HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use ACZONE® Gel, 7.5% safely and effectively. See full prescribing information for ACZONE® Gel, 7.5%.

ACZONE® (dapsone) Gel, 7.5%, for topical use
Initial U.S. Approval: 1955

INDICATIONS AND USAGE

ACZONE® Gel, 7.5%, is a sulfone indicated for the topical treatment of acne vulgaris in patients 12 years of age and older (1).

DOSAGE AND ADMINISTRATION

• Apply once daily (2).
• Apply approximately a pea-sized amount of **ACZONE** Gel, 7.5%, in a thin layer to the entire face. A thin layer can also be applied to other affected areas (2).
• If there is no improvement after 12 weeks, treatment with **ACZONE** Gel, 7.5% should be reassessed (2).
• For topical use only. Not for oral, ophthalmic, or intravaginal use (2).

DOSAGE FORMS AND STRENGTHS

Gel, 7.5% (3).

CONTRAINDICATIONS

None (4).

WARNINGS AND PRECAUTIONS

• Methemoglobinemia: Cases of methemoglobinemia have been reported. Discontinue **ACZONE** Gel if signs of methemoglobinemia occur (5.1).
• Hemolysis: Some patients with Glucose-6-phosphate Dehydrogenase (G6PD) deficiency using topical dapsone developed laboratory changes suggestive of hemolysis (5.1)(8.6).

ADVERSE REACTIONS

Most common (incidence ≥ 0.9%) adverse reactions are application site dryness and pruritus (6.1).

To report SUSPECTED ADVERSE REACTIONS, contact Allergan at 1-800-433-8871 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

• Trimethoprim/sulfamethoxazole (TMP/SMX) increases the systemic level of dapsone and its metabolites (7.1).
• Topical benzoyl peroxide used at the same time as **ACZONE** Gel, 7.5% may result in temporary local yellow or orange skin discoloration (7.2).

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 02/2016

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

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

2 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 (2).

3 DOSAGE FORMS AND STRENGTHS

Gel, 7.5%. Each gram of **ACZONE** Gel, 7.5% contains 75 mg of dapsone in an off-white to yellow gel with suspended particles.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Hematological Effects

Methemoglobinemia

Cases of methemoglobinemia, with resultant hospitalization, have been reported postmarketing 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 grey cyanosis seen in e.g., 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 (7.4)]*.

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 (8.6)]*.

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 (7.1)]*.

5.2 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.

5.3 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.

6 ADVERSE REACTIONS

6.1 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 subjects were treated with **ACZONE** Gel, 7.5%, for 12 weeks in 2 controlled clinical trials. The population ranged in age from 12 to 63 years, 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% appear in Table 1 below.

Table 1 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%)

6.2 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).

6.3 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 (5.1)]*.

7 DRUG INTERACTIONS

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

7.1 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.

7.2 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.

7.3 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.

7.4 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 for developing methemoglobinemia *[see Warnings and Precautions (5.1)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 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.

8.3 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.

8.4 Pediatric Use

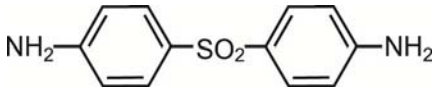
Safety and efficacy was evaluated in 1066 subjects aged 12-17 years old treated with **ACZONE** Gel, 7.5% in the clinical trials. The safety profile for **ACZONE** Gel, 7.5%, was similar to the vehicle control group. Safety and effectiveness of **ACZONE** Gel, 7.5%, have not been established in pediatric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

8.5 Geriatric Use
Clinical trials of **ACZONE** Gel, 7.5% did not include sufficient numbers of subjects aged 65 years and over to determine whether they respond differently from younger subjects.

8.6 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 (5.1)]*.

ACZONE Gel, 5% and vehicle were evaluated in a randomized, double-blind, cross-over 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 (5.1)]*.

11 DESCRIPTION
ACZONE (dapsone) Gel, 7.5%, contains dapsone, a sulfone, in an aqueous gel base for topical dermatologic use. **ACZONE** Gel, 7.5% is an off-white to yellow gel with suspended particles. Chemically, dapsone has an empirical formula of $C_{12}H_{12}N_2O_2S$. It is a white or slightly yellow-white, crystalline powder that has a molecular weight of 248.30. Dapsone's chemical name is 4-[(4-aminobenzene) sulfonyl] aniline and its structural formula is:



Each gram of **ACZONE** Gel, 7.5%, contains 75 mg of dapsone, USP, in a gel of diethylene glycol monoethyl ether, methylparaben, acrylamide/sodium acryloyldimethyl taurate copolymer, isohexadecane, polysorbate 80, and purified water.

12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
The mechanism of action of dapsone gel in treating acne vulgaris is not known.

12.3 Pharmacokinetics
In a pharmacokinetic study, male and female subjects 16 years of age or older with acne vulgaris (N=19) received 2 grams of **ACZONE** Gel, 7.5%, topically to the face, upper chest, upper back and shoulders once daily for 28 days. Steady state for dapsone was reached within 7 days of dosing. On Day 28, the mean dapsone maximum plasma concentration (Cmax) and area under the concentration-time curve from 0 to 24 hours post dose ($AUC_{0\text{-}24h}$) were 13.0 ± 6.8 ng/mL and 282 ± 146 ng·h/mL, respectively. The systemic exposure from **ACZONE** Gel, 7.5% is expected to be about 1% of that from a 100 mg oral dose.

Long-term safety studies were not conducted with **ACZONE** Gel, 7.5%, however, in a long-term clinical study of dapsone gel, 5% treatment (twice daily), periodic blood samples were collected up to 12 months to determine systemic exposure of dapsone and its metabolites in approximately 500 subjects. Based on the measurable dapsone concentrations from 408 subjects (M=192, F=216), obtained at Month 3, neither gender nor race appeared to affect the pharmacokinetics of dapsone. Similarly, dapsone exposures were approximately the same between the age groups of 12-15 years (N=155) and those greater than or equal to 16 years (N=253). There was no evidence of increasing systemic exposure to dapsone over the study year in these subjects.

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