

ACNEDAP Gel (Dapsone)

Composition

ACNEDAP Gel, 5%

Each gram contains:

Dapsone, IP 5.00% w/w

Methylparaben IP..... 0.20% w/w (As preservative)

In a gel base..... q.s.

Dosage Form

Gel

Pharmacology

Pharmacodynamics

The antimicrobial action of dapsone is similar to that of the sulphonamides. It inhibits the bacterial synthesis of dihydrofolic acid by competing with para-aminobenzoate for the active site on dihydropteroate synthetase. In susceptible organisms, this produces a bacteriostatic action. With regards to the acne-associated bacterium *Propionibacterium acnes*, dapsone's effect has yet to be determined. *In vitro* studies have shown that (1) dapsone interferes with neutrophil chemotactic migration by inhibiting the release of interleukin (IL)-8 (a neutrophil chemotactic agent); (2) blocks B2 integrin (CD11b/CD18) adherence of human neutrophils; and (3) inhibits neutrophil myeloperoxidase-mediated iodination and cytotoxicity.

Pharmacokinetics

An open-label, crossover study compared the pharmacokinetics of dapsone gel, 5%, (n=18, 110 ± 60 mg/day) with a single 100 mg dose of oral dapsone administered to a subgroup of patients (n=10). Dapsone gel, 5%, was applied twice daily (~BSA 22.5%) for 14 days.

On day 14, the mean dapsone AUC_{0-24h} was 415 ± 224 ng•h/mL for dapsone gel, 5%, whereas following a single 100 mg dose of oral dapsone the AUC_{0-infinity} was 52,641 ± 36,223 ng•h/mL. Exposure after the oral dose of 100 mg dapsone was approximately 100 times greater than after the topical dapsone gel, 5%, twice a day.

In a long-term safety study of dapsone gel, 5%, periodic blood samples were collected up to 12 months to determine the systemic exposure of dapsone and its metabolites in approximately 500 patients. Based on the measurable dapsone concentrations from 408 patients (males=192, females=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 and 15 years (n=155) and those greater than or equal to 16 years (n=253). There was no evidence of increasing systemic exposure to dapsone over the study year in these patients.

Indications

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

Dosage and Administration

For topical use only. Not for oral, ophthalmic or intravaginal use.

ACNEDAP Gel, 5%, should be applied to the affected areas twice daily. The patient should follow the instructions given below while using **ACNEDAP Gel**, 5%:

- The affected areas should be thoroughly washed with water.
- The pinpoint tube should be squeezed to extract the required amount of **ACNEDAP Gel**, 5%, onto your fingertip.
- A thin film of **ACNEDAP Gel**, 5%, should be gently applied on the affected areas.
- The cap of the tube should be kept tightly closed after use.

If there is no improvement after 12 weeks, treatment with **ACNEDAP Gel**, 5%, should be reassessed.

Contraindications

None.

Warnings and Precautions

General

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. There was no evidence of clinically relevant haemolysis or anaemia in patients treated with dapsone gel, 5%, including patients who were G6PD-deficient. Some subjects with G6PD deficiency using dapsone gel developed laboratory changes suggestive of mild haemolysis. If signs and symptoms suggestive of haemolytic anaemia occur, **ACNEDAP Gel**, 5%, should be discontinued. **ACNEDAP Gel**, 5%, should not be used in patients who are taking oral dapsone or antimalarial medications because of the potential for haemolytic reactions. Combination of dapsone gel, 5%, with trimethoprim/sulphamethoxazole (TMP/SMX) may increase the likelihood of haemolysis in patients with G6PD deficiency.

Methemoglobinemia

Cases of methemoglobinemia, with resultant hospitalization, have been reported with dapsone gel, 5%, treatment. Patients with glucose-6-phosphate dehydrogenase deficiency or congenital or idiopathic methemoglobinemia are more susceptible to drug-induced methemoglobinemia. Avoid use of dapsone 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 dapsone gel, 5%, and seek immediate medical attention in the event of cyanosis. Dapsone can cause elevated methemoglobin levels particularly in conjunction with methemoglobin-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 trials with topical dapsone 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 dapsone gel, 5%, treatment.

G6PD Deficiency

Dapsone gel, 5%, and vehicle were evaluated in a randomized, double-blind, crossover 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. There were 56 out of 64 subjects who had a week 2 blood draw and applied at least 50% of the treatment applications. The results from the testing of relevant haematology parameters for these two treatment periods are presented in Table 1. Dapsone gel was associated with a 0.32 g/dL drop in haemoglobin after 2 weeks of treatment, but haemoglobin levels generally returned to baseline levels at week 12.

Table 1: Mean haemoglobin, bilirubin and reticulocyte levels in acne subjects with G6PD

		Dapsone Gel, 5%,		Vehicle	
		N	Mean	N	Mean
Haemoglobin (g/dL)	Pre-treatment	53	13.44	56	13.36
	2 weeks	53	13.12	55	13.34
	12 weeks	50	13.42	50	13.37
Bilirubin (mg/dL)	Pre-treatment	54	0.58	56	0.55
	2 weeks	53	0.65	55	0.56
	12 weeks	50	0.61	50	0.62
Reticulocytes (%)	Pre-treatment	53	1.30	55	1.34
	2 weeks	53	1.51	55	1.34
	12 weeks	50	1.48	50	1.41

There were no changes from baseline in haptoglobin or lactate dehydrogenase during dapsone gel, 5%, or vehicle treatment at either the 2-week or 12-week time point.

The proportion of subjects who experienced decreases in haemoglobin ≥ 1 g/dL was similar between dapsone gel, 5%, and vehicle treatment (8 of 58 subjects had such decreases during dapsone gel treatment compared to 7 of 56 subjects during vehicle treatment among subjects, with at least one

on-treatment haemoglobin 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 haemolytic anaemia in this study. Some of these subjects developed laboratory changes suggestive of mild haemolysis.

Drug Interactions

TMP/SMX

A drug-drug interaction study evaluated the effect of the use of dapsones gel, 5%, in combination with double-strength (160 mg/800 mg) TMP/SMX. During co-administration, systemic levels of TMP and SMX were essentially unchanged. However, the levels of dapsones and its metabolites increased in the presence of TMP/SMX. Systemic exposure (AUC_{0-12}) of dapsones and N-acetyl-dapsones (NAD) were increased by about 40% and 20%, respectively, in the presence of TMP/SMX. Notably, systemic exposure (AUC_{0-12}) of dapsones 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 dapsones gel, 5%, followed by benzoyl peroxide in subjects with acne vulgaris resulted in a temporary, localized yellow or orange discolouration of the skin and facial hair (reported by 7 out of 95 subjects in a clinical study), with resolution in 4 to 57 days.

Oral Dapsones

Certain concomitant medications (such as rifampin, anticonvulsants, St. John's wort) may increase the formation of dapsones hydroxylamine, a metabolite of dapsones associated with haemolysis. With oral dapsones treatment, folic acid antagonists such as pyrimethamine have been noted to possibly increase the likelihood of haematologic reactions.

Concomitant Use with Drugs that Induce Methaemoglobinemia

Concomitant use of dapsones gel, 5%, with drugs that induce methaemoglobinemia such as sulfonamides, acetaminophen, acetanilide, aniline dyes, benzocaine, chloroquine, dapsones, naphthalene, nitrates and nitrites, nitrofurantoin, nitroglycerin, nitroprusside, pamaquine, para-aminosalicylic acid, phenacetin, phenobarbital, phenytoin, primaquine, and quinine may increase the risk for developing methaemoglobinemia

Pregnancy

Pregnancy Category C: Teratogenic Effects

There are no adequate and well-controlled studies in pregnant women. Dapsones 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. **ACNEDAP Gel, 5%**, should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus.

Lactation

Although systemic absorption of dapsones following topical application of dapsones 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 dapsone gel, 5%, taking into account the importance of the drug to the mother.

Paediatric Use

Safety and efficacy was evaluated in 1,169 children aged 12–17 years and treated with dapsone gel, 5%, in the clinical studies. The adverse event rate for dapsone gel, 5%, was similar to the vehicle control group. Safety and efficacy was not studied in paediatric patients less than 12 years of age; therefore, **ACNEDAP Gel, 5%**, is not recommended for use in this age group.

Geriatric Use

Clinical studies of dapsone gel, 5%, did not include sufficient number of patients aged 65 years and over to determine whether they respond differently from younger patients.

Undesirable Effects

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.

Dapsone gel, 5%, was evaluated for 12 weeks in four controlled studies for local cutaneous events in 1,819 patients. The most common events reported from these studies include oiliness/peeling, dryness and erythema. These data are shown by severity in Table 2 below.

Table 2: Application site adverse reactions by maximum severity

Application Site Event	Dapsone gel (N=1819)			Vehicle (N=1660)		
	Mild	Moderate	Severe	Mild	Moderate	Severe
Erythema	9%	5%	<1%	9%	6%	<1%
Dryness	14%	3%	<1%	14%	4%	<1%
Oiliness/Peeling	13%	6%	<1%	15%	6%	<1%

The adverse reactions occurring in at least 1% of patients in either arm in the four vehicle-controlled studies are presented in Table 3.

Table 3: Adverse reactions occurring in at least 1% of patients

	Dapsone Gel, 5% (n=1,819)	Vehicle (n=1,660)
Application site reaction NOS*	18%	20%
Application site dryness	16%	17%
Application site erythema	13%	14%
Application site burning	1%	2%
Application site pruritus	1%	1%

Pyrexia	1%	1%
Nasopharyngitis	5%,	6%
Upper respiratory tract infection NOS*	3%	3%
Sinusitis NOS*	2%	1%
Influenza	1%	1%
Pharyngitis	2%	2%
Cough	2%	2%
Joint sprain	1%	1%
Headache NOS*	4%	4%

*NOS: Not otherwise specified

One patient treated with dapson gel, 5%, 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.

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

Serious adverse reactions reported in patients treated with dapson 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 4,032 patients were reported to have depression (3 of 1,660 treated with vehicle and 9 of 2,372 treated with dapson gel, 5%). Psychosis was reported in 2 of 2,372 patients treated with dapson, 5%, and in 0 of 1,660 patients treated with vehicle.

Experience with Oral Use of Dapsone

Although not observed in the clinical trials with topical dapson, 5%,, serious adverse reactions have been reported with oral use of dapson, 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).

If you experience any side effects, talk to your doctor or pharmacist or write to drugsafety@cipla.com. You can also report side effects directly via the national pharmacovigilance program of India by calling on 1800 180 3024.

By reporting side effects you can help provide more information on the safety of this product.

Overdosage

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

Shelf-Life

2 years

Storage and Handling Instructions

Store below 30°C. Protect from freezing and light.

Packaging Information

ACNEDAP Gel: Tube of 15g

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