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RECOGNIZING AND TREATING

ADULT FEMALE ACNE

Adult Female Acne: A Unique Clinical Challenge

Whether adult female acne is a distinct clinical entity remains in doubt; whether it affects patients' quality of life seems indisputable.

Although acne vulgaris (AV) is known to affect teenagers, recent evidence suggests that it is also prevalent after adolescence, and, in particular, among adult females. According to many researchers, there are more questions than answers about adult acne, especially regarding whether a unique morphology observed among a subset of adult patients constitutes a distinct clinical entity. Nevertheless, most agree that adult acne, whether continuing from childhood or making its first appearance in adulthood, is a serious problem, as a growing body of literature suggests that acne has a very real psychosocial impact on adult females.

SIMILARITIES AND DIFFERENCES

Adolescent males and females account for the largest proportion of acne cases. About 50 million individuals will develop acne each year,[1] including roughly 85 percent of those between the ages of 12 and 24;[2] yet, cases among adult women may be underrecognized. Among adults, women account for about 82 percent of cases, and while the prevalence of acne among adult females decreases with age, roughly 10 percent or more of women age 41 to 50 may have active acne.[4]

While adult female acne constitutes a not uncommon problem, questions abound as to its etiology. As many as one-third of adult females presenting to their dermatologist for assessment and care report never having acne as a teenager.[5] Yet, it is unknown if post-adolescent acne is morphologically distinct from adolescent acne and, therefore, requires a different management strategy.

According to Julie C. Harper, MD, of Dermatology and Skin Care Center of Birmingham, AL, there have not been studies comparing adolescent to adult female acne in a head-to-head fashion. Yet, her experience in the clinic dealing with patients leads her to believe that adult cases present differently, and, thus, do require different management approaches.

"The condition appears to be different from a clinical standpoint," she said. "There is at least a group of adult women who present very differently than adolescent acne."

At least some of that different presentation may be due to hormonal influence, especially if flares appear around the time of the menstrual cycle, according to Diane S. Berson, MD, of Diane Berson Dermatology in New York City. "There is a subset of women who have a mild acne that tends to flare in relation to their menstrual cycle, and is therefore hormonally linked. It often flares in the lower part of the face, most commonly the jawline, chin, and neck. These patients may get papules and cysts on the chin related to their cycle," she said.

Yet, she added, while hormonally influenced acne represents a distinct clinical subset, most adult cases are indistinguishable from adolescent.

"For many patients it is exactly the same [in adult and adolescence], but for others, there is this different clinical presentation" that requires a different approach to treatment, Dr. Berson said. "If they have a hormonal component to their acne and a hormonal influence in terms of flares, then adding a hormonal aspect to the treatment may help prevent breakouts."

MORPHOLOGY: IS ADULT FEMALE ACNE A DISTINCT ENTITY?

The exact role of androgen in the etiology of acne is unclear. According to Dr. Harper, if there were a simple and direct correlation between high androgen levels and acne breakouts, then it would follow that males would be much more affected than what is described in the literature. As well, only a portion of adult women with acne display hyperandrogenemia, studies

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report prevalnce from 30 percent[6] up to 80 percent.[7]

In some cases, use of oral contraceptives may mask acne if there is a hormonal link; cessation of hormonal therapy for whatever reason may lead to outbreaks that can be interpreted as novel onset. In many cases, whether the particular case is persistent acne (or early-onset: continuing from adolescence) or late-onset (first appearing in adulthood) is unknown, and likely inconsequential to the treatment and management plan.

If androgen abnormalities are a significant driver of late onset acne, then adult females may display a pathognomonic presentation. In fact, at one point, it was widely held that post-adolescent acne was morphologically distinct.[9] Classification schemas recognized early-onset acne as comedonal in appearance rising from impacted pilosebaceous units on the face, especially in the forehead, nose, and chin, with papules and pustules appearing if inflammation develops. On the other hand, it was believed that adult acne, more mild-to-moderate in appearance, was generally more refractory to treatment, and included more inflammatory lesions, which appeared on the lower chin, jawline, and neck; comedones, if present, were more often believed to be closed.[8]

More recent surveys, however, suggest that adult female acne is fairly similar in appearance to presentations in adolescents, at least in the majority of cases.[9] In a prospective, observational international study of 374 patients evaluating the clinical characteristics and lifestyle correlates of acne in adults, Dréno, et al. noted that mixed facial acne was the most common presentation, only 6.4 percent of women had inflammatory acne only, and 17.1 percent had comedonal acne with no inflammatory lesions. Truncal acne, once believed to be almost exclusive to adolescent cases, was noted in 48.4 percent of patients in the survey, and only 11.2 percent of women had acne localized to the mandibular area. The authors concluded that most adult women surveyed displayed a spectrum of facial acne severity that was similar to adolescents.

However, while the survey noted many similarities between adolescent and adult acne, it also highlighted distinct features among those women with mandibular acne: they were less likely to have moderate or severe acne (7.1 percent vs 50.1 percent), truncal acne (19.0 percent vs 51.9 percent), postinflammatory hyperpigmentation (23.8 percent vs 51.9 percent), and erythema (19.0 percent vs 48.4 percent).

A recent report from the American Acne & Rosacea Society (AARS), suggests that while the appearance is often similar in adolescent and adult females, "in other cases, a more selectively distributed U-shaped pattern is noted, characterized predominantly by inflammatory papules and/or nodules involving the lower cheeks and jawline margin, with lesions also commonly noted on the anterior and lateral neck … A U-shaped pattern is believed to be more common in late-onset [AV], often with persistence into the mid-40s."[10]

WHAT DOES ADULT FEMALE ACNE LOOK LIKE?

Until relatively recently, dermatologists tended to think that the proportion of adult females affected by acne was somewhat small. Today, thanks to ongoing dialogue and a growing body of research, clinicians agree that many more women have acne than previously thought. What they can't agree on is what "adult female acne" looks like.

When Dreno, et al reported in 2015[9] that the majority of adult female acne patients had a presentation similar to adolescent acne—with only about six percent presenting with inflammatory acne only, 17 percent having no inflammatory lesions, and about 11 percent with acne localized to the mandibular area—many dermatologists scratched their heads. According to Emil Tanghetti, MD, of Sacramento, CA, those findings did not reflect what he sees in his community-based medical and cosmetic dermatology practice. He believes that the findings from the Global Alliance study may have been influenced by the nature of the study population, which seems to have included mostly patients referred to specialty acne treatment centers.

"At my community dermatology practice, I see women with a lot of inflammatory lesions, very aggressive, and hormonally related," Dr. Tanghetti says. "My guess is that this presentation far exceeds the mixed or adolescent type." While he is careful to note that he has no hard data to support his view, Dr. Tanghetti says he is supported by his own experience and intuition.

The type of acne women experiences affects the treatment they receive, Dr. Tanghetti says. Treatments that target inflammation without causing undue irritation or dryness are ideal, he notes. Topical dapsone is a go-to in his practice, Dr. Tanghetti says. Subgroup analysis of clinical trial data showed that women treated with Aczone gel 5.0% had better outcomes compared to the overall study population or to men. The data also showed that the vehicle alone was beneficial in adult female acne patients. The availability of Aczone 7.5% gel with once-daily dosing is a welcome development, he says, that adds convenience and simplifies the regimen.

Dr. Tanghetti's typical regimen for women with inflammatory acne begins with topical dapsone gel 7.5% along with once-daily refrigerated benzoyl peroxide/clindamycin. For patients with a hormonal component to their acne, he may add spironolactone. This regimen is well-tolerated, he notes.

Dr. Harper, who was one of the authors of that report, said that while adolescent and adult acne can look alike, "my personal experience is that doesn't happen very often. The adolescent usually has a bumpy forehead and blackheads on the nose and shiny skin and appearance. Adults may have some

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Considerations in the Treatment of Adult Female Acne

Distinct skin manifestations, the relative health of the skin, and potential hormonal influences may influence treatment in adult female patients.

In some ways the approach to treating acne among adults is similar to adolescents in that the morphology and severity of the presentation are crucial factors in designing a management strategy. However, other factors, including the potential for hormonal influences and the relative health of the skin in adult patients, may have to be addressed.

Although roughly a third of adults with acne report never having had it as teenagers,[1] most cases in adults are morphologically identical to those typically seen in teens.[2] However, according to Katie Beleznay, MD, a clinical dermatologist in Vancouver, British Columbia, the skin manifestations should play an important role in determining the treatment approach, but there may be important context.

"I think the presentation does impact treatment, both how it appears clinically and the history of when it first appeared," said Dr. Beleznay. "Many adult females have a more comodonal type of acne or deeper cystic papular acne, particularly around the jaw line, that may occur around the time of their menstrual cycle. Depending on the type of presentation and correlation with the menstrual cycle, I might approach the treatment differently."

Another factor in adult female patients is the overall health of the skin. For instance, patients may unwittingly be using comedonal cosmetics that contribute to the etiology. As well, there is suggestive evidence in the literature that directing efforts to maintain epidermal barrier function—either through active treatment or by educating about use of astringents or other harmful hygiene regimens—may be beneficial in reducing flares and/or minimizing the harsh effects prescription topical therapy may have on the skin.

"Many women have an acne that is distinct from what they had as an adolescent, and then there is a subset of women who have acne that is continued," said Diane S. Berson, MD, of Diane Berson Dermatology in New York City. "Adult females frequently get acne, and it tends to be more stubborn. Part of that may be because of hormonal component. Another reason may be because some of the treatments can be drying or irritating, and so we need to educate patients about how to use treatments."

DIFFERENT MORPHOLOGY, DIFFERENT SKIN, DIFFERENT TREATMENT

The potential for a hormonal component may influence the approach to adult female acne. One study of 230 adult women noted that acne worsened before, during, or after menses in 56 percent, 17 percent, and three percent of women, respectively.[3] Hormonally mediated acne, though, may not necessarily be linked to menses. For instance, there may be upregulation in androgen production due to stress. One study noted that a U-shaped pattern of inflammatory and potentially refractory lesions along the jaw line was more common among women who were employed (90.5 percent vs 78.6 percent), had greater daily stress levels (5.8 vs 5.1), and had psychologically stressful jobs (71.4 percent vs 57.5 percent).[2]

> "It is always important to talk about sunscreen and photoprotection, because with acne, you can get post inflammatory erythema and post inflammatory hyperpigmentation, and so minimizing the side effects and the left over effects of acne are important as well."
>
> *—Dr. Beleznay*

Common features of hyperandrogenemia, such as hirsutism, may be unreliable for establishing androgen abnormalities. Up to 50 percent of women with male-pattern hair growth have normal androgen levels.[4] Conducting additional laboratory work-up may be more selective. Citing data from several studies,[2,5-7] a recent report from the American Acne & Rosacea Society (AARS) highlighted four instances where the clinical appearance or patient history may signal a need to conduct additional laboratory testing: "It is suggested that screening for underlying endocrinopathy should be conducted in women presenting with (1) [acne vulgaris] recalcitrant to conventional treatment, (2) sudden emergence of severe [acne vulgaris], (3) concurrent signs/symptoms of androgen excess, and/or (4) [acne vulgaris] relapse shortly after isotretinoin therapy."[8]

When it comes to treatment, the potential role of hormones in adult female patients may necessitate a need to adjust the approach, according to Julie C. Harper, MD, of Dermatology and Skin Care Center of Birmingham, AL. "Things like hormonal treatments in adolescent are add-ons or a last resort, and in the adult female acne, it may be a first line treatment," Dr. Harper said. "Oral contraceptives can work very well, and a lot of times, women want those for other reasons, anyway. Drugs like spironolactone, which is not FDA approved for acne, work particularly well from the very first visit. A problem with using hormonal treatments early is that those are long-term treatments, and so once someone signs up, they have to be on them for a long time."

Cosmetic products are a commonly cited etiologic and/or exacerbating factor in acne.[9-11] According to some surveys, 50 percent of women attempt to treat their own acne rather than seek the expertise of a dermatologist.[12] However, a delay in seeking treatment has been identified as a risk factor in the development of acne scars.[13]

"It is important to find out what over-the-counter agents patients have been using when they come into the clinic, and also what they are using currently," said Dr. Beleznay. "You want to know what patients are using because it could irritate their skin. For example, I would not want a patient to be using an exfoliant, salicylic acid, or harsh cleanser with a prescription topical. A lot of times, patients discontinue the topical because their skin is too irritated, but they will continue with the over-the-counter product because they think it will be more effective."

PRESCRIPTION TOPICALS AND THE ROLE OF COSMETICS AND COSMECEUTICALS

While topical therapy forms the basis for management in adult cases, there is limited data in controlled clinical trials specifically on the efficacy and tolerability in adult females, and there are fewer studies of the classic U-shaped, jawline acne that many consider unique to adult-onset acne.

"The topical therapies are largely effective for adult women, but they are less effective for deeper more cystic acne. I don't find them to be effective, certainly as a solitary agent, if I am trying to treat more nodular cystic acne or more hormonally distributed acne. I do often use them as an adjunct if I am prescribing someone an anti-androgen therapy. For example, I would use a topical in combination with the oral, because I think that is effective," Dr. Beleznay said.

Topical dapsone has been shown to have anti-inflammatory effects and superior efficacy in female patients compared to efficacy in the general study population. A pooled data analysis evaluated more than 3,000 patients receiving topical dapsone and showed a clear gender difference in response to therapy. Women had a significantly greater reduction in acne lesion counts and a significantly higher clinical success rate following 12 weeks of treatment. Of note, female patients in the active treatment and the vehicle control groups fared better than their respective male counterparts.[14]

> "If these women are a bit older and have concomitant photodamage or skin dryness, then the topical therapy chosen may have to be altered and you might have to pick products that have more emollients."
>
> —*Dr. Berson*

The topical dapsone data raise intriguing questions about the pathophysiology of acne in different sexes as well as the effects of different drugs in different sexes. They indicate that prescribers might consider how patients may respond to a particular therapy as they build treatment regimens.

Treatment may be complicated in adult females in terms of compliance. Some topical therapies can be irritating to the skin, especially when therapy is first started, and there is often a latency period before topicals show efficacy—and these issues may be compounded by the fact that adult females tend to have skin that is drier, may have experienced photodamage, or may have a compromised epidermal barrier due to aging.

"If these women are a bit older and have concomitant photodamage or skin dryness, then the topical therapy chosen may have to be altered and you might have to pick products that have more emollients or you might have to suggest mositurizers or emollients to be used adjunctively," said Dr. Berson.

Redondo Beach, CA dermatologist Annie Chiu, MD finds that, in addition to its efficacy, topical dapsone offers good tolerability, especially for women with "dry" or "sensitive" skin. The new once-daily, 7.5% formulation of dapsone (Aczone, Allergan) is convenient for busy adults, she notes. Plus, once-a-day dosing allows patients to apply dapsone in the morning and a retinoid in the evening, she says.

According to Dr. Beleznay, the difference in health of the skin in adult patients highlights a need to educate patients about general skin health topics. "It is always important to talk about sunscreen and photoprotection, because with acne, you can get post inflammatory erythema and post inflammatory hyperpigmentation, and so minimizing the side effects and the left over effects of acne are important as well," she said.

Patients may also be needlessly harsh on their skin in an attempt to treat their acne. Dr. Beleznay regularly sees patients

who are scrubbing with astringents multiple times a day, in effect reducing moisture and further damaging the epidermal barrier.

THERAPEUTIC ADJUNCTS AND OCPs

In difficult to treat cases, oral therapy may be a reasonable option. Studies suggest a role for oral antibiotics as an adjunct to topical therapy in moderate to severe inflammatory lesions,[15,16] although their use is becoming less common, due to ressitance concerns. Isotretinoin remains an option for adult females, Dr. Chiu reminds. In cases in which the U-shaped pattern predominates, combination oral contraceptive therapy may be of benefit.[17] Other modalities, such as laser and light therapy, may be additive in some select cases, especially if the patient is looking for a cosmetic outcome.

"Light based therapy may be effective, but the evidence is pretty small and inconsistent," said Dr. Beleznay. "Its' an adjunct, but its certainly not the gold standard, and I wouldn't use that as a second or third line therapy, but its something that you can offer to patients. Other things that are important are physical therapies, like extracting comodones or intralesional kenalog."

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(Continued from page 3)

blackheads, but she also usually has recurrent, painful nodules on the chin and lower face, and so it looks different."

Dr. Berson believes that at least some of the different clinical appearance may be attributable to hormonal influence. "I treat a lot of adult women and I can look at someone and tell if its hormonal...The clinical appearance may lead you to explore the history to see if there is hormonal component," she said.

PSYCHOSOCIAL IMPLICATIONS

The effect of acne on patients' quality of life is significant regardless of age, and it may have an even more important impact on adult females. In one oft-cited survey using validated questionnaires patients reported levels of psychosocial and emotional problems due to their skin condition that were on par with reports from patients with chronic disabling asthma, epilepsy, diabetes, back pain, or arthritis.[11] Of note, in the survey, low quality of life metrics were independent of acne severity.

Adult female acne may carry a level of stigma and embarrassment, and many patients attempt to use over-the-counter medications to self-treat or use cosmeceuticals to mask its appearance.[12] Such approaches, however, may offer insufficient management, which can compound frustration, or may exacerbate flares. Some OTC benzoyl peroxide formulations are thought to be especially irritating for adult women.

Adult acne has been linked to severe stress, including depression, anxiety, and suicidal ideation. "Quality of life is a huge component of this," said Dr. Harper. "While no teen wants acne, it is somewhat an accepted part of adolescence. It's accepted as more normal. And although we have data that shows that adult female acne is more common than we think—about one in four women in their 40s still has acne, one in three in their 30s—there is a feeling that 'I am the only one.' People withdraw from activities and there is some suggestion in the literature that more people with acne are unemployed as adults."

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ACZONE® (dapsone) Gel 7.5%

BRIEF SUMMARY—PLEASE SEE THE ACZONE® PACKAGE INSERT FOR FULL PRESCRIBING INFORMATION

INDICATIONS AND USAGE

ACZONE® Gel 7.5% is indicated for the topical treatment of acne vulgaris in patients aged 12 years and older.

DOSAGE AND ADMINISTRATION

For topical use only. Not for oral, ophthalmic, or intravaginal use. After the skin is gently washed and patted dry, apply approximately a pea-sized amount of **ACZONE®** Gel 7.5% in a thin layer to the entire face once daily. In addition, a thin layer may be applied to other affected areas once daily. Rub in **ACZONE®** Gel 7.5% gently and completely.

If there is no improvement after 12 weeks, treatment with **ACZONE®** Gel 7.5% should be reassessed.

CONTRAINDICATIONS

None.

WARNINGS AND PRECAUTIONS

Hematological Effects

Methemoglobinemia

Cases of methemoglobinemia, with resultant hospitalization, have been reported post marketing in association with twice-daily dapsone gel, 5%, treatment. Patients with glucose-6-phosphate dehydrogenase deficiency or congenital or idiopathic methemoglobinemia are more susceptible to drug-induced methemoglobinemia. Avoid use of **ACZONE®** Gel 7.5% in those patients with congenital or idiopathic methemoglobinemia.

Signs and symptoms of methemoglobinemia may be delayed some hours after exposure. Initial signs and symptoms of methemoglobinemia are characterized by a slate-gray cyanosis seen in, eg, buccal mucous membranes, lips, and nail beds. Advise patients to discontinue **ACZONE®** Gel 7.5% and seek immediate medical attention in the event of cyanosis.

Dapsone can cause elevated methemoglobin levels particularly in conjunction with methemoglobin-inducing agents (see *Drug Interactions*).

Hemolysis

Oral dapsone treatment has produced dose-related hemolysis and hemolytic anemia. Individuals with glucose-6-phosphate dehydrogenase (G6PD) deficiency are more prone to hemolysis with the use of certain drugs. G6PD deficiency is most prevalent in populations of African, South Asian, Middle Eastern, and Mediterranean ancestry.

In clinical trials, there was no evidence of clinically relevant hemolysis or hemolytic anemia in subjects treated with topical dapsone. Some subjects with G6PD deficiency using dapsone gel, 5%, twice daily developed laboratory changes suggestive of hemolysis (see *Use in Specific Populations*).

Discontinue **ACZONE®** Gel 7.5% if signs and symptoms suggestive of hemolytic anemia occur. Avoid use of **ACZONE®** Gel 7.5% in patients who are taking oral dapsone or antimalarial medications because of the potential for hemolytic reactions. Combination of **ACZONE®** Gel 7.5% with trimethoprim-sulfamethoxazole (TMP/SMX) may increase the likelihood of hemolysis in patients with G6PD deficiency (see *Drug Interactions*).

Peripheral Neuropathy

Peripheral neuropathy (motor loss and muscle weakness) has been reported with oral dapsone treatment. No events of peripheral neuropathy were observed in clinical trials with topical dapsone treatment.

Skin Reactions

Skin reactions (toxic epidermal necrolysis, erythema multiforme, morbilliform and scarlatiniform reactions, bullous and exfoliative dermatitis, erythema nodosum, and urticaria) have been reported with oral dapsone treatment. These types of skin reactions were not observed in clinical studies with topical dapsone treatment.

ADVERSE REACTIONS

Clinical Studies 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.

A total of 2161 patients were treated with **ACZONE®** Gel 7.5% for 12 weeks in 2 controlled clinical studies. The population ranged in age from 12 to 63 years, and was 56% female and 58% Caucasian.

Adverse drug reactions that were reported in at least 0.9% of subjects treated with **ACZONE®** Gel 7.5% included:

Adverse Reactions Occurring in at Least 0.9% of Subjects With Acne Vulgaris in 12-Week Controlled Clinical Trials

	ACZONE® Gel 7.5% (N = 2161)	**Vehicle** (N = 2175)
Application-site Dryness	24 (1.1%)	21 (1.0%)
Application-site Pruritus	20 (0.9%)	11 (0.5%)

Experience With Oral Use of Dapsone

Although not observed in the clinical trials with topical dapsone, serious adverse reactions have been reported with oral use of dapsone, including agranulocytosis, hemolytic anemia, peripheral neuropathy (motor loss and muscle weakness), and skin reactions (toxic epidermal necrolysis, erythema multiforme, morbilliform and scarlatiniform reactions, bullous and exfoliative dermatitis, erythema nodosum, and urticaria).

Postmarketing Experience

The following adverse reactions have been identified during post-approval use of topical dapsone. 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.

Methemoglobinemia has been identified during postmarketing use of topical dapsone (see *Warnings and Precautions*).

DRUG INTERACTIONS

No formal drug-drug interaction studies were conducted with **ACZONE®** Gel 7.5%.

Trimethoprim-Sulfamethoxazole

A drug-drug interaction study evaluated the effect of the use of dapsone gel, 5%, in combination with double-strength (160 mg/800 mg) trimethoprim-sulfamethoxazole (TMP/SMX). During co-administration, systemic levels of TMP and SMX were essentially unchanged, however, levels of dapsone and its metabolites increased in the presence of TMP/SMX. The systemic exposure from **ACZONE®** Gel 7.5% is expected to be about 1% of that from the 100 mg oral dose, even when co-administered with TMP/SMX.

Topical Benzoyl Peroxide

Topical application of dapsone gel followed by benzoyl peroxide in patients with acne vulgaris may result in a temporary local yellow or orange discoloration of the skin and facial hair.

Drug Interactions With Oral Dapsone

Certain concomitant medications (such as rifampin, anticonvulsants, St. John's wort) may increase the formation of dapsone hydroxylamine, a metabolite of dapsone associated with hemolysis. With oral dapsone treatment, folic acid antagonists, such as pyrimethamine, have been noted to possibly increase the likelihood of hematologic reactions.

Concomitant Use With Drugs That Induce Methemoglobinemia

Concomitant use of **ACZONE®** Gel 7.5% with drugs that induce methemoglobinemia such as sulfonamides, acetaminophen, acetanilide, aniline dyes, benzocaine, chloroquine, dapsone, naphthalene, nitrates and nitrites, nitrofurantoin, nitroglycerin, nitroprusside, pamaquine, para-aminosalicylic acid, phenacetin, phenobarbital, phenytoin, primaquine, and quinine may increase the risk of developing methemoglobinemia (see *Warnings and Precautions*).

USE IN SPECIFIC POPULATIONS

Pregnancy

Teratogenic Effects: Pregnancy Category C

There are no adequate and well-controlled studies in pregnant women. **ACZONE®** Gel 7.5% should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Dapsone has been shown to have an embryocidal effect in rats and rabbits when administered orally during the period of organogenesis in doses of 75 mg/kg/day and 150 mg/kg/day, respectively (approximately 1400 and 425 times, respectively, the systemic exposure that is associated with the maximum recommended human dose [MRHD] of **ACZONE®** Gel 7.5% based on AUC comparisons). These effects may have been secondary to maternal toxicity.

Nursing Mothers

Although systemic absorption of dapsone following topical application of **ACZONE®** Gel 7.5% is minimal relative to oral dapsone administration, it is known that dapsone is excreted in human milk. Because of the potential for oral dapsone to cause adverse reactions in nursing infants, a decision should be made whether to discontinue nursing or to discontinue **ACZONE®** Gel 7.5%, taking into account the importance of the drug to the mother.

Pediatric Use

Safety and efficacy was evaluated in 1066 subjects aged 12 to 17 years treated with **ACZONE®** Gel 7.5% in the clinical trials. The safety profile for **ACZONE®** Gel 7.5% was similar to the vehicle control group. Safety and effectiveness of **ACZONE®** Gel 7.5% have not been established in pediatric patients below the age of 12 years.

Geriatric Use

Clinical trials of **ACZONE®** Gel 7.5% did not include sufficient numbers of subjects aged 65 years and older to determine whether they respond differently than younger subjects.

Glucose-6-phosphate Dehydrogenase (G6PD) Deficiency

Individuals with glucose-6-phosphate dehydrogenase (G6PD) deficiency may be more prone to methemoglobinemia and hemolysis (see *Warnings and Precautions*).

ACZONE® Gel 5% and vehicle were evaluated in a randomized, double-blind, crossover design clinical study of 64 subjects with G6PD deficiency and acne vulgaris. Subjects were Black (88%), Asian (6%), Hispanic (2%), or of other racial origin (5%). Blood samples were taken at Baseline, Week 2, and Week 12 during both vehicle and **ACZONE®** Gel 5% treatment periods. Some of these subjects developed laboratory changes suggestive of hemolysis, but there was no evidence of clinically significant hemolytic anemia in this study (see *Warnings and Precautions*).

Rx ONLY

Allergan

Irvine, CA 92612 U.S.A.

APC24AJ16 160549
Based on package insert 72780US10

START STRONG

- Once-daily dosing[1]
- Proven efficacy and tolerability at week 12[1,2]
  - GAAS success rate was 30% (n = 2162) with ACZONE® (dapsone) Gel 7.5% vs 21% (n = 2178) with vehicle*
  - Inflammatory lesions were reduced by 15.9 (55.2%) vs 14.2 (48.5%) with vehicle*
  - Noninflammatory lesions were reduced by 20.8 (45.6%) vs 18.4 (39.7%) with vehicle*
  - 1.1% (n = 2161) of ACZONE® Gel 7.5% patients experienced application-site dryness vs 1.0% (n = 2175) with vehicle, and 0.9% experienced pruritus vs 0.5% with vehicle

Begin bold. Write NEW ACZONE® Gel 7.5%.

*From baseline ($P<.001$).

INDICATIONS AND USAGE
ACZONE® (dapsone) Gel 7.5% is indicated for the topical treatment of acne vulgaris in patients aged 12 years and older.

IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS
Hematological Effects
Methemoglobinemia: Cases of methemoglobinemia with resultant hospitalization have been reported post marketing in association with twice-daily dapsone gel 5% treatment. Patients with glucose-6-phosphate dehydrogenase deficiency or congenital or idiopathic methemoglobinemia are more susceptible to drug-induced methemoglobinemia. Avoid use of **ACZONE®** Gel 7.5% in patients with congenital or idiopathic methemoglobinemia.

Signs and symptoms of methemoglobinemia may be delayed some hours after exposure. Initial signs and symptoms of methemoglobinemia are characterized by a slate-gray cyanosis seen in, eg, buccal mucous membranes, lips, and nail beds. Advise patients to discontinue **ACZONE®** Gel 7.5% and seek immediate medical attention in the event of cyanosis.

Dapsone can cause elevated methemoglobin levels, particularly in conjunction with methemoglobin-inducing agents.

Hemolysis: Oral dapsone treatment has produced dose-related hemolysis and hemolytic anemia. Individuals with glucose-6-phosphate dehydrogenase (G6PD) deficiency are more prone to hemolysis with the use of certain drugs. G6PD deficiency is most prevalent in populations of African, South Asian, Middle Eastern, and Mediterranean ancestry.

In clinical trials, there was no evidence of clinically relevant hemolysis or hemolytic anemia in subjects treated with topical dapsone. Some subjects with G6PD deficiency using dapsone gel 5% twice daily developed laboratory changes suggestive of hemolysis.

Discontinue **ACZONE®** Gel 7.5% if signs and symptoms suggestive of hemolytic anemia occur. Avoid use of **ACZONE®** (dapsone) Gel 7.5% in patients who are taking oral dapsone or antimalarial medications because of the potential for hemolytic reactions. Combination of **ACZONE®** Gel 7.5% with trimethoprim/sulfamethoxazole (TMP/SMX) may increase the likelihood of hemolysis in patients with G6PD deficiency.

Peripheral Neuropathy
Peripheral neuropathy (motor loss and muscle weakness) has been reported with oral dapsone treatment. No events of peripheral neuropathy were observed in clinical trials with topical dapsone treatment.

Skin Reactions
Skin reactions (toxic epidermal necrolysis, erythema multiforme, morbilliform and scarlatiniform reactions, bullous and exfoliative dermatitis, erythema nodosum, and urticaria) have been reported with oral dapsone treatment. These types of skin reactions were not observed in clinical trials with topical dapsone treatment.

ADVERSE REACTIONS
The most common adverse reactions of **ACZONE®** Gel 7.5% are dryness and pruritus at the application site.

Methemoglobinemia has been identified during postmarketing use of topical dapsone.

DRUG INTERACTIONS
Topical application of dapsone gel followed by benzoyl peroxide in patients with acne vulgaris may result in a temporary local yellow or orange discoloration of the skin and facial hair.

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

NEW Aczone (dapsone) Gel, 7.5%™

References: 1. ACZONE® Gel 7.5% Prescribing Information. **2.** Data on file, Allergan, 2016; Integrated Summary of Effectiveness.