PRODUCT MONOGRAPH

PrACZONE®
Dapsone
Topical Gel 5% w/w

Anti-acne Therapy

Bausch Health, Canada Inc.
2150 St-Elzear Blvd. West
Laval, Quebec
H7L 4A8

Date of Approval:
June 3, 2020

Submission Control No: 237591

TABLE OF CONTENTS

PrACZONE®
Dapsone
Topical Gel 5% w/w

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	All Non-Medicinal Ingredients
Topical	Topical Gel 5% w/w	Carbomer 980, Diethylene Glycol, Monoethyl Ether (DGME), Methylparaben, Sodium Hydroxide and Purified Water.

INDICATIONS AND CLINICAL USE

ACZONE (dapsone topical gel 5%) is indicated for the topical treatment of acne vulgaris. ACZONE contains an antibacterial ingredient, dapsone. To reduce the development of drug-resistant bacteria and maintain the effectiveness of dapsone, ACZONE should only be used for the authorized indication and clinical use.

Geriatrics (> 65 years of age)
Clinical studies with ACZONE did not include a sufficient number of these patients to determine whether they respond differently from younger patients.

Pediatrics (12-15 years of age)
ACZONE was studied in 578 12-15-year-old patients, demonstrating a similar safety and efficacy profile to the adult acne vulgaris patient population. ACZONE was not studied in patients less than 12 years of age thus ACZONE is not recommended for use in this age group.

CONTRAINDICATIONS

Patients who are hypersensitive to dapsone, which is a sulfa-containing drug, or to any ingredient in the formulation or component of the container. For a complete listing, see the Dosage Forms, Composition and Packaging section of the Product Monograph.

WARNINGS AND PRECAUTIONS

General

ACZONE (dapsone topical gel 5%) is for external dermatological use only. It is not for ophthalmic use.

Physicians should ascertain whether the patient has a history of any drug sensitivity before prescribing ACZONE.

See **PART III: CONSUMER INFORMATION** (patient package insert) on safety, efficacy, general use and storage of ACZONE.

Carcinogenesis and Mutagenesis

Dapsone increased both numerical and structural aberrations in a chromosome aberration assay conducted with Chinese hamster ovary (CHO) cells. Dapsone was not mutagenic in a bacterial reverse mutation assay (Ames test) with and without metabolic activation and was negative in a micronucleus assay conducted in mice. For further details on carcinogenesis and mutagenesis refer to the TOXICOLOGY section.

Hematologic

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. A sex-linked trait, G6PD deficiency is more common in males but does occur in females. G6PD-deficient persons are more sensitive to oxidative stress, and therefore may have a history of hematological abnormalities following drug exposure, infection, or a history of favism.

In patients treated with ACZONE, including patients who were G6PD deficient, there was no evidence of clinically relevant hemolysis or anemia. A randomized, double-blind, vehicle-controlled, cross-over clinical study was conducted in G6PD-deficient patients with acne vulgaris to evaluate the risk of hemolysis and/or hemolytic anemia with ACZONE treatment. In this study 56 safety-evaluable patients showed no evidence of clinically relevant hemolysis or anemia. Some subjects with G6PD deficiency using ACZONE developed laboratory changes suggestive of mild hemolysis. For further details on this study refer to the CLINICAL TRIALS section.

If signs or symptoms suggestive of hemolytic anemia appear (persistent fatigue, loss of stamina, breathlessness, tachycardia, jaundice, red-brown urine (hemoglobinuria), acute back pain, and splenomegaly) ACZONE should be discontinued. ACZONE should not be used in patients who

are taking oral dapsone or antimalarial medications because of the potential for hemolytic reactions.

Although not observed in the clinical trials with topical dapsone, agranulocytosis (often presenting with lethargy, weakness, fever, sore throat and other signs of infection) has been reported with oral dapsone treatment.

Combination of ACZONE with trimethoprim/sulfamethoxazole (TMP/SMX) may increase the likelihood of hemolysis in patients with G6PD deficiency (See DRUG INTERACTIONS).

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 with congenital or idiopathic methemoglobinemia, are more susceptible to drug-induced methemoglobinemia. Avoid use of ACZONE Gel, 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, 5%, and to 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).

Neurologic

Although not observed in the clinical trials with topical dapsone, peripheral neuropathy (motor loss and muscle weakness), has been reported with oral dapsone treatment.

Ophthalmologic

Patients should avoid contact with the eyes. In case of accidental contact the patient should be advised to rinse with a large amount of water.

Psychiatric

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). Psychosis was reported in 2 of 2372 patients treated with ACZONE, and in 0 of 1660 patients treated with vehicle.

Sexual Function/Reproduction

In rats, dapsone reduced sperm count, motility and density with concomitant increase in non-viable embryos and microscopic changes in the testes and epididymis at oral dosages of ≥ 0.5 mg/kg/day (corresponding to 2.6 times the Maximum Recommended Human Dose

[MRHD], based on AUC comparisons). This dose level did not show any adverse impacts on mating or fertility. Effects on sperm parameters and other changes in testes and epididymis were reversible following a 10-week recovery period (see TOXICOLOGY). There are no adequate and well controlled fertility studies in men.

Skin

Although not observed in the clinical trials with topical dapsone, 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.

Special Populations

Pregnant Women
Dapsone administered to rabbits at oral doses of 150 mg/kg/day (corresponding to 193 times the MRHD, based on AUC comparison) during the major period of organogenesis was associated with an increase in early embryonic loss. Dapsone has also been shown to have an embryocidal effect in rats when given in doses of 75 mg/kg/day (corresponding to 404 times the MRHD, based on AUC comparison). Dapsone given to rats orally at ≥12 mg/kg/day (corresponding to 64.6 times the MRHD respectively, based on AUC comparison) during organogenesis and lactation caused maternal toxicity with increased number of stillborn pups and decreased pup weight with no effects on offspring survival, growth, behavior or reproductive capacity (see TOXICOLOGY). There are no adequate and well controlled studies in pregnant women. ACZONE should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Women
Although systemic absorption of dapsone following topical application of ACZONE 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, taking into account the importance of the drug to the mother.

Pediatrics (12-15 years of age)
Safety and efficacy was evaluated in 578 ACZONE -treated children aged 12-15 years old in two pivotal studies. The adverse event profile in these pediatric patients was no different from the overall study population. However, ACZONE was not studied in patients less than 12 years of age and therefore is not recommended in this age group.

Geriatrics (> 65 years of age)
Clinical studies of ACZONE did not include sufficient number of patients over the age of 65 to determine whether they respond differently from younger patients.

Susceptibility/Resistance

Development of Drug-Resistant Bacteria

Prescribing ACZONE in the absence of the authorized indications is unlikely to provide benefit to the patient and risks the development of drug-resistant bacteria.

The pathogenesis of acne lesions involves inflammation and dapsone has been demonstrated to exert anti-inflammatory effects. Although dapsone resistance studies have not been conducted during dapsone topical gel clinical trials, therapeutic resistance to dapsone has been reported for Mycobacterium leprae, when patients have been treated with oral dapsone. Nevertheless, to reduce any potential risk of the development of resistant organisms, use of ACZONE should be restricted to acne treatment.

Potential for Microbial Overgrowth

Prolonged use of ACZONE Topical Gel may result in overgrowth of non-susceptible organisms. If there is no improvement after 12 weeks, appropriateness of treatment with ACZONE should be reassessed.

No dapsone resistance studies were conducted during dapsone topical gel clinical trials. Therapeutic resistance to dapsone has been reported for Mycobacterium leprae, when patients have been treated with oral dapsone.[3]

ADVERSE REACTIONS

Adverse Drug Reaction Overview

Serious adverse events reported in patients treated with ACZONE (dapsone topical gel 5%) during clinical trials included but were not limited to the following:

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

The most common events reported from these studies include oiliness/peeling, dryness, and erythema.

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse drug reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

The adverse events whether or not related to treatment occurring in at least 1% of patients in either arm in the four vehicle-controlled studies are presented in Table 1.

Table 1 – Adverse events occurring in at least 1% of patients in four vehicle-controlled studies

Adverse Reaction	ACZONE N=1819	Vehicle N=1660
Administrative Site Condition		
Application Site Reaction NOS	18%	21%
Application Site Dryness	17%	17%
Application Site Erythema	14%	15%
Application Site Burning	2%	3%
Application Site Pruritus	1%	2%
Pyrexia	1%	1%
Infections		
Nasopharyngitis	5%	6%
Upper Respiratory Tract Inf. NOS	3%	3%
Sinusitis NOS	2%	1%
Influenza	1%	1%
Respiratory Disorders		
Pharyngitis	2%	2%
Cough	2%	2%
Injury		
Joint Sprain	1%	1%
Nervous System Disorders		
Headache NOS	4%	4%

1819 patients who used ACZONE for 12 weeks in four controlled studies were evaluated for local cutaneous events. The most common events reported from these studies include oiliness/peeling, dryness, and erythema. Application site adverse event data from four controlled clinical trials are presented in Table 2.

Table 2 – Application site adverse events in the four vehicle-controlled studies

	Percentage of Patients by Severity (N=1819)		
Application Site Event	Mild	Moderate	Severe
Erythema	8.5%	4.7%	0.3%
Dryness	13.1%	3.2%	0.3%
Oiliness/Peeling*	12.0%	5.6%	0.3%

* MedDRA Term – Application Site Reaction NOS

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

One patient treated with topical dapsone in the clinical trials had facial swelling which led to discontinuation of medication.

Less Common Clinical Trial Adverse Drug Reactions (<1%)

Adverse reactions (events related to treatment) reported for ACZONE with frequency of <1% in the four vehicle-controlled studies included:

- Application site rash, irritation, edema, pigmentation changes, sunburn, acne aggravated, contact dermatitis, exfoliative dermatitis, dry lip
- Blood creatine phosphokinase, alanine aminotransferase, bilirubin increased, neutrophil count decreased, lymphocyte count increased
- Biopsy tongue abnormal, hypoaesthesia, migraine, ear infection, wheezing, depression.

Post-Market Adverse Drug Reactions

Methemoglobinemia, urticaria, and hypersensitivity, which may occur with one or more of the following adverse reactions: rash (including rash erythematous, application site rash), swelling face (including lip swelling, eye swelling) have been identified during post marketing use of ACZONE Gel, 5% (frequency unknown).

DRUG INTERACTIONS

Overview

Toxicity of dapsone, especially hemolysis is largely attributed to the hydroxylamine metabolite. Enzymes thought to be involved in hydroxylation include CYP 3A4, 2E1, 2C8 and especially 2C9; some of these are inducible by other drugs.

Certain concomitant medications such as rifampin (a CYP 2C enzyme expression inducer), anticonvulsants, and St. John's wort may increase the formation of dapsone hydroxylamine. With oral dapsone treatment, folic acid antagonists such as pyrimethamine have been noted to possibly increase the likelihood of hematologic reactions.

Administering ACZONE (dapsone topical gel) with double strength (160 mg/800 mg) trimethoprim/sulfamethoxazole (TMP/SMX) elevates levels of dapsone and its metabolites, notably the hydroxylamine.

Topical application of ACZONE 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.
Concomitant use of ACZONE 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).

Drug-Drug Interactions

Table 3 – Established or Potential Drug-Drug Interactions

Proper name	Ref	Effect $AUC_{(0-12)}$	Clinical comment
Trimethoprim/sulfa-methoxazole (TMP/SMX: 160 mg/800 mg)	CT (ACZONE)	Dapsone ↑ 40% N-acetyl-dapsone ↑ 20% dapsone hydroxylamine ↑ 100% TMP/SMX essentially unchanged	Exposure from the topical dose is about 1% of that from the 100 mg oral dose, even when co-administered with TMP/SMX.
Rifampin	CS (oral dapsone)	Dapsone hydroxylamine formation is increased	This metabolite associated with hemolysis-relevance to topical application unknown.
St. John's wort	CS (oral dapsone)		
Anticonvulsants	CS (oral dapsone)		
Folic acid antagonists e.g. pyrimethamine (25 mg) and Dapsone (100 mg)	CS (oral dapsone)	There is no change in the AUC but a 17% reduction in the C-max of dapsone.[1]	Increases likelihood of hematologic reactions -relevance to topical application unknown.

Legend: CS = Case Study; CT = Clinical Trial

Drug-Food Interactions

Interactions of ACZONE with food have not been established.

Drug-Herb Interactions

Interactions of ACZONE with herbal products have not been established.

Drug-Laboratory Interactions

Interactions of ACZONE with laboratory tests have not been established.

DOSAGE AND ADMINISTRATION

Recommended Dose and Dosage Adjustment

- Apply twice daily.
- Apply approximately a pea-sized amount of ACZONE (dapsone topical gel 5%), in a thin layer to the acne affected area.
- If there is no improvement after 12 weeks, appropriateness of treatment with ACZONE should be reassessed.

Missed Dose

If an application of ACZONE is missed, it should be applied as soon as possible. However, if it is almost time for the next application, skip the missed application and return to the regular schedule. Applications should not be doubled.

Administration

- After gently washing the skin with a non-medicated soap, pat skin dry.
- Rub in ACZONE gently and completely.
- Wash hands after applying ACZONE.

OVERDOSAGE

ACZONE (dapsone topical gel 5%) is not for oral use. If oral ingestion occurs, seek medical advice or consult a poison control centre. Some symptoms of oral dapsone overdose may include nausea, vomiting, excitation, seizures, and bluish skin color.

ACTION AND CLINICAL PHARMACOLOGY

Pharmacodynamics

The mechanism of action of dapsone topical gel 5% in treating acne vulgaris is not known.

Pharmacokinetics

Male and female patients applied approximately 1 gm ACZONE (dapsone topical gel 5%) to acne affected skin for 28 days either once or twice a day (n=10-13/group) and had plasma samples analyzed by an HPLC method (limit of quantitation of 0.05 ng/mL).

Table 4 – Pharmacokinetics of Dapsone Topical Gel during 28 days of application (N=12)

Parameter	Day	Regimen and dosage	
		q.d.	b.i.d
		50 mg/day	100 mg/day
C_{max} (ng/mL)	1	5.0 ± 2.2	6.2 ± 2.8
	28	10.8 ± 7.0	15.1 ± 7.5
T_{max} (hr)	1	20.3 ± 5.7	22.6 ± 4.6
	28	10.9 ± 7.5	7.5 ± 8.7
AUC $_{0-24}$ (ng·hr/mL)	1	81.9 ± 34.0	84.2 ± 42.6
	28	232.9 ± 144.7	317.9 ± 159.2
T½ (hr)	28	30.5 ± 8.4	27.8 ± 8.3

Absorption

Systemic absorption was very low and reached steady state by week one. After the last dose, concentrations were essentially constant for the first 12 hours then fell with a half life of approximately 30 hours. Notably, a doubling of topical dose had negligible effect on the plasma kinetic parameters.

The pharmacokinetics of dapsone topical gel 5% after twice daily application for 14 days (n=18) was compared with a single 100 mg dose of oral dapsone (after a 14-day washout)

administered to a subgroup of patients (n=10) in a crossover design. The total systemic exposure after repeated application to a maximum intended area of use for 2 weeks were 112 to 145-fold lower that after a single oral 100 mg dose. See Table 5. In 3 patients, eight-hour urinary excretion of dapsone hydroxylamine was 32 to 119-fold lower following 15 days of topical dapsone treatment than a single oral 100 mg dose.

Table 5 – Comparison of pharmacokinetics of dapsone and n-acetyldapsone following repeated topical exposure and a single oral dose

Analyte	Parameter	Topical (Day 14) 110 ± 60 mg/day*	Oral Single Dose 100 mg	Ratio (Oral/Topical)
Dapsone	**C_{max} (ng/mL)**	19.7 ± 10.2	1375.0 ± 517.3	70
	AUC† (ng·hr/mL)	415.0 ± 224.4	52641.0 ± 36223.8	127
	T½ (hr)	46.3	19.3	0.42
N-acetyl dapsone	**C_{max} (ng/mL)**	8.2 ± 6.3	553.0 ± 568.7	67
	AUC_{0-24}(ng·hr/mL)	167.8 ± 134.5	18047.0 ± 18128.3	108
	t½ (hr)	44.9	18.8	0.40

*(~BSA 22.5%)
†-For topical AUC = AUC over 1 dosing interval at steady state. For single oral dose AUC= AUC†(0-∞)

Distribution
About 70% of dapsone is bound to plasma protein. Sulphones such as dapsone are distributed throughout total body water and in many tissues, most especially in liver, kidney and skin following oral administration.

An *in vitro* skin penetration study of single and repeated doses showed that high dapsone concentrations are achieved in the stratum corneum, dermis and epidermis, with minimal penetration of dapsone into the receiver cell.

Metabolism
Dapsone is acetylated in the liver. It is hydroxylated to the hydroxylamine metabolite by CYP 3A4, 2E1, 2C8 and especially 2C9 (see DRUG INTERACTIONS).

Excretion
Urinary excretion accounts for 70-80% of dapsone as mono-M-glucuronide and mono-M-sulfamate, and other metabolites.

Special Populations and Conditions

Pediatrics
In an ACZONE clinical study, periodic determinations of systemic exposure to dapsone and its metabolites were done for 12 months and showed that 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).

Geriatrics
ACZONE was not studied in a geriatric population.

Gender
In an ACZONE clinical study, measurable dapsone concentrations from 408 patients (M=192, F=216) obtained at Month 3, showed that gender did not appear to affect the dapsone pharmacokinetics.

Race
In the same study as described above under '**Gender**', race did not appear to affect the dapsone pharmacokinetics.

Hepatic Insufficiency
ACZONE kinetics were not studied in patients with hepatic insufficiency.

Renal Insufficiency
ACZONE kinetics were not studied in patients with renal insufficiency.

Genetic Polymorphism
Polymorphism exists for the hepatic N-acetylation of dapsone. This is the same enzyme that acetylates isoniazid.

STORAGE AND STABILITY

Store at controlled room temperature (15-30°C). Protect from freezing.

SPECIAL HANDLING INSTRUCTIONS

None required.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Each gram of ACZONE (dapsone topical gel 5%) contains (w/w) 5% dapsone, USP, in an aqueous gel of Carbomer 980; Diethylene glycol Monoethyl Ether (DGME), NF; Methylparaben, NF; Sodium Hydroxide, NF; and Purified Water, USP.
ACZONE is available in the following sizes:

- Physician Sample: 3 g laminate tube.
- Commercially: 60 g laminate tube.

PART II : SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

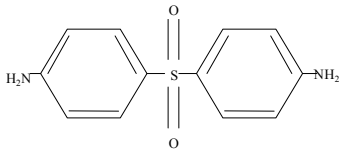
Proper name: Dapsone

Chemical name: 4,4'-Diaminodiphenylsulfone

Molecular formula: $C_{12}H_{12}N_2O_2S$,

Molecular mass: 248.30 g/mol

Structural formula:



Physicochemical properties

Physical description: White to off-white crystalline powder

Polymorphism: There are five or more polymorphic forms possible; only Forms I (anhydrous crystalline polymorph) & III (crystalline hydrate of dapsone) are observed

pH and pK values: pK_b: 13.0

Solubilities: Dapsone is very slightly soluble in water, freely soluble in acetone, sparingly soluble in alcohol, and dissolves freely in dilute mineral acids

Melting point range: Approximately 175-181°C

CLINICAL TRIALS

Pivotal Clinical Studies

Study demographics and trial design

Table 6 – Summary of patient demographics for clinical trials in specific indication[2]

Study #	Trial design*	Dosage, route of administration and duration	Study subjects (n=number) VC/DTG	Mean age (Range) VC/DTG	Gender (%) VC/DTG
DAP0203	R, DB, PG VC, MC	Median dose ≈ 0.6 g gel/application, b.i.d. topical application for 12 weeks	740/745	19.5/19.0	M 45.8/48.1 F 54.2/51.9
DAP0204	R, DB, PG VC, MC	Median dose ≈ 0.6 g gel/application, b.i.d. topical application for 12 weeks	764/761	19.6/19.5	M 47.0/48.2 F 53.0/51.8

*R-randomized, DB-double blind, VC-vehicle controlled, PG-parallel group, MC-Multi-centre, DTG-dapsone topical gel

The clinical studies enrolled about equal proportions of male and female subjects (12 years of age or older). The breakdown by race in the clinical studies was about 73% Caucasian, 14% Black, 9% Hispanic, and 2% Asian.

In the pivotal trials, patients had clinical diagnosis of acne vulgaris of the face, with 20 to 50 inflammatory lesions and 20 to 100 non-inflammatory lesions above the mandibular line at baseline. No nodules or cysts were eligible to enroll in these studies.
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 (commonly referred to as an Investigator's Global Assessment (IGA)) 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.

Study results

The success rates on the Global Acne Assessment Score (no or minimal acne) at Week 12 are presented in Table 7.

Table 7 – Success (No or Minimal Acne) on the Global Acne Assessment Score at Week 12 (MITT* with LOCF§)

	DAP0203			DAP0204		
	ACZONE™ N=699	Vehicle N=687	P value†	ACZONE™ N=729	Vehicle N=738	P value†
No or Minimal Acne	291 (42%)	223 (32%)	0.0001	253 (35%)	206 (28%)	0.0032

*Modified Intent-To-Treat analysis that excludes subjects classified with minimal acne at baseline
†Cochran-Mantel-Haentzel test stratified by centre
§Last-Observation-Carried-Forward (LOCF)

Table 8 presents the mean percent reduction in inflammatory, non-inflammatory, and total lesions from baseline to Week 12.

Table 8 – Percent Reduction in Lesions from Baseline to Week 12 (ITT with LOCF†)

	DAP0203			DAP0204		
Lesion Type	ACZONE™ N=745	Vehicle N=740	P value*	ACZONE™ N=761	Vehicle N=764	P value*
Inflammatory	46%	42%	0.0302	48%	40%	<0.0001
Non-Inflammatory	31%	24%	0.0022	30%	21%	<0.0001
Total	38%	32%	0.0004	37%	29%	<0.0001

†Last-Observation-Carried-Forward (LOCF)
*ANCOVA with baseline count as covariate and centre and treatment as factors

Female patients tended to have greater percent reductions in lesions and greater success on the Global Acne Assessment Score than males. Efficacy results were similar across the racial subgroups.

Glucose-6-phosphate Dehydrogenase (G6PD) Deficiency

ACZONE and vehicle were evaluated in a randomized, double-blind, cross-over design clinical study of 64 G6PD-deficient patients with 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 treatment periods. There were 56 safety-evaluable subjects (those who had a period 1 week 2 blood draw and applied at least 50% of period 1 treatment applications). Table 9 contains results from testing of relevant hematology parameters for these two treatment periods. ACZONE 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.

Table 9 – Hemoglobin, Bilirubin, Reticulocyte, Haptoglobin, and Lactate Dehydrogenase Levels in Acne Subjects With G6PD Deficiency (<7 U/g Hb) in the Cross-Over Study ACZ ACN 01

Parameter	Time Point	Safety-Evaluable (N=56)			
		ACZONE		Vehicle	
		n	Mean ± SD	n	Mean ± SD
Hemoglobin (g/dL)	Pre-treatment	53	13.44 ± 1.34	56	13.36 ± 1.25
	2 weeks	53	13.12 ± 1.36	55	13.34 ± 1.25
	12 weeks	50	13.42 ± 1.24	50	13.37 ± 1.38
Bilirubin (mg/dL)	Pre-treatment	54	0.58 ± 0.28	56	0.55 ± 0.27
	2 weeks	53	0.65 ± 0.32	55	0.56 ± 0.26
	12 weeks	50	0.61 ± 0.32	50	0.62 ± 0.36
Reticulocytes (%)	Pre-treatment	53	1.30 ± 0.46	55	1.34 ± 0.58
	2 weeks	53	1.51 ± 0.52	55	1.34 ± 0.52
	12 weeks	50	1.48 ± 0.59	50	1.41 ± 0.56
Haptoglobin (mg/dL)	Pre-treatment	53	108 ± 44	56	112 ± 51
	2 weeks	53	109 ± 42	54	115 ± 44
	12 weeks	49	114 ± 46	50	111 ± 50
Lactate Dehydrogenase (IU/L)	Pre-treatment	54	175 ± 35	56	175 ± 38
	2 weeks	52	171 ± 32	55	176 ± 39
	12 weeks	49	176 ± 37	50	177 ± 36

The proportion of subjects who experienced decreases in hemoglobin ≥1 g/dL was similar between ACZONE and vehicle treatment (11% compared to 7% at Week 2 and 4% compared to 7% at Week 12 for ACZONE and vehicle, respectively). Subgroups based on gender, race, or G6PD enzyme activity did not display any differences in laboratory results from the overall safety-evaluable group. There was no evidence of clinically relevant hemolysis or anemia in this study. Some subjects with G6PD deficiency using ACZONE developed laboratory changes suggestive of mild hemolysis.

DETAILED PHARMACOLOGY

The anti-inflammatory effect of dapsone does not appear to be related to either the release or metabolism of arachadonic acid in the human skin and must therefore act at loci other than phospholipase A2 or cyclo-oxygenase. The significance of anti-inflammatory activities in treating patients with acne vulgaris is unknown. While the pathogenesis of acne is not clearly established, early inflammatory events may contribute to follicular hyperkeratinization and microcomedone formation. The acne associated bacteria, *Propionibacterium acnes,* is postulated to induce secretion of pro-inflammatory cytokines, release of degradative enzymes, and recruitment and activation of neutrophils and monocytes.

MICROBIOLOGY

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

TOXICOLOGY

The toxicology studies were conducted with dapsone topical gel 5%, dapsone, or the principal excipient, Diethylene Glycol Monoethyl Ether (DGME). The formulation of ACZONE contains 5% dapsone and 25% DGME.

Species/Strain	No. & Gender	Regimen	Formulation				Results	Study
			Dapsone		DGME			
			%	mg/kg	%	mg/kg		
Single-Dose Oral Toxicity: Gavage with topical gel								
Rat Crl:CD(SD)BR	5M + 5F	Single dose 5 g/kg	5	250	25	1250	No deaths during the 14-day study. All rats clinically normal throughout the study. No treatment-related macroscopic changes at necropsy.	ATLS-99
Single-Dose Dermal Toxicity: Topical gel prototype formulation (contains additional propyl parabens)								
Rabbit New Zealand White (NZW)	5M + 5F	Single dose 2 g/kg	1	20	10	200	Very slight (barely perceptible) erythema observed. No treatment-related deaths. Two rabbits had reduced feces on Day 8. Fecal output returned to normal with supplemental water source. No treatment-related macroscopic changes at necropsy.	ATLS-91

Species/Strain	No. & Gender	Duration	Dose				Results	Study
			Dapsone		DGME			
			%	mg/kg/ day	%	mg/kg/ day		
Repeat-Dose Dermal Toxicity: Topical gel								
Mice FVB/N	Range-Finding Phase: 5M + 5F /group (4 groups) Main Phase: 6M + 6F /group (4 groups) TK: 18M + 18F /group (3 groups) 3M + 3F 40% DGME	Range-Finding: 5 days Main: 28 days	0 3 5 10	0 150 250 500	40 17.5 25 40	2000 875 1250 2000	Range-Finding Phase: No mortality or dermal irritation seen, but a tendency toward ↓ BW in mid- and high-dose ♂, and a dose-dependent hyperactivity in both sexes. Main Phase: Mortality, morbidity (2M, 1F) at high dose. Spleen was target organ of toxicity (↑ weight relative to BW). Dapsone dose-related hyperactivity (all groups). Thin appearance (2/6M mid, 5/6M high dose). BW, BW gain, was ↓ mid/high dose. Food consumption ↓ in mid/high dose ♂, high dose ♀. Thyroid follicular cell hyperplasia (4/5M, 6/6F high dose, 1/6F mid dose). TK: High exposures in mice. TK: ♀ > ♂. NOEL: < 3% dapsone/17.5% DGME. The high dose selected for a 6-month study should be <10% dapsone in 40% DGME gel.	ATLS-150

Species/Strain	No. & Gender	Duration	Dose				Results	Study
			Dapsone		DGME			
			%	mg/kg/ day	%	mg/kg/ day		
Mice FVB/N	Range-Finding Phase: 5M + 5F /group (5 groups) Main Phase and TK: 10M[1] + 10F 20M[2] + 20F 25M[3] + 25F 5M[4] + 5F	Range-Finding: 5 days Main: 30 days	0 3 5 10 0 3 10	0[1] 150*[1, 2] 250*[1, 2] 500*[1, 3] 0[4] 150[2] 500[3]	0 0 0 0 25 25 25	0 0 0 0 1250 1250 1250	Range-Finding Phase: All mice survived to termination. Hyperactivity seen in the 3 & 5% dapsone groups, hyper-reactive/excitable 10% ♂ & 3, 5, 10% ♀. ↓ BW in 5, 10% dapsone in ♀ & 10% dapsone in ♂. No signs of dermal irritation. Main Phase: 30-day main study-dermal application of dapsone in either acetone or DGME formulations produced significant toxicological changes including: mortality and morbidity, hyperactivity, evidence of hemolysis (↓ RBC, Hb and Hct, ↑ MCV) with erythropoetic response affecting ♂ > ♀, ↑ heart and liver weights, ↑ bilirubin, and thyroid follicular hyperplasia. Dermal irritation was seen in all acetone formulations, but dapsone/DGME irritation was only in ♀. TK: Both formulations produced much higher exposure in mice than in rats and rabbits. TK: ♀ > ♂. MTD for mouse is 3-5% dapsone in DGME administered at 2 mL/kg.	ATLS-171

*Dapsone in acetone vehicle instead of DGME. Note: toxicokinetics (TK) were performed in main phase as well with dapsone in acetone vehicle. Second superscript denotes group size for toxicokinetic (TK) study.

Species/Strain	No. & Gender	Duration	Dose				Results	Study
			Dapsone		DGME			
			%	mg/kg/ day	%	mg/kg/ day		
Rat Hsd:(SD)CD	10M + 10F /group (4 groups) <u>TK:</u> 6M + 6F /group (2 groups 5%/25% + 10%/40%)	6 months	0 0 5 10	0 0 50 100	0 40 25 40	0 400 250 400	No deaths were attributed to the administration of test or control articles. Hematologic changes including ↓ RBC, Hb and Hct, ↑ MCV, and ↑ splenic weights, affecting ♂ > ♀. Mild subacute mesenteric fat inflammation in ♀. Liver changes seen (↑ ALT, AST, inflammation) not definitively attributed to test article. There were no noteworthy necropsy or histopathology findings. <u>TK:</u> ♀ > ♂.	ATLS-114
Rabbit HM(NZW)/BR	10M + 10F /group (4 groups)	3 months	0 1 5 10	0 10 50 100	40 10 25 40	400 100 250 400	↑ ALT, AST levels, mostly in ♂ treated with high dose, but exact cause could not be determined. There were no noteworthy clinical observations, gross pathology, histopathology, hematology or serum chemistry findings. NOEL: 10% Dapsone/40% DGME.	ATLS-111
Rabbit HM(NZW)/BR	8M + 8F /group (4 groups)	9 months	0 0 5 10	0 0 50 100	0 40 25 40	0 400 250 400	There were no noteworthy clinical observations, gross pathology, histopathology, hematology or serum chemistry findings. NOEL: 10% dapsone/40% DGME.	ATLS-113

Species/Strain	No. & Gender	Duration	Dose				Results	Study
			Dapsone		DGME			
			%	mg/kg/ day	%	mg/kg/ day		
Repeat-Dose Oral Toxicity: Gavage with 0.5% carboxymethyl cellulose (CMC) suspension								
Albino Rats Crl:CD(SD) IGS BR	10M + 10F /group (5 groups) <u>TK:</u> 10M + 10F /group (4 groups - no control)	90 days	N/A	0 0 3 30 100	N/A	0 180 0 0 0	↑ methemoglobin, leukocytes, lymphocytes, and segmented neutrophil counts, especially in ♂ (dose-dependant). Spleen major target organ: ↑ splenic iron, extramedullary haematopoiesis, congested spleens, seen in ♂. Hematological (↓ RBC and Hb, ↑ MCV) and clinical chemistry changes seen (e.g., ↑ ALT, ALP, GGT, bilirubin). ↓ BW in high dose ♂. Hyperactivity. <u>TK:</u> ♀ > ♂. NOAEL: 3 mg/kg/day dapsone, 180 mg/kg/day DGME.	ATLS-117

Genotoxicity: *In vitro*							
System/Cell Type	**Test**	**Metabolic Activation**	**Control**	**Dapsone Conc. (µg/plate)**	**System**	**Results**	**Study**
S. typhimurium and *E. coli* WP2 uvrA	(Ames test) Bacterial reverse mutation assay +/- metabolic activation	Aroclor 1254-induced rat liver S9 fraction	2-Aminoanthracene 2-Nitrofluorene Sodium azide 9-Aminoacridine Methyl methanesulfonate	75 200 600 1800 5000 (in DMSO)	Plate incorporation for 48 to 72 hours	Cytotoxic Effects: None. Genotoxic Effects: None.	ATLS-102
CHO-K_1 Cells	Chromosome aberration +/- metabolic activation	Aroclor 1254-induced rat liver S9 fraction	Mitomycin C	250 500 750 (in DMSO)	Cells treated for 4 and 20 hours in the non-activated, and 4 hours in the S9-activated test systems. All cells harvested at 20 hours after treatment start.	Cytotoxic Effects: Dose-related ↑ in mitotic indices at 4 & 20 hours. Genotoxic Effects: Statistically significant ↑ in numerical chromosome aberrations in the non-activated, 4-hour exposure, 750 µg/mL dapsone groups. Significant structural chromosome aberrations in the non activated, 4-hour exposure, 1500 µg/mL dapsone group. Significant ↑ in structural chromosome aberrations were seen with non-activated, 20-hour exposure, 750 µg/mL dapsone.	ATLS-101

Genotoxicity: *In vivo*							
Species/Strain	**Test**	**Route**	**Control**	**Dose (mg/kg)**	**Cells Evaluated**	**Results**	**Study**
Mice ICR (Single dose)	Bone marrow micronuclei	Intraperitoneal injection	Cyclophos -phamide	160 320 640 (in water)	Polychromatic erythrocytes (PCE)	Toxic/Cytotoxic Effects: At 640 mg/kg/day, clinical signs, three deaths, and ↓ in bone marrow PCEs. Genotoxic Effects: None at 640 mg/kg/day. Evidence of Exposure: Overt toxicity at 1200 mg/kg/day in the pilot assay.	ATLS-103

Species/Strain	**No. & Gender**	**Duration**	**Dose**				**Result**	**Study**
			Dapsone		**DGME**			
			%	**mg/kg**	**%**	**mg/kg**		
Carcinogenicity Oral: Gavage with 0.5% carboxymethyl cellulose (CMC) suspension								
Albino Rats Crl:CD(SD) IGS BR	50M + 50F /group (5 groups)	24 months (104 weeks)	0 0 0.01 0.05 0.15	0 0 1 5 15	0 5.4 0 0 0	0 540 0 0 0	Owing to ↑ mortality in the vehicle groups, sacrifice was early in ♀ (Week 93) & in ♂ (Week 100). Skin discoloration consistent with methemoglobinemia in dapsone ♂. Splenic enlargement in high dose dapsone ♂. No differences in BW, food consumption or hematology. No histopathic, non-neoplastic or neoplastic changes associated with either DGME or dapsone. DGME or dapsone was not potential carcinogens at the doses tested. NOAEL: 5 mg/kg/day dapsone.	ATLS-123

Carcinogenicity Oral: In food								
Mice B6C3F1	14M + 14F (Control) 35M + 35F /group (2 groups)	78 weeks (5 days/ week)	N/A	0 83 (500 ppm) 167 (1000 ppm)	N/A	N/A	↓ BW in ♂. BW effects on ♀ are indeterminate owing to unusually heavy controls. Survival in ♂ mice was 73% in high dose, 63% in low dose, and only 8% in controls. Survival in ♀ was 23% in high dose, 31% in low dose, and 43% in controls. A variety of neoplasms was seen in treated and controls with approximate equal frequency. In this study, dapsone was not carcinogenic.	NCI-CG-TR-20
Rats Fisher 344	15M + 15F (Control) 35M + 35F /group (2 groups)	78 weeks (5 days/ week)	N/A	0 20 (600 ppm) 40 (1200 ppm)	N/A	N/A	↓ BW in ♂ & ♀. Survival in ♂ rats was 51% in treated and 73% in controls, while 80% of ♀ treated & controlled survived. Malignant lymphomas and mesenchymal tumors (primarily spleen, but also pancreas, peritoneum, mesentery, abdominal cavity) were seen in low & high dose treated ♂. Neoplastic and non-neoplastic changes of the connective tissue were seen (osseous metaplasia). In this study, dapsone was carcinogenic (sarcomagenic) in ♂ but not in ♀.	NCI-CG-TR-20

Species/Strain	No. & Gender	Duration	Dose				Result	Study
			Dapsone		DGME			
			%	mg/kg	%	mg/kg		
Carcinogenicity Dermal: Topical gel								
Mice Tg.AC	25M + 25F /group (7 groups) 10M + 10F (TPA in acetone)	26 weeks- 33-week extension	0* 3 5 10 5	0 150 250 500 250	25 25 25 25 Aceto ne	1250 1250 1250 1250 N/A	Treatment-related follicular thyroid hyperplasia seen in dapsone treated ♀ & ♂. Toxicologic findings (mortality, clinical signs, body and organ weights, hematology, spleen effects, and gross and microscopic pathology) showed that the mid- & high doses are ≥ species MTD. No dose relationship in squamous papillomas at the site of application or elsewhere. There was no tumorogenic response even at doses exceeding the maximally tolerated.	ATLS-163
*Controls groups of 20 mcg TPA in 25% DGME, 1.25 mcg TPA in acetone & acetone alone were also studied.								
Hairless Albino Mice Crl:SKH1-hrBR	10F /group (5 groups)	2 weeks (5 days/ week)	0 5 5 10 10	0 100 200 200 400	0 25 25 40 40	0 500 1000 800 1600	Two animals died in the high dose group. ↓ BW. Hyperactivity was elicited in all dapsone/DGME formulations. No irritation elicited at the application site. TK: High systemic exposure.	ATRS-427
Hairless Albino Mice Crl:SKH1-hrBR	10M + 10F /group (10 groups)	13 weeks (5 days/ week) ± UV (600RBU M, W, F)	0 0 1 5 10	0 0 10 50 100	0 40 10 25 40	0 400 100 250 400	Hyperactivity was seen at mid and high doses and hyper-reactivity and ↓ in mean BW was seen at high dose. No erythema, edema or flaking was observed. Based on data, 1/10, 3/17.5 & 5/25 (%DAP/% DGME) at 0.05 mL be used for a 12-month study.	ATLS-118

Species/Strain	No. & Gender	Duration	Dose				Result	Study
			Dapsone		DGME			
			%	mg/kg	%	mg/kg		
Hairless Albino Mice Crl:SKH1-hrBR (Photo-carcinogenicity)	36M + 36F /group (6 groups)*	40 weeks (5 days/ week) + UV (600RBU 5 days/ week) +12 weeks observed	0 1 3 5	0 10 30 25	25 10 17.5 25	250 100 175 250	Hyperactivity was seen at mid and high doses. Skin tumor development was identical in DGME and vehicle controls and reduced with dapsone/DGME (fewer and smaller tumors, smaller tumor yield and delayed tumor onset). Erythema, edema, flaking, thickening, wrinkling, residue, and erythemic raised areas seen in all groups. Erythema grade 1-3 and edema grade 1 was reduced in some dapsone/DGME groups.	ATLS-122
*Two calibration groups were untreated and were exposed to UV only (600RBU or 1200 RBU).								
Reproduction Oral Toxicity: Gavage with 0.5% carboxymethyl cellulose (CMC) suspension								
Range-Finding								
Rats Crl:CD®(SD) IGS BR VAF/Plus®	8F pregnant /group (6 groups)	F: Day of Gestation (DG) 7 to 17	N/A	0 0 3 30 100 300	N/A	0 180 0 0 0 0	The 300 mg dapsone group was terminated early due to severe maternal toxicity. Transient BW and food consumption changes were seen in the 30 mg group. Maternal toxicity (↓ BW & food consumption, clinical observations) was seen with 100 mg. ↓ fetal BW was seen with 100 mg. No adverse effects were seen with 180 mg DGME. Data suggested that 12, 30 and 75 mg dapsone, and 180 mg DGME be used in further testing.	ATLS-115
Rabbit Hra:(NZW)SPF	8F pregnant /group (6 groups) TK: 3F pregnant /group (5 groups)	F: DG 6 to DG 18	N/A	0 0 3 30 100 300	N/A	0 180 0 0 0 0	Dose dependant ↓ in BW gain, food consumption with dapsone >30 mg/kg/day. Maternal death, weight loss, whole litter resorption, ↓ fetal weights seen with dapsone 300 mg/kg/day. TK: Dapsone exposure was nearly linear over a wide dose range. Suggested dose for further testing: 6, 30, 150 dapsone, and 180 DGME mg/kg/day.	ATLS-116

Species/Strain	No. & Gender	Duration	Dose				Result	Study
			Dapsone		DGME			
			%	mg/kg	%	mg/kg		
Reproduction Oral Toxicity (Male Fertility): Gavage with 0.5% carboxymethyl cellulose (CMC) suspension								
Rats Crl:CD®(SD) IGS BR VAF/Plus® Main Study	25M + 25F un-treated for mating /group (5 groups)	M: 63 days prior to and 19 days during cohabi-tation	N/A	0 0 12 30 75	N/A	0 180 0 0 0	Paternal NOAEL: Dapsone <12, DGME 180 mg/kg/day, based on clinical observations, enlarged spleens, ↓ BW, BW gain, and food consumption seen with dapsone. Reproductive NOAEL: Dapsone <12, DGME 180 mg/kg/day based on ↓ sperm count & motility, implantations and viable embryos seen with dapsone.	ATLS-119
Rats Crl:CD®(SD) IGS BR VAF/Plus® Study Extension	25M + 25F un-treated for mating /group (4 groups)	M: 63 days prior to and 19 days during cohabi-tation	N/A	0 0.5 3 12	N/A	N/A	Paternal NOAEL: 0.5 mg/kg/day dapsone based on clinical observations, enlarged spleens, ↓ BW gain, and ↑ relative food consumption seen with higher dapsone dosages. Reproductive NOAEL: 0.5 mg/kg/day dapsone based on ↓ sperm count, density, motility, corpora lutea, implantations and viable embryos, and ↑ non-viable embryos. Microscopic changes in testes and epididymis.	ATLS-119 continuation
Rats Crl:CD®(SD) IGS BR VAF/Plus®	40M + 40F un-treated for mating /group (5 groups) 3M/group were also used for TK	M: 63 days prior to and until the end of cohabi-tation + 4 & 10 weeks recovery	N/A	0 0.25 0.5 1 2	N/A	N/A	1 & 2 mg/kg/day dapsone caused germ cell necrosis and germ cell related changes in seminiferous and epididymal tubules (↑ residual bodies in the lumen of the seminiferous tubules & ↑ exfoliated germ cells/residual bodies in the epididymal tubules). Percent motile sperm was ↓ with 2 mg/kg/day dapsone. The effects were not all reversible following a 4-week recovery period but were after 10-weeks recovery. Paternal NOEL (general toxicity): > 2 mg/kg/day dapsone. Reproductive NOEL: 0.5 mg/kg/day dapsone.	ATLS-183

Species/Strain	No. & Gender	Duration	Dose				Result	Study
			Dapsone		DGME			
			%	mg/kg	%	mg/kg		
Segment I/II Oral Toxicity (Fertility and Teratogenicity): Gavage with 0.5% carboxymethyl cellulose (CMC) suspension								
Rats Crl:CD®(SD) IGS BR VAF/Plus®	25F /group (5 groups)	F: 15 days prior to cohabi-tation to DG 17	N/A	0 0 12 30 75	N/A	0 180 0 0 0	Maternal and Developmental NOEL: Dapsone 12, DGME 180 mg/kg/day. Dapsone 30 & 75 mg/kg/day were associated with ↓ BW, feed consumption, or weight gain. Significantly ↑ resorptions and significantly ↓ corpora lutea, implantation, litter size and number of live fetuses with 30 & 75 mg/kg/day. Reproductive NOEL: Dapsone 75, DGME > 180 mg/kg/day (no effects on fertility and mating).	ATLS-120
Segment II Oral Toxicity (Teratogenicity): Gavage with 0.5% carboxymethyl cellulose (CMC) suspension								
Rabbit Hra:(NZW)SPF	20F /group (5 groups)	DG 6 to DG 18	N/A	0 0 6 30 150	N/A	0 180 0 0 0	Maternal NOAEL: Dapsone 30, DGME 180 mg/kg/day. Dapsone was associated with abortion, premature delivery, adverse clinical observations, ↓ BW and food consumption at 150 mg/kg/day. Developmental NOEL: Dapsone 30, DGME 180 mg/kg/day. Dapsone 150 mg/kg/day produced early resorptions.	ATLS-121
Rat Sprague-Dawley	25F /group (4 groups)	DG 6 to DG 17	N/A	N/A	N/A	0 300 1000 2000	2000 mg/kg/day DGME produced maternal toxicity (↓ BW and food consumption). Skeletal embryo-fetal effects were observed, such as a dose-dependent ↓ in cranial, mandibular, sternebrae, vertebrae, and cervical bone ossifications. The skeletal findings were not considered indicative of teratogenicity. DGME had no effect on pregnancy parameters, fetal weights, or sex ratios. Maternal NOAEL: 1000 mg/kg/day DGME. Embryo-fetal NOAEL: 300 mg/kg/day DGME.	Gattefossé 935/122

Species/Strain	No. & Gender	Duration	Dose				Result	Study
			Dapsone		DGME			
			%	mg/kg	%	mg/kg		
Segment III Oral Toxicity (Perinatal and Postnatal): Gavage with 0.5% carboxymethyl cellulose (CMC) suspension								
Rats Crl:CD®(SD) IGS BR VAF/Plus®	25F /group (5 groups)	F: DG 7 to DG 24* or DL -27 *if no litter born	N/A	0 0 3 12 30	N/A	0 180 0 0 0	Maternal NOEL: Dapsone 3 mg/kg/day (higher doses produced ↓ BW, BW gains, food consumption), DGME <180 mg/kg/day (a dose that ↓ BW during gestation). Developmental NOEL: Dapsone 3 mg/kg/day, DGME <180 mg/kg/day-based on ↑ in stillborn pups and ↓ pup weight with 12 &/or 30 mg/kg/day dapsone. F_1 Generation NOAEL: dapsone 30, DGME 180 mg/kg/day. No adverse effects on viability, growth or reproductive capacity.	ATLS-137
Local Tolerance Dermal (Intact and Abraded Skin, 24 Hour Exposure): Topical gel, FHSA Draize methodology								
Rabbit NZW	2M + 4F single animals	Single dose 0.5 mL /site	5	N/A	25	N/A	Under the conditions tested, 5% dapsone/25% DGME was not considered a primary irritate on normal or abraded skin.	ATLS-96
Acute Dermal Toxicity (Intact and Abraded Skin): Topical gel, FHSA Draize methodology								
Rabbit NZW	5M + 5F single animals	Single dose 2 g/kg	5	N/A	25	N/A	There was barely perceptible dermal irritation on Day 1, all animals. There were no deaths, change in BW or clinical observations. Under the conditions tested, 5% dapsone/25% DGME was not considered toxic at a dose of 2000 mg/kg by the dermal route.	ATLS-100
Local Tolerance Single Ocular Instillation: Topical gel, FHSA Draize methodology								
Rabbit NZW	6 (any sex) single animals	Single dose 0.1 mL /eye	5	N/A	25	N/A	At 24, 48- and 72-hours post-installation no significant ocular irritation was found.	ATLS-97

Species/Strain	No. & Gender	Duration	Dose				Result	Study
			Dapsone		DGME			
			%	mg/kg	%	mg/kg		
Sensitization Dermal								
Delayed 3-Week Dermal Contact Sensitization: Topical gel								
Guinea Pig Crl:(HA)BR	15F 10-test 5-saline	Induction: 3 weeks (3 days /week) (M, W, F) Challenge: 13 days after induction	5	40	25	200	No dermal reactions were seen in the 3-week repeated-dose induction phase of the study. There was no evidence of delayed dermal sensitivity, at 24, 48, and 72 hours after challenge.	ATLS-98

Phototoxicity Dermal: Topical gel prototype formulation (contains additional propyl parabens) with UVA and UVB irradiation with 8-methoxypsoralen (8-MOP) as positive control						
Species/Strain	**No. & Gender**	**Vehicle for active***	**Tested Agent***	**Irradiation**	**Results**	**Study**
Guinea Pig Crl:(HA)BR	5M /group (7 groups)	10% DGME	dapsone 1, 5%, vehicle	UVA/UVB	Single topical application of formulations of 10 and 25% DGME and 1 and 5% dapsone did not elicit any skin responses from irradiation. The active comparator, 8-MOP, produced evidence of phototoxicity with UVA or UVB irradiation.	ATLS-95a
		25% DGME	dapsone 1, 5%, vehicle	UVA/UVB		
		Methanol	8-MOP 0.01, 0.1, 1.0 mg/mL, vehicle	UVA/UVB		
		10% DGME	dapsone 1, 5%, vehicle	None		
		25% DGME	dapsone 1, 5%, vehicle	None		
		25% DGME	dapsone 1, 5%, 5%/10% DGME, vehicle	UVA		
		Methanol	8-MOP 0.01, 0.1, 1.0 mg/mL, vehicle	UVA		
*10% DGME: 5 mg/kg; 25% DGME: 12.6 mg/kg; 1% dapsone: 0.5 mg/kg; 5% dapsone: 2.5 mg/kg.						

Photoallergy Dermal: Topical gel prototype formulation (contains additional propyl parabens). 4-day induction with 5% dapsone/25% DGME or 30 mg/mL TCSA* as positive control							
Species/Strain	**No. & Gender**	**Challenge Agent**	**Challenge Strengths**	**Induction**	**Challenge**	**Results**	**Study**
Guinea Pig Crl:(HA)BR	5M /group (6 groups)	TCSA	0, 3, 10, 30 (mg/mL)	UV	UV	DGME alone or with dapsone produced no photoallergy or hypersensitivity. Minor skin irritation was attributed to induction procedures. No effects seen on BW, mortality or clinical signs. The positive control, TCSA, induced strong dose-dependant photoallergy response.	ATLS-95b
				UV	--		
		Dapsone/ DGME	0/25, 1/10, 1/25, 5/10 (%/%)	UV	UV		
				UV	--		
				--	UV		
				--	--		
*3,3',4',5'-tetrachlorosalicyanilide in acetone: corn oil (4:1).							

Immunotoxicity Oral: Gavage with 0.5% carboxymethyl cellulose (CMC) suspension				
Species/Strain	**Treatment Regimen**		**Results**	**Study**
	Dapsone	**Cyclophosphamide**		
Mice (F) C57BL/6	0, 3.4, 13.5, 54.0 mg/kg/day (0.5% CMC suspension) 30 days	25 mg/kg I.P. 4 days prior to sacrifice	Immunotoxicity was seen at the highest dose. Significant ↑ in spleen weights (enlarged and dark red). Significant ↑ in nucleated spleen cell numbers seen in the high-dose group (139% of control), although the PFC response following SRBC immunization was not altered. ↑ in leukocytes & ↓ in B cells in the high-dose group. Erythropenia was observed at the highest dose and was associated with ↓ hematocrit, which was significant at both the middle- and high-dose levels. No effects on cell-mediated immunity (MLR response or CTL response) or NK cell activity. The immunotoxicity pattern appeared to be related to sensitivity in humoral immunity manifested as augmented responses.	IMM90015

REFERENCES

1. Ahmad RA, Rogers, HJ. Pharmacokinetics and Protein Binding Interactions of Dapsone and Pyrimethamine. Br J Clin Pharmac. 1980 (10):519-24.

2. Draelos ZD, Carter E, Maloney JM, Elewski B, Poulin Y, Lynde C, Garrett S. Two randomized studies demonstrate the efficacy and safety of dapsone gel, 5% for the treatment of acne vulgaris. J Am Acad Dermatol 2007;56:439.e1-e10.

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

PART III: CONSUMER INFORMATION

PrACZONE®
Dapsone topical gel 5%

This leaflet is part III of a three-part "Product Monograph" published when ACZONE was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about ACZONE. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:
ACZONE is a topical prescription medicine used to help treat acne in people 12 years of age and older. ACZONE can be used to help treat acne on the face, chest, back, and shoulders.

ACZONE contains an antibacterial ingredient called dapsone, and it should be used exactly as directed by your healthcare professional. Misuse or overuse of ACZONE could lead to the growth of bacteria that will not be killed by dapsone. This means that ACZONE or other medicines that contain dapsone may not work for you in the future. Do not share your medicine.

What it does:
It is not known exactly how ACZONE works.

When it should not be used:
Do not use ACZONE if you are allergic to dapsone (a drug that contains sulfa) or any of the non-medicinal ingredients in ACZONE. See the section 'What the non-medicinal ingredients are', below.

What the medicinal ingredient is:
The active ingredient in ACZONE is dapsone.

What the important nonmedicinal ingredients are:
Carbomer 980, Diethylene Glycol Monoethyl Ether (DGME), Methylparaben, Sodium Hydroxide, and Purified Water.

What dosage forms it comes in:
ACZONE is a topical gel of 5% dapsone w/w in an aqueous base.

WARNINGS AND PRECAUTIONS

BEFORE you use ACZONE talk to your doctor or pharmacist if you:

- are pregnant or planning to be pregnant. Your doctor will decide with you whether the benefit justifies the risk to the foetus.
- are breast feeding or planning to breast feed. Dapsone is excreted in human breast milk. Your doctor will decide with you whether you should continue breastfeeding or discontinue ACZONE.
- are less than 12 years of age.
- are using other products including cosmetics or medicines applied to the skin.
- have glucose-6-phosphate dehydrogenese (G6PD) deficiency.
- have history of slate grey or blueish discoloration of skin, mucous membranes, lips and nail beds due to lack of sufficient oxygen in the blood (methemoglobinemia).

It is important to let your doctor know about all the medicines you are taking including prescription and non-prescription medicines, vitamins and herbal supplements.

When using ACZONE avoid contact with, eyes mouth and mucous membranes. If you experience excessive redness or peeling contact your doctor.

INTERACTIONS WITH THIS MEDICATION

Use of benzoyl peroxide together with ACZONE at the same time may cause your skin and facial hair to temporarily turn yellow or orange at the site of application. The use of any other topical medications, including benzoyl peroxide at the same time as ACZONE should be discussed with your doctor or pharmacist.

PROPER USE OF THIS MEDICATION

Usual dose - Adults and children over 12 years of age:
Be sure to follow your doctor's instructions on how to use ACZONE.

Use ACZONE once in the morning and once in the evening or as your doctor has prescribed.

A pea-sized amount of ACZONE will usually be enough to cover the cheeks, chin, and forehead.

To use ACZONE correctly follow these steps:

- Wash the areas of your skin where you will apply ACZONE with a mild non-medicated soap. Gently pat your skin dry with a clean towel.
- Apply a thin layer of ACZONE to the areas of your skin that have acne.
- Avoid contact with eyes, mouth, and mucous membranes. In case of accidental contact rinse with large amounts of water.
- Rub the medicine in gently and completely.
- Make sure to put the cap back on the tube and close it tightly.
- Wash your hands after applying ACZONE.
- Do not expect to see an immediate improvement in your acne but be patient and continue to use your medication as directed.
- ACZONE has been prescribed by your doctor for you. Do not allow others to use this medication.

Overdose:
ACZONE is not for oral use. If oral ingestion occurs, seek medical advice or consult a poison control centre.

Missed Dose:
If an application of ACZONE is missed, it should be applied as soon as possible. This will help to keep a constant amount of medication in the skin. However, if it is almost time for the next application, skip the missed application and go back to the regular schedule. Do not double applications.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Like all medicines, ACZONE can cause some side effects, including dryness, redness, oiliness, peeling, rash, hives, and swelling of the face including lips and eyes. These side effects are usually mild. Call your doctor if you have any side effects that do not go away or bother you.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

The active ingredient of ACZONE (called dapsone) has been associated with blood cell abnormalities, usually when taken orally as a pill. Applying ACZONE on the skin is not expected to put enough dapsone in the blood to cause these abnormalities, and they have not been seen in ACZONE clinical trials. Nonetheless, methemoglobinemia has been reported during use of ACZONE Gel, 5%.

You are advised to be alert for the symptoms suggestive of these conditions (see "Anemia", "Methemoglobinemia "and "Low white blood cell" symptoms below) and follow the instructions indicated if they happen to you.

Symptom / effect		Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
		Only if severe	In all cases	
Uncommon				
Pancreatitis symptoms (pancreas inflammation)				
	persistent low-grade fever		✓	
	nausea		✓	
	vomiting		✓	
	persistent abdominal pain			✓
Anemia symptoms				
	rapid heart beat			✓
	breathlessness			✓
	loss of stamina			✓
	red-brown urine			✓
	persistent fatigue			✓
	acute back pain			✓
	jaundice (yellow eyes or skin)			✓

Symptom / effect		Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
		Only if severe	In all cases	
Uncommon				
Methemoglobinemia symptoms (high levels of methemoglobin in the blood)				
	headache		✓	
	fatigue		✓	
	dizziness			✓
	slate grey or blueish coloring of the skin, especially in: buccal mucous membranes, lips and nail beds			✓
	breathlessness			✓
Low white blood cell symptoms				
	persistent lethargy		✓	
	weakness		✓	
	sore throat		✓	
	persistent fever		✓	
	other symptoms of infections			✓

This is not a complete list of side effects. For any unexpected effects while taking ACZONE, contact your doctor or pharmacist.

HOW TO STORE IT

Store at controlled room temperature, 15-30ºC. Protect from freezing. Keep out of reach of children and pets.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

Visiting the Web page on Adverse Reaction Reporting (http://www.hc-sc.gc.ca/dhp-mps/medeff/report-declaration/index-eng.php) for information on how to report online, by mail or by fax; or

Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

Talk to your healthcare professional.

Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html); by contacting the sponsor: Bausch Health, Canada Inc., 2150 St-Elzéar Blvd. West, Laval, (Quebec) H7L 4A8; or by calling 1-800-361-4261.

This leaflet was prepared by Bausch Health, Canada Inc.

Last revised: June 3, 2020