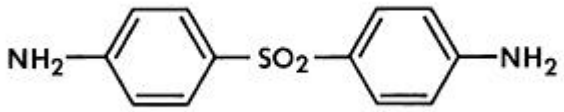
ACZONE™ Gel 5% PACKAGE INSERT

ACZONE™ (dapsone) Gel, 5%

FOR TOPICAL USE ONLY
NOT FOR ORAL, OPHTHALMIC, OR INTRAVAGINAL USE

DESCRIPTION

ACZONE™ Gel, 5%, contains dapsone, a sulfone, in an aqueous gel base for topical dermatologic use. ACZONE™ Gel is a gritty, translucent material with visible drug substance particles. Chemically, dapsone has an empirical formula of $C_{12}H_{12}N_2O_2S$. It is a white, odorless crystalline powder that has a molecular weight of 248. Dapsone's chemical name is 4,4'-diaminodiphenylsulfone and its structural formula is:



Each gram of ACZONE™ (dapsone) Gel, 5%, contains 50 mg of dapsone, USP, in a gel of carbomer 980; diethylene glycol monoethyl ether, NF; methylparaben, NF; sodium hydroxide, USP; and purified water, USP.

CLINICAL PHARMACOLOGY

Mechanism of Action:
The mechanism of action of dapsone gel in treating acne vulgaris is not known.

Pharmacokinetics:
An open-label study compared the pharmacokinetics of dapsone after ACZONE™ Gel, 5%, (110 ± 60 mg/day) was applied twice daily (~BSA 22.5%) for 14 days (n=18) with a single 100 mg dose of oral dapsone administered to a subgroup of patients (n=10) in a crossover design. On Day 14 the mean dapsone $AUC_{0\text{-}24\ h}$ was 415 ± 224 ng•h/mL for ACZONE™ Gel, 5%, whereas following a single 100 mg dose of oral dapsone the $AUC_{0\text{-}infinity}$ was 52,641 ± 36,223 ng•h/mL.

Special Populations: In a clinical study, periodic blood samples were collected up to 12 months to determine systemic exposure of dapsone and its metabolites in approximately 500 patients. Based on the measurable dapsone concentrations from 408 patients (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).

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MICROBIOLOGY

In Vivo Activity: No microbiology or immunology studies were conducted during dapsone gel clinical trials.

Drug Resistance: No dapsone resistance studies were conducted during dapsone gel clinical trials. Therapeutic resistance to dapsone has been reported for *Mycobacterium leprae*, when patients have been treated with oral dapsone.*

*Matsuoka, M. A. Dec 2000. *Mycobacterium leprae* isolate resistant to dapsone, rifampin, ofloxacin and sparfloxacin. Int J Lepr Other Mycobact Dis. 68(4):452-5.

CLINICAL STUDIES

Two randomized, double blind, vehicle controlled, clinical studies were conducted to evaluate ACZONE™ Gel, 5%, for the treatment of patients with acne vulgaris (N=1475 and 1525). The studies were designed to enroll patients 12 years of age and older with 20 to 50 inflammatory and 20 to 100 non-inflammatory lesions at baseline. In these studies patients applied either ACZONE™ Gel, 5%, or vehicle control twice daily for up to 12 weeks. Efficacy was evaluated in terms of success on the Global Acne Assessment Score (no or minimal acne) and in the percent reduction in inflammatory, non-inflammatory, and total lesions.

The Global Acne Assessment Score was a 5-point scale as follows:

- 0 None: no evidence of facial acne vulgaris
- 1 Minimal: few non-inflammatory lesions (comedones) are present; a few inflammatory lesions (papules/pustules) may be present
- 2 Mild: several to many non-inflammatory lesions (comedones) are present; a few inflammatory lesions (papules/pustules) are present
- 3 Moderate: many non-inflammatory (comedones) and inflammatory lesions (papules/pustules) are present; no nodulo-cystic lesions are allowed
- 4 Severe: significant degree of inflammatory disease; papules/pustules are a predominant feature; a few nodulo-cystic lesions may be present; comedones may be present.

The success rates on the Global Acne Assessment Score (no or minimal acne) at Week 12 are presented in Table 1.

Table 1 - Success (No or Minimal Acne) on the Global Acne Assessment Score at Week 12

	Study 1*		Study 2*	
	ACZONE™ N=699	Vehicle N=687	ACZONE™ N=729	Vehicle N=738
Subjects with No or Minimal Acne	291 (42%)	223 (32%)	253 (35%)	206 (28%)

*Analysis excludes subjects classified with minimal acne at baseline

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Table 2 presents the mean percent reduction in inflammatory, non-inflammatory, and total lesions from baseline to Week 12.

Table 2 - Percent Reduction in Lesions from Baseline to Week 12

	Study 1		Study 2	
	ACZONE™ N=745	Vehicle N=740	ACZONE™ N=761	Vehicle N=764
Inflammatory	46%	42%	48%	40%
Non-Inflammatory	31%	24%	30%	21%
Total	38%	32%	37%	29%

The clinical studies enrolled about equal proportions of male and female subjects. Female patients tended to have greater percent reductions in lesions and greater success on the Global Acne Assessment Score than males. The breakdown by race in the clinical studies was about 73% Caucasian, 14% Black, 9% Hispanic, and 2% Asian. Efficacy results were similar across the racial subgroups.

INDICATIONS AND USAGE

ACZONE™ Gel, 5%, is indicated for the topical treatment of acne vulgaris.

Glucose 6-phosphate dehydrogenase (G6PD) levels should be obtained prior to initiating therapy with ACZONE™ Gel, 5%. In patients with a history of anemia and predisposition to increased hemolytic effect with dapsone (e.g., glucose-6-phosphate dehydrogenase deficiency), closer follow-up for blood hemoglobin levels and reticulocyte counts should be implemented (see PRECAUTIONS). Alternatively, other therapies for acne than ACZONE™ Gel, 5%, may be considered.

CONTRAINDICATIONS

ACZONE™ Gel, 5%, is contraindicated in persons with a hypersensitivity to dapsone or any other component of the formulation.

PRECAUTIONS

General

Glucose 6-phosphate dehydrogenase levels should be obtained in all patients prior to initiating therapy with ACZONE™ Gel, 5%. Baseline complete blood counts, including a reticulocyte count, should be obtained in patients who are G6PD deficient or with a history of anemia. Routine follow-up for complete blood count and reticulocyte count

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should be implemented for patients at risk. If signs, symptoms or laboratory evidence of anemia develop during treatment, use of ACZONE™ Gel, 5%, should be discontinued. Dose-related hemolysis is the most common adverse event seen in patients treated with oral Dapsone (with or without glucose-6-phosphate dehydrogenase deficiency). Hemolysis may be exaggerated in individuals with G6PD deficiency, methemoglobin reductase deficiency, or hemoglobin M.

While clinical studies conducted did not demonstrate evidence of clinically significant anemia, an increased reticulocyte count and a decreased hemoglobin level were noted to be associated in a G6PD deficient patient treated with ACZONE™ Gel, 5%, for acne vulgaris who had a complete blood count performed. Only 25 patients with low plasma glucose 6-phosphate dehydrogenase activity treated with ACZONE™ Gel, 5%, were included in the clinical study program. Safety of ACZONE™ Gel, 5%, has not been fully evaluated in patients with G6PD deficiency.

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).

In the clinical trials, a total of 12 out of 4032 patients were reported to have depression (3 of 1660 treated with vehicle and 9 of 2372 treated with ACZONE™ Gel, 5%). Psychosis was reported in 2 of 2372 patients treated with ACZONE™ Gel, 5%, and in 0 of 1660 patients treated with vehicle.

Information for Patients

1. Patients should use ACZONE™ Gel, 5%, as directed by the physician. ACZONE™ Gel, 5%, is for external topical use only. ACZONE™ Gel, 5%, is not for oral, ophthalmic or intravaginal use.
2. Patients should not use this medication for any disorder other than that for which it was prescribed.
3. Patients should tell their physician if they have any history of anemia or an enzyme deficiency (such as G6PD deficiency).
4. Patients should be informed as to the need for laboratory evaluation prior to starting ACZONE™ Gel, 5%.
5. Patients should report any signs of adverse reactions to their physician.
6. Protect ACZONE™ Gel, 5%, from freezing and light. Return to the original carton after application to protect from light.
7. See Patient Information for additional information on safety, efficacy, general use, and storage of ACZONE™ Gel, 5%.

Laboratory Tests

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Glucose 6-phosphate dehydrogenase levels should be obtained in all patients prior to initiating therapy with ACZONE™ Gel, 5%. Baseline complete blood counts, including a reticulocyte count, should be obtained in patients who are G6PD deficient or with a history of anemia. Routine follow-up for complete blood count and reticulocyte count should be implemented for patients at risk.

Drug Interactions

A drug-drug interaction study evaluated the effect of the use of ACZONE 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. Systemic exposure (AUC_{0-12}) of dapsone and N-acetyl-dapsone (NAD) were increased by about 40% and 20% respectively in presence of TMP/SMX. Notably, systemic exposure (AUC_{0-12}) of dapsone hydroxylamine (DHA) was more than doubled in the presence of TMP/SMX. Exposure from the proposed topical dose is about 1% of that from the 100 mg oral dose, even when co-administered with TMP/SMX.

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.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Dapsone was not mutagenic in a bacterial reverse mutation assay (Ames test) using *S. typhimurium* and *E. coli*, with and without metabolic activation and was negative in a micronucleus assay conducted in mice. Dapsone increased both numerical and structural aberrations in a chromosome aberration assay conducted with Chinese hamster ovary (CHO) cells.

In studies conducted for ACZONE Gel, 5%, dapsone was not carcinogenic to rats when orally administered to females for 92 weeks or males for 100 weeks at dose levels up to 15 mg/kg/day (approximately 160 times the systemic exposure observed in human males and 300 times the systemic exposure observed in human females as a result of use of the maximum recommended topical dose, based on AUC comparisons).

No evidence of potential to induce carcinogenicity was obtained in a dermal study in which dapsone gel was topically applied to Tg.AC transgenic mice for approximately 26 weeks. Dapsone concentrations of 3%, 5%, and 10% were evaluated; 3% material was judged to be the maximum tolerated dosage.

ACZONE Gel, 5%, did not increase the rate of formation of ultra violet light-induced skin tumors when topically applied to hairless mice in a 12-month photocarcinogenicity study.

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