

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

RECENT MAJOR CHANGES

Indications and Usage (1) 09/2019

INDICATIONS AND USAGE

ACZONE® Gel, 7.5%, is a sulfone indicated for the topical treatment of acne vulgaris in patients 9 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 \geq 0.9%) adverse reactions are application site dryness and pruritus (6.1).

To report SUSPECTED ADVERSE REACTIONS, contact **Almirall at 1-866-665-2782 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: 09/2019

FULL PRESCRIBING INFORMATION: CONTENTS*

- | | | | |
|----------|--|-----------|--|
| 1 | INDICATIONS AND USAGE | 8 | USE IN SPECIFIC POPULATIONS |
| 2 | DOSAGE AND ADMINISTRATION | 8.1 | Pregnancy |
| 3 | DOSAGE FORMS AND STRENGTHS | 8.2 | Lactation |
| 4 | CONTRAINDICATIONS | 8.4 | Pediatric Use |
| 5 | WARNINGS AND PRECAUTIONS | 8.5 | Geriatric Use |
| 5.1 | Hematological Effects | 8.6 | Glucose-6-phosphate Dehydrogenase (G6PD) Deficiency |
| 5.2 | Peripheral Neuropathy | 11 | DESCRIPTION |
| 5.3 | Skin Reactions | 12 | CLINICAL PHARMACOLOGY |
| 6 | ADVERSE REACTIONS | 12.1 | Mechanism of Action |
| 6.1 | Clinical Studies Experience | 12.3 | Pharmacokinetics |
| 6.2 | Experience with Oral Use of Dapsone | 12.4 | Microbiology |
| 6.3 | Postmarketing Experience | 13 | NONCLINICAL TOXICOLOGY |
| 7 | DRUG INTERACTIONS | 13.1 | Carcinogenesis, Mutagenesis, Impairment of Fertility |
| 7.1 | Trimethoprim-Sulfamethoxazole | 14 | CLINICAL STUDIES |
| 7.2 | Topical Benzoyl Peroxide | 16 | HOW SUPPLIED/STORAGE AND HANDLING |
| 7.3 | Drug Interactions with Oral Dapsone | 17 | PATIENT COUNSELING INFORMATION |
| 7.4 | Concomitant Use with Drugs that Induce Methemoglobinemia | | |

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

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

ACZONE® (dapson) Gel, 7.5%, is indicated for the topical treatment of acne vulgaris in patients 9 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.

3 DOSAGE FORMS AND STRENGTHS

Gel, 7.5%. Each gram of ACZONE Gel, 7.5% contains 75 mg of dapson 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 dapson 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.

Dapson can cause elevated methemoglobin levels particularly in conjunction with methemoglobin-inducing agents [*see Drug Interactions (7.4)*].

Hemolysis

Oral dapson 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 dapson. Some subjects with G6PD deficiency using dapson 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 dapson or antimalarial medications because of the

(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

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.

The following adverse reactions have been identified during post-approval use of topical dapsone: methemoglobinemia, rash (including erythematous rash, application site rash) and swelling of face (including lip swelling, eye swelling).

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

Risk Summary

There are no available data on ACZONE Gel, 7.5%, use in pregnant women to inform a drug-associated risk for adverse developmental outcomes. The systemic absorption of ACZONE in humans following topical application is low relative to oral dapsone administration [*see Clinical Pharmacology (12.3)*]. In animal reproduction studies, oral doses of dapsone administered to pregnant rats and rabbits during organogenesis that resulted in systemic exposures more than 400 times the systemic exposure at the maximum recommended human dose (MRHD) of ACZONE Gel, 7.5%, resulted in embryocidal effects. When orally administered to rats from the onset of organogenesis through the end of lactation at systemic exposures approximately 500 times the exposure at the MRHD, dapsone resulted in increased stillbirths and decreased pup weight [*see Data*].

The estimated background risks of major birth defects and miscarriage for the indicated population are unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Data

Animal Data

Dapsone has been shown to have an embryocidal effect in rats and rabbits when administered orally daily to females during organogenesis at dosages of 75 mg/kg/day and 150 mg/kg/day, respectively. These dosages resulted in systemic exposures that represented approximately 1407 times [rats] and 425 times [rabbits] the systemic exposure observed in human females as a result of use of the MRHD of ACZONE Gel, 7.5%, based on AUC comparisons. These effects were probably secondary to maternal toxicity.

Dapsone was assessed for effects on perinatal/postnatal pup development and postnatal maternal behavior and function in a study in which dapsone was orally administered to female rats daily beginning on the seventh day

and food consumption) and developmental effects (increase in stillborn pups and decreased pup weight) were seen at a dapson dose of 30 mg/kg/day (approximately 563 times the systemic exposure that is associated with the MRHD of ACZONE Gel, 7.5%, based on AUC comparisons). No effects were observed on the viability, physical development, behavior, learning ability, or reproductive function of surviving pups.

8.2 Lactation

Risk Summary

There is no information regarding the presence of topical dapson in breastmilk, the effects on the breastfed infant or the effects on milk production. Orally administered dapson appears in human milk and could result in hemolytic anemia and hyperbilirubinemia especially in infants with G6PD deficiency. Systemic absorption of dapson following topical application is low relative to oral dapson administration.

The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for ACZONE Gel, 7.5% and any potential adverse effects on the breastfed child from ACZONE Gel, 7.5% or from the underlying maternal condition.

8.4 Pediatric Use

The safety and effectiveness of ACZONE Gel, 7.5% for the topical treatment of acne vulgaris have been established in patients 9 years of age and older. Use of ACZONE Gel, 7.5% in patients 9 to 11 years of age for this indication is supported by evidence from adequate and well-controlled clinical trials in 1066 subjects 12 years of age and older and with additional pharmacokinetic and safety data in pediatric subjects 9 to 11 years of age from an open label study of 100 subjects with acne [see *Adverse Reactions (6.1)*, and *Clinical Pharmacology (12.3)*].

The safety profile for ACZONE Gel, 7.5% in clinical trials 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 9 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.

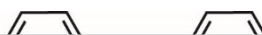
8.6 Glucose-6-phosphate Dehydrogenase (G6PD) Deficiency

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 (dapson) Gel, 7.5%, contains dapson, 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, dapson 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. Dapson's chemical name is 4-[(4-aminobenzene) sulfonyl] aniline and its structural formula is:



Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts



Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research



With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips



Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS

Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS

Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS

Sync your system to PACER to automate legal marketing.