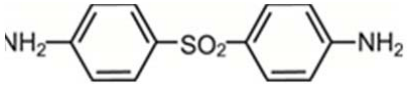
ACZONE®

NAME OF THE DRUG
The active constituent of ACZONE® 7.5% w/w gel is dapsone.

DESCRIPTION
The molecular weight of dapsone is 248.

Chemical structure of dapsone:



CAS: 80-08-0

Chemical Name: 4,4'-diaminodiphenylsulfone.

Empirical formula: $C_{12}H_{12}N_2O_2S$

Composition:
Each gram of ACZONE® gel, 7.5% w/w, contains 75 mg of dapsone, in a gel of: diethylene glycol monoethyl ether (DGME); methyl hydroxybenzoate; acrylamide/sodium acryloyldimethyltaurate copolymer; isohexadecane; polysorbate 80 and purified water.

PHARMACOLOGY

PHARMACODYNAMICS
The anti-inflammatory properties of dapsone result from inhibition of granulocyte cytotoxicity, via inhibition of peroxidases and scavenging of reactive oxygen species. The antimicrobial properties of dapsone result from competitive inhibition of dihydropteroate synthase, a bacterial enzyme necessary for synthesis of folic acid. The mechanism of action of dapsone gel in treating acne vulgaris is not known.

PHARMACOKINETICS
Absorption:
In a pharmacokinetic study, male and female subjects with acne vulgaris were randomised to receive either 2 grams of ACZONE® gel, 7.5% w/w, topically to the entire face, upper chest, upper back and shoulders once daily for 28 days (N=19) or 2 grams of dapsone gel, 5%, topically to the same application area twice daily for 28 days (N=18). Steady state for dapsone was reached within 7 days of dosing for both treatment groups. On Day 28, the mean dapsone $AUC_{0\text{-}24h}$ was 282 ± 146 ng·h/mL for ACZONE® gel, 7.5% w/w, given once daily, whereas the mean dapsone $AUC_{0\text{-}24h}$ was 379 ± 142 ng·h/mL for dapsone gel, 5%, given twice daily. The daily systemic exposure following once daily application of ACZONE® gel, 7.5% w/w, was approximately 28.7% lower relative to dapsone gel, 5%, given twice daily. The systemic exposure from ACZONE® gel, 7.5% w/w is expected to be about 1% of that from a 100 mg oral dose.

Distribution:
Following oral administration, approximately 74% of dapsone is bound to plasma proteins.

Metabolism:
Following oral administration, dapsone is metabolised by two major pathways to form N-acetyl dapsone and dapsone hydroxylamine.

Excretion:
Following oral administration, approximately 85% of the administered dapsone is recovered in urine, mainly as soluble metabolites, and only a small fraction (5% to 15%) is excreted as unchanged drug in humans.

CLINICAL STUDIES

The safety and efficacy of once daily use of ACZONE® 7.5% w/w gel was assessed in two large 12-week multicentre, randomised, double-blind, vehicle-controlled studies (Studies 1 and 2). Efficacy was assessed in a total of 4340 patients 12 years of age and older with moderate acne vulgaris, 20 to 50 inflammatory and 30 to 100 non-inflammatory lesions at baseline, who were randomised to receive either ACZONE® 7.5% w/w gel or vehicle, where vehicle has the same formulation as ACZONE® 7.5% w/w gel without the active ingredient dapsone

The co-primary efficacy variables for these studies were:

- Proportion of patients with either 0 (none) or 1 (minimal) on the Global Acne Assessment Score at week 12
- Mean reduction in absolute lesion count from baseline at week 12 in
    - inflammatory lesions
    - non-inflammatory lesions

Additional efficacy variables were:

- Mean reduction in absolute total lesion count from baseline at week 12
- Percent reduction in lesion count from baseline at week 12 in
    - total lesions
    - inflammatory lesions
    - non-inflammatory lesions

Success was defined as a score of “none” (Score 0) or “minimal” (Score 1) on the Global Acne Assessment Score (GAAS) at week 12. The GAAS used a 5-point scale as shown in Table 1. There was an improvement in GAAS and lesion count in both the ACZONE® 7.5% w/w and vehicle groups. There was a statistically significant treatment effect favouring ACZONE® 7.5% w/w gel compared to vehicle at week 12 (Table 2).

Table 1 Global Acne Assessment Score

Grade		Description
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

Table 2 GAAS Success and Reduction in Lesion Counts at Week 12

	Study 1				Study 2			
	ACZONE® gel, 7.5% w/w (N=1044)	**Vehicle (N=1058)**	**ACZONE® vs Vehicle**	**P-value**	**ACZONE® gel, 7.5% w/w (N=1118)**	**Vehicle (N=1120)**	**ACZONE® vs Vehicle**	**P-value**
Global Acne Assessment Score								
GAAS Success (Score 0 or 1)	30%	21%	9%	< 0.001[a]	30%	21%	9%	< 0.001[a]
Inflammatory Lesions								
Mean absolute reduction	16	14	2	< 0.001[b]	16	14	2	< 0.001[b]
Mean percent reduction	56%	49%	7%	< 0.001[b]	54%	47%	7%	< 0.001[b]
Non-inflammatory Lesions								
Mean absolute reduction	21	18	3	< 0.001[b]	21	19	2	0.004[b]
Mean percent reduction	44%	38%	6%	< 0.001[b]	46%	40%	6%	< 0.001[b]
Total Lesions								
Mean absolute reduction	37	32	5	< 0.001[b]	36	32	4	< 0.001[b]
Mean percent reduction	49%	42%	7%	< 0.001[b]	49%	43%	6%	< 0.001[b]

a P-values for the test of general association between the responder and treatment group used a Cochran Mantel-Haenszel test stratified by sex.

b P-values for between-group comparison were obtained from an analysis of covariance model including treatment, baseline, and sex.

INDICATIONS

For the topical treatment of acne vulgaris in patients 12 years of age and older.

CONTRAINDICATIONS

ACZONE® 7.5% w/w gel is contraindicated in individuals who have shown hypersensitivity to any of its components.

ACZONE® 7.5% w/w gel is contraindicated in individuals with congenital or idiopathic methaemoglobinaemia

PRECAUTIONS

Haematological Effects

Oral dapsone treatment has produced dose-related haemolysis and haemolytic anaemia. Individuals with glucose-6-phosphate dehydrogenase (G6PD) deficiency are more prone to haemolysis with the use of certain drugs. G6PD deficiency is most prevalent in populations of African, South Asian, Middle Eastern and Mediterranean ancestry.

In clinical studies, there was no evidence of clinically relevant haemolysis or haemolytic anaemia in patients treated with topical dapsone.

ACZONE® 7.5% w/w gel, should be discontinued if signs and symptoms suggestive of haemolytic anaemia occur. Avoid use of ACZONE® 7.5% w/w gel in patients who are taking oral dapsone or antimalarial medications because of the potential for haemolytic reactions.

The combination of topical dapsone with trimethoprim/sulfamethoxazole (TMP/SMX) may increase the likelihood of haemolysis in patients with G6PD deficiency.

Methaemoglobinaemia has been reported for oral dapsone and has been reported in postmarketing cases for topical dapsone. Patients with G6PD deficiency or congenital or

idiopathic methaemoglobinaemia are more susceptible to drug-induced methaemoglobinaemia. Use of ACZONE® 7.5% w/w gel should be avoided in those patients with congenital or idiopathic methaemoglobinaemia.

Signs and symptoms of methaemoglobinaemia may be delayed for some hours after exposure. Initial signs and symptoms of methaemoglobinaemia are characterised by a slate grey cyanosis seen in, for example, buccal mucous membranes, lips and nail beds. Patients should be advised to discontinue ACZONE® 7.5% w/w gel and seek immediate medical attention in the event of cyanosis.

Dapsone can cause elevated methaemoglobin levels particularly in conjunction with methaemoglobin-inducing agents.

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 studies with topical dapsone 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. With the exception of urticaria, these types of skin reactions were not observed in clinical studies with topical dapsone treatment.

Topical application of ACZONE® 7.5% w/w gel followed by benzoyl peroxide in patients with acne vulgaris may result in a temporary local yellow or orange discolouration of the skin and facial hair.

Effects on Fertility: The effects of dapsone on fertility and general reproductive performance were assessed in male and female rats following oral (gavage) dosing. Sperm motility was decreased in male rats that received 2 mg/kg/day or more, with a reduction in sperm count and density also observed in rats treated with 3 mg/kg/day or more (approximately 16 and 24 times the systemic exposure observed in humans under maximal topical use conditions based on AUC comparisons). Reductions in the mean numbers of embryo implantations and viable embryos in untreated females mated with males that had been dosed at 12 mg/kg/day or greater were likely due to reduced numbers or effectiveness of sperm, indicating impairment of male fertility (approximately 95 times the systemic exposure observed in humans under maximal topical use conditions based on AUC comparisons).

Dapsone reduced the mean number of corpora lutea and implantations in female rats treated with 30 mg/kg/day or more from 15 days prior to mating and for 17 days thereafter (approximately 900 times the systemic exposure observed in humans under maximal topical use conditions based on AUC comparisons). Maternal toxicity also occurred at these dose levels. Doses of 12 mg/kg/day did not affect the number of corpora lutea or implantations, which was associated with relative systemic exposures approximately 350 times than that expected clinically.

Use in pregnancy: Category B3.
Use in pregnancy is not recommended

There are no adequate and well controlled studies in pregnant women. Dapsone has been shown to have an embryocidal effect (increased early resorptions and decreased live litter size) when administered orally in rats at 75 mg/kg/day and in rabbits at 150 mg/kg/day (approximately

1400 and 400 times the systemic exposure observed in humans under maximal topical use conditions, based on AUC comparisons, respectively). These effects were associated with maternal toxicity.

Dapsone was assessed for effects on perinatal/postnatal pup development and postnatal maternal behaviour and function in a study in which dapsone was orally administered to female rats daily beginning around the time of implantation and continuing throughout lactation. Maternal toxicity (decreased body weight and food consumption) and developmental effects (increase in stillborn pups and decreased pup weight and growth during lactation) were seen at a dapsone dose of 30 mg/kg/day (approximately 900 times the systemic exposure observed in humans under maximal topical use conditions, based on AUC comparisons). In addition, oral dosing with the excipient diethylene glycol monoethyl ether (DGME) alone also increased the incidence of stillbirths in rats at a dose estimated to be only 2 times that given clinically based on body surface area. No effects were observed on the viability, maturation, behaviour, learning ability, or reproductive function of surviving pups following treatment with dapsone or DGME in pregnancy and lactation.

Use in Lactation: Although systemic absorption of dapsone following topical application of ACZONE® 7.5% w/w gel 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® 7.5% w/w gel taking into account the importance of the drug to the mother.

Genotoxicity: Dapsone was not mutagenic in a bacterial reverse mutation assay (Ames test) using *S. typhimurium* and *E. coli*, with and without metabolic activation. Dapsone increased both numerical and structural aberrations in a chromosome aberration assay conducted with Chinese hamster ovary (CHO) cells. Systemic exposure to dapsone did not induce chromosomal aberrations in *in vivo* micronucleus assays conducted in mice and rats.

Carcinogenicity: 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 (associated with AUC values greater than 460 times the systemic exposure observed in humans under maximal topical use conditions). At higher doses, dapsone has been reported to induce mesenchymal and thyroid tumours in rats.

Topical dapsone at 5% w/w, did not increase the rate of formation of ultraviolet light-induced skin tumours when topically applied to hairless mice in a 12-month photocarcinogenicity study.

Paediatric Use: The safety and efficacy of ACZONE® 7.5% w/w gel have not been established in patients under the age of 12 years.

Geriatric Use: The safety and efficacy of ACZONE® 7.5% w/w gel have not been established in patients above the age of 65 years.

Interactions: Systemic exposure is lower with once daily ACZONE® 7.5% w/w gel than with twice daily dapsone gel, 5% w/w. No formal drug-drug interaction studies were conducted with ACZONE® 7.5% w/w gel.

Trimethoprim-Sulfamethoxazole
A drug-drug interaction study evaluated the effect of the use of dapsone gel, 5% w/w in combination with double strength (160 mg/800 mg) 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®

7.5% w/w gel is expected to be about 1% of that from the 100 mg oral dose, even when co-administered with TMP/SMX.

Topical Benzoyl Peroxide
Topical application of ACZONE® 7.5% w/w gel followed by benzoyl peroxide in patients with acne vulgaris may result in a temporary local yellow or orange discolouration of the skin and facial hair.

Concomitant Use with Drugs that Induce Methaemoglobinaemia
Concomitant use of ACZONE® 7.5% w/w gel with drugs that induce methaemoglobinaemia 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 methaemoglobinaemia (See Precautions).

There is currently limited data on effects of use with topical antibiotics or topical retinoids.

ADVERSE REACTIONS

Pre-marketing clinical trials:
A total of 2161 patients were treated with ACZONE® 7.5% w/w gel for 12 weeks in 2 controlled clinical studies. Adverse drug reactions that were reported in at least 1% of patients treated with either ACZONE® 7.5% w/w gel or Vehicle appear in Table 3 below.

Most adverse drug reactions were mild in severity. One patient treated with ACZONE® 7.5% w/w gel discontinued the study due to application site pruritus, which resolved without sequelae.

Table 3 Adverse Drug Reactions Occurring in at Least 1% of Patients

	ACZONE® gel, 7.5% w/w (N=2161)	**Vehicle (N=2175)**
Application Site Dryness	26 (1.2%)	22 (1.0%)
Application Site Pruritus	23 (1.1%)	14 (0.6%)
Application Site Pain	11 (0.5%)	33 (1.5%)

Cutaneous irritation evaluations, presented in Table 4, were conducted at each study visit in the two clinical studies. Incidences of erythema, scaling, dryness, and stinging/burning were similar before treatment (baseline visit) and at each subsequent study visit.

Table 4 Incidence of Local Cutaneous Irritation in Controlled Clinical Studies for ACZONE® 7.5% w/w gel Patients Whose Irritation Score was Higher than at Baseline (N=2161)

	Maximum Severity (during treatment)			**End of Treatment (Week 12)**		
Local Cutaneous Irritation	**Mild**	**Moderate**	**Severe**	**Mild**	**Moderate**	**Severe**
Erythema	9.7%	2.7%	0.2%	3.8%	0.7%	0%
Scaling	12.4%	1.3%	0.2%	3.6%	0.3%	<0.1%
Dryness	17.7%	2.0%	0.2%	5.2%	0.3%	<0.1%
Stinging/ burning	23.5%	5.6%	1.0%	11.6%	1.3%	0.2%

In human dermal safety studies in healthy patients, ACZONE® 7.5% w/w gel did not show any potential for cumulative irritation, sensitisation, phototoxicity or photoallergy.

Experience with Oral Use of Dapsone:
Although not observed in the clinical studies with topical dapsone, serious adverse reactions have been reported with oral use of dapsone, including agranulocytosis, haemolytic anaemia, 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).

Post-marketing experience:
Methaemoglobinaemia has been identified during postmarketing use of topical dapsone in clinical practice. Because it was reported voluntarily from a population of unknown size, estimates of frequency cannot be made (See Precautions).

DOSAGE AND ADMINISTRATION

For dermatological (topical) use only.

ACZONE® 7.5% w/w gel should only be applied to affected areas. For external use only. Not for oral, ophthalmic or intravaginal use. Not for use on broken skin. If contact with eyes occurs, rinse thoroughly with water.

After the skin is gently washed and patted dry, approximately a pea-sized amount of ACZONE® 7.5% w/w gel, should be applied in a thin layer to the entire face once daily. In addition, a thin layer may be applied to other affected areas once daily. ACZONE® 7.5% w/w gel should be rubbed in gently and completely.

Patients should be instructed to wash their hands after application of ACZONE® 7.5% w/w gel.

If there is no improvement after 12 weeks, treatment with ACZONE® 7.5% w/w gel should be reassessed.

OVERDOSAGE

ACZONE® 7.5% w/w gel is not for oral use. If oral ingestion occurs, medical advice should be sought.

PRESENTATION

Gel: 7.5% w/w off-white to yellow gel supplied in 30g, 60g and 90g airless pump polypropylene bottles. Also supplied as a 3g physician sample in a tube.

Storage: Store below 25^{o}C. DO NOT REFRIGERATE OR FREEZE.
Discard any remaining gel after 14 weeks from the date of opening.
Keep tube tightly closed when not in use.

Shelf life: 24 months.

NAME AND ADDRESS OF THE SPONSOR:

Allergan Australia Pty Ltd
810 Pacific Highway
Gordon NSW 2072
ABN 85 000 612 831

ACZONE® 7.5% w/w dapsone gel AUST R 266267

POISON SCHEDULE OF THE MEDICINE: S4

DATE OF FIRST INCLUSION IN THE ARTG: 10 January 2017

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