

ACZONE® (dapson) Gel 5%

INDICATIONS AND USAGE

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

CONTRAINDICATIONS

None.

WARNINGS AND PRECAUTIONS

Hematological Effects

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.

There was no evidence of clinically relevant hemolysis or anemia in patients treated with **ACZONE®** Gel, 5%, including patients who were G6PD deficient. Some subjects with G6PD deficiency using **ACZONE®** Gel developed laboratory changes suggestive of mild hemolysis.

If signs and symptoms suggestive of hemolytic anemia occur, **ACZONE®** Gel, 5% should be discontinued. **ACZONE®** Gel, 5% should not be used in patients who are taking oral dapsone or antimalarial medications because of the potential for hemolytic reactions. Combination of **ACZONE®** Gel, 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 **ACZONE®** Gel, 5% treatment.

Skin

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 **ACZONE®** Gel, 5% treatment.

ADVERSE REACTIONS

Clinical Studies Experience

Because clinical trials are conducted under prescribed 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.

Serious adverse reactions reported in patients treated with **ACZONE®** Gel, 5%, during clinical trials included but were not limited to the following:

- Nervous system/Psychiatric – Suicide attempt, tonic clonic movements.
- Gastrointestinal – Abdominal pain, severe vomiting, pancreatitis.
- Other – Severe pharyngitis

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.

Combined contact sensitization/irritation studies with **ACZONE®** Gel, 5%, in 253 healthy subjects resulted in at least 3 subjects with moderate erythema. **ACZONE®** Gel, 5%, did not induce phototoxicity or photoallergy in human dermal safety studies.

ACZONE® Gel, 5%, was evaluated for 12 weeks in four controlled studies for local cutaneous events in 1819 patients. The most common events reported from these studies include oiliness/peeling, dryness, and erythema.

One patient treated with **ACZONE®** Gel in the clinical trials had facial swelling which led to discontinuation of medication.

In addition, 486 patients were evaluated in a 12 month safety study. The adverse event profile in this study was consistent with that observed in the vehicle-controlled studies.

Experience with Oral Use of Dapsone

Although not observed in the clinical trials with **ACZONE®** Gel (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).

DRUG INTERACTIONS

Trimethoprim-Sulfamethoxazole

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 (AUC₀₋₁₂) of dapsone and N-acetyl-dapsone (NAD) were increased by about 40% and 20% respectively in presence of TMP/SMX. Notably, systemic exposure (AUC₀₋₁₂) 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.

Topical Benzoyl Peroxide

Topical application of **ACZONE®** Gel followed by benzoyl peroxide in subjects with acne vulgaris resulted in a temporary local yellow or orange discoloration of the skin and facial hair (reported by 7 out of 95 subjects in a clinical study) with resolution in 4 to 57 days.

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.

USE IN SPECIFIC POPULATIONS

Pregnancy

Teratogenic Effects: Pregnancy Category C

There are no adequate and well controlled studies in pregnant women. Dapsone has been shown to have an embryocidal effect in rats and rabbits when administered orally in doses of 75 mg/kg/day and 150 mg/kg/day (approximately 800 and 500 times the systemic exposure observed in human females as a result of use of the maximum recommended topical dose, based on AUC comparisons), respectively. These effects were probably secondary to maternal toxicity. **ACZONE®** Gel, 5%, should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers

Although systemic absorption of dapsone following topical application of **ACZONE®** Gel, 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, 5%, taking into account the importance of the drug to the mother.

Pediatric Use

Safety and efficacy was evaluated in 1169 children aged 12-17 years old treated with **ACZONE®** Gel, 5%, in the clinical studies. The adverse event rate for **ACZONE®** Gel, 5%, was similar to the vehicle control group. Safety and efficacy was not studied in pediatric patients less than 12 years of age, therefore **ACZONE®** Gel, 5%, is not recommended for use in this age group.

Geriatric Use

Clinical studies of **ACZONE®** Gel, 5%, did not include sufficient number of patients aged 65 and over to determine whether they respond differently from younger patients.

G6PD Deficiency

ACZONE® Gel, 5% and vehicle were evaluated in a randomized, double-blind, cross-over design clinical study of 64 patients 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. There were 56 out of 64 subjects who had a Week 2 blood draw and applied at least 50% of treatment applications. **ACZONE®** Gel was associated with a 0.32 g/dL drop in hemoglobin after two weeks of treatment, but hemoglobin levels generally returned to baseline levels at Week 12.

There were no changes from baseline in haptoglobin or lactate dehydrogenase during **ACZONE®** or vehicle treatment at either the 2-week or 12-week time point.

The proportion of subjects who experienced decreases in hemoglobin ≥ 1 g/dL was similar between **ACZONE®** Gel, 5% and vehicle treatment (8 of 58 subjects had such decreases during **ACZONE®** treatment compared to 7 of 56 subjects during vehicle treatment among subjects with at least one on-treatment hemoglobin assessment). Subgroups based on gender, race, or G6PD enzyme activity did not display any differences in laboratory results from the overall study group. There was no evidence of clinically significant hemolytic anemia in this study. Some of these subjects developed laboratory changes suggestive of mild hemolysis.

OVERDOSAGE

ACZONE® Gel, 5%, is not for oral use. If oral ingestion occurs, medical advice should be sought.

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U.S. Patents 5,863,560; 6,060,085; and 6,620,435