 15 rating or higher should be used.

To report SUSPECTED ADVERSE REACTIONS, contact Ortho Dermatologics at 1-800-321-4576 or FDA at 1-800-FDA-1088 or visit [www.fda.gov/medwatch](http://www.fda.gov/medwatch).

Please see Brief Summary of full Prescribing Information on the following page.

References: 1. ONEXTON [prescribing information]. Bridgewater, NJ: Valeant Pharmaceuticals North America LLC. 2. Pariser DM, Rich P, Cook-Bolden FE, Korotzer A. An aqueous gel fixed combination of clindamycin phosphate 1.2% and benzoyl peroxide 3.75% for the once-daily treatment of moderate to severe acne vulgaris. *J Drugs Dermatol*. 2014;13(9):1083-1089.

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**ONEXTON**<sup>®</sup>  
(clindamycin phosphate and benzoyl peroxide)  
Gel, 1.2%/3.75%