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ADIS DRUG EVALUATION

# Dapsone 7.5% Gel: A Review in Acne Vulgaris

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**Abstract** Dapsone 7.5% gel (Aczone®) is indicated for the once-daily topical treatment of acne vulgaris in patients aged ≥12 years. Dapsone is a sulfone antibacterial with anti-inflammatory actions, which are thought to be largely responsible for its efficacy in treating acne vulgaris. In two phase III trials of 12 weeks' duration in patients aged ≥12 years with moderate acne vulgaris, once-daily dapsone 7.5% gel reduced acne severity (as per the Global Acne Assessment Score) and lesion counts versus vehicle. The benefits of dapsone 7.5% gel over vehicle were seen as early as week 2 for inflammatory lesion counts, and from week 4 or 8 for other outcomes. Dapsone 7.5% gel was well tolerated, with a low incidence of treatment-related adverse events, with the majority of adverse events being administration-site related and mild or moderate in severity. Thus, dapsone 7.5% gel is an effective and well tolerated option for the topical treatment of acne vulgaris in patients aged ≥12 years, with the convenience of once-daily application.

| Dapsone 7.5% gel: clinical considerations in acne vulgaris |
|---|
| Has anti-inflammatory properties that may account for its efficacy in acne |
| Convenient once-daily application |
| Effective in the treatment of moderate acne in patients aged ≥12 years, with inflammatory lesion counts being reduced from as early as week 2 of treatment onwards |
| Well tolerated |

## 1 Introduction

Acne vulgaris (hereafter referred to as acne) is a multifactorial inflammatory skin disease commonly affecting adolescents and young adults; however, it can persist into adulthood [1]. Acne affects ≈50 million people in the USA, and the direct cost of the disease is estimated to be >$US 3 billion/year, as well as exerting a significant physical, psychological, and psychosocial burden on those affected [1].

There are four key processes implicated in the pathogenesis of acne, including abnormal keratinization, abnormal sebum production, release of inflammatory mediators onto the skin, and *Propionibacterium acnes* (*P. acnes*) follicular colonization [2]. The clinical features of acne include seborrhea, lesion formation, and various degrees of scarring, distributed across the face, neck, upper chest, shoulders, and back [2]. Typically, lesions have been characterized as being noninflammatory (open and closed

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comedones), or inflammatory [acne papules, pustules, cysts and nodules (the latter two lesions, when present together, comprise severe nodulocystic acne [2])] [3]. However, recent evidence suggests that inflammation is involved at every stage of acne pathogenesis, including subclinical inflammation preceding the formation of comedones [4].

Topical therapies are widely used for the management of acne in adolescents and adults, either alone or in combination with oral or other topical agents, depending on the severity of disease [1]. Dapsone, a synthetic sulfone antibacterial with anti-inflammatory properties, has been available in an oral dosage form since the 1950s [5], although it was poorly adopted for the treatment of acne due to the potential of systemic toxicities. Topical dapsone 5% gel was developed to reduce the systemic absorption and hence improve the tolerability of the drug; however, it requires twice-daily application, which some patients may find inconvenient. A higher concentration gel formulation of the drug [dapsone 7.5% gel (Aczone®)] is now approved in the USA for the once-daily topical treatment of acne in patients ≥12 years of age [6]. This article reviews pharmacological, therapeutic efficacy, and tolerability data relevant to the use of dapsone 7.5% gel in this indication.

## 2 Pharmacodynamic Properties of Dapsone 7.5% Gel

The exact mechanism underlying the benefits of dapsone 7.5% gel in treating patients with acne has not yet been established [6], but is thought to be linked to its anti-inflammatory properties [1]; its activity against *P. acnes* remains poorly understood. Dapsone exerts its anti-inflammatory activity by inhibiting neutrophil myeloperoxidase, eosinophil peroxidase, and chemoattractant-induced signal transduction [7]. It also suppresses production of hypochlorous acid and toxic respiratory and secretory products, suppresses neutrophil recruitment, and minimizes inflammation associated with highly reactive oxygen species through scavenger actions on these species [7]. The antimicrobial activity of dapsone is similar to that of sulfonamides, and is independent of its anti-inflammatory activity [7].

## 3 Pharmacokinetic Properties of Dapsone 7.5% Gel

In patients aged 16−35 years with moderate acne applying 2 g of dapsone 7.5% gel once daily for 28 days to the entire face, upper chest, upper back, and shoulders, dapsone plasma concentrations reached steady state within 1 week of the initial dose [8]. Systemic exposure to dapsone following dapsone 7.5% gel application is minimal (estimated to be ≈1% of that from a 100 mg oral tablet) [6]. Compared with twice-daily dapsone 5% gel, daily systemic exposure was 25−40% lower with the once-daily dapsone 7.5% gel formulation [8]. Furthermore, following twice-daily application of dapsone 5% gel in patients aged ≥12 years with acne vulgaris for 12 months, there was no evidence of systemic accumulation of the drug [6, 9]. Similar effects would be expected following once-daily administration of dapsone 7.5% gel.

Dapsone is metabolized predominantly by *N*-acetyl transferase (to *N*-acetyl dapsone), and by CYP2EI and CYP3A4 [to dapsone hydroxylamine, which has been linked to adverse reactions such as methemoglobinemia (Sect. 5)] [7]. Topical administration is not expected to alter dapsone metabolism, and there was no evidence of increased exposure to dapsone metabolites following administration of the 5% formulation. Similar results for dapsone 7.5% gel are likely.

Results of a long-term clinical study of dapsone 5% gel indicate that neither sex nor race affect the pharmacokinetics of dapsone at 3 months [6]. Moreover, dapsone exposure was similar across different age groups of 12–15 and ≥16 years [6]. Consistently, there were no significant effects of sex or age on plasma concentrations of dapsone in pharmacokinetic studies of dapsone 7.5% formulations [8].

Drug interaction studies have not been conducted with dapsone 7.5% gel [6]. However, previous studies indicate that using dapsone 5% gel in combination with oral trimethoprim-sulfamethoxazole may increase the maximum plasma concentration and systemic exposure of dapsone (by ≈39 and ≈45%) and its metabolites *N*-acetyl dapsone (by ≈20 and ≈20%) and dapsone hydroxylamine (by ≈114 and ≈145%), over the first 12 h [5, 7]. Despite these apparent increases, systemic exposure following dapsone gel application is estimated to remain ≈1% of that from a 100 mg oral tablet, in the presence of trimethoprim-sulfamethoxazole; however, caution is advised, as coadministration of dapsone 7.5% gel with trimethoprim-sulfamethoxazole may increase the likelihood of hemolysis in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency (Sect. 5) [6].

## 4 Therapeutic Efficacy of Dapsone 7.5% Gel

The short-term efficacy of topical dapsone 7.5% gel in treating patients aged ≥12 years with moderate acne [i.e. grade 3 on the Global Acne Assessment Score (GAAS) scale] was evaluated in two identically designed, randomized, double-blind, vehicle-controlled, phase III trials, denoted here as study 1 [10] and study 2 [11]. The trials were

of 12 weeks' duration and enrolled patients with 20–50 inflammatory facial lesions (papules/pustules) and 30–100 noninflammatory facial lesions (open/closed comedones). Key exclusion criteria included patients who had other forms of acne (severe cystic acne, acne conglobata, acne fulminans, and secondary acne) or who had recently received certain cosmetic or topical procedures/treatments [10, 11].

Eligible patients were randomized to receive topical dapsone 7.5% gel or vehicle in studies 1 and 2 (Table 1) [10, 11]. In a pooled analysis of the two trials, patients had a mean age of 20.3 years, 50.5% of patients were adults (≥18 years), and 55.8% were female [12]. The majority of patients in studies 1 [10] and 2 [11] were Caucasian (≈57.4%); ≈18.7, ≈16.0, and ≈3.9% of patients were Black, Hispanic, and Asian, respectively. All patients had a baseline GAAS severity of 3 (except for one patient in study 1, who had a score 4 [10]); the mean inflammatory lesion count was 29.5 and the mean noninflammatory lesion count was 47.2 [12]. Participants were advised to choose a suitable time for daily dosing, to apply the study drug once daily to the entire face and to other acne-affected areas within reach, and to avoid changing the dosing time or bathing or swimming for 2 h after application [10, 11]. The use of topical products (e.g. sunscreens, cosmetics, moisturizers) on treatment areas was to be avoided for 1 h before and after application of study drug [11].

The co-primary efficacy endpoints at 12 weeks were the GAAS success rate, defined as the proportion of patients with a GAAS score of 0 (none) or 1 (minimal), and the mean change from baseline in inflammatory and noninflammatory lesion counts, in the intent-to-treat population [10, 11].

Once-daily dapsone 7.5% gel was effective in the treatment of moderate acne in patients aged ≥12 years [10, 11]. After 12 weeks, significantly more dapsone 7.5% gel than vehicle recipients achieved GAAS success (co-primary endpoint) in both study 1 and study 2 (Table 1). Consistent with these findings, there was a significantly greater least-squares mean reduction in absolute inflammatory and noninflammatory lesion counts (co-primary endpoints) in dapsone 7.5% gel than in vehicle recipients, with the least-squares mean percent reductions from baseline in all lesion-count endpoints (i.e. inflammatory, noninflammatory and total) also being significantly greater with dapsone than vehicle in both trials (Table 1) [10, 11].

In both studies, inflammatory lesion counts improved rapidly with dapsone 7.5% gel, with the least-squares mean percentage reduction from baseline significantly ($p \leq 0.05$) favoring dapsone over vehicle from week 2 of therapy onwards [10, 11]. For mean percent reductions in noninflammatory lesion count and total lesion count, a significant ($p \leq 0.05$) benefit with dapsone versus vehicle was evident at week 8 in both studies [10, 11]. For GAAS success rates, the between-group difference began to significantly ($p \leq 0.05$) favor dapsone over vehicle at week 8 in study 1 [10] and at week 4 in study 2 [11].

In a subgroup analysis of study 1, recipients of dapsone 7.5% gel had a significantly ($p \leq 0.035$) higher GAAS success rate than vehicle recipients, as well as greater percent reductions in inflammatory and noninflammatory lesion counts, in all age, sex, and race subgroups, except for in noninflammatory lesions in adults [10]. In recipients

**Table 1** Efficacy of dapsone 7.5% gel in the treatment of moderate acne in patients aged ≥12 years, at week 12 of treatment

| Outcome measures | Study 1 [10][a] | | Study 2 [11][a] | | Pooled data [12][a] | |
|---|---|---|---|---|---|---|
| | DAP | VEH | DAP | VEH | DAP | VEH |
| GAAS success rate (% pts)[b,c] | 29.9** | 21.2 | 29.8** | 20.9 | 29.8** | 21.1 |
| Absolute change from BL in inflammatory lesion count[c] [BL] | −16.1** [28.8] | −14.1 [29.3] | −15.6** [29.6] | −13.8 [30.0] | −15.8** [29.2] | −13.9 [29.7] |
| Absolute change from BL in noninflammatory lesion count[c] [BL] | −20.8** [46.9] | −17.6 [48.6] | −20.7* [46.7] | −18.5 [46.7] | −20.7** [46.8] | −18.0 [47.6] |
| Percent change from BL in inflammatory lesion count (%) | −55.5** | −49.0 | −53.8** | −47.3 | −54.6** | −48.1 |
| Percent change from BL in noninflammatory lesion count (%) | −44.4** | −38.4 | −45.9** | −40.4 | −45.1** | −39.4 |
| Percent change from BL in total lesion count (%) | −48.7** | −42.4 | −48.9** | −43.2 | −48.8** | −42.8 |

Where reported, changes from BL are least-squares means [10, 11]. Where specified, inflammatory facial lesions comprised papules and pustules and noninflammatory (comedonal) facial acne comprised open and closed comedones

*BL* baseline *DAP* dapsone 7.5% gel, *GAAS* global acne assessment score, *NR* not reported, *pts* patients, *VEH* vehicle

* $p < 0.01$, ** $p < 0.001$ vs. VEH

[a] The number of DAP and VEH recipients was 1044 and 1058 in study 1, 1118 and 1120 in study 2, and 2162 and 2178 in the pooled analysis

[b] Proportion of patients with a GAAS score of 0 (none) or 1 (minimal)

[c] Co-primary efficacy endpoint in studies 1 and 2

of dapsone 7.5% gel, numerically greater GAAS success rates and percent reductions in inflammatory and noninflammatory lesions were observed in adults than in adolescents (aged 12–17 years) and in female than in male patients [10]. Insufficient numbers of patients aged ≥65 years were included in clinical trials of dapsone 7.5% gel for a comparison of response with younger patients [6].

### 4.1 Pooled Analyses

Results of a pooled analysis [12] that combined data from the dapsone 7.5% gel and vehicle groups of the two pivotal studies in Sect. 4 were consistent with those of the individual trials. At week 12, GAAS success rates, least-squares mean reduction in inflammatory and noninflammatory lesion counts, and the percent reduction from baseline in inflammatory and noninflammatory lesion counts were significantly greater in dapsone than vehicle recipients (Table 1) [12]. The onset of response to dapsone was rapid, with significant ($p < 0.05$) improvements compared with vehicle seen at week 2 for inflammatory lesion counts, week 4 for total lesion counts, and week 8 for both noninflammatory lesion counts and GAAS success rates [12]. Improvements with dapsone versus vehicle continued to be significant ($p < 0.001$) from these dates through to week 12 for all outcome measures.

When data from this pooled analysis were assessed by age (adolescents and adults), sex, and race (Caucasian and non-Caucasian), dapsone 7.5% gel generally significantly ($p < 0.01$ vs. vehicle) improved measures of acne severity (including GAAS success rates and inflammatory, noninflammatory, and total lesion counts) regardless of subgroup [13]. However, numerically greater GAAS success rates and lesion count improvements were observed for adults versus adolescents and for female versus male patients. Dapsone treatment, age, and sex were all significant ($p \leq 0.029$) predictors of GAAS success rates and improvements in inflammatory and noninflammatory lesions [13].

## 5 Tolerability of Dapsone 7.5% Gel

Once-daily dapsone 7.5% gel was well tolerated in patients aged ≥12 years with moderate acne in the two 12-week pivotal studies [10, 11] (Sect. 4) and their pooled analysis [12] (Sect. 4.1), with most adverse events being mild or moderate in severity where specified [10, 11]. The safety population of these trials included 1044 dapsone and 1058 vehicle recipients in study 1 (this excluded patients from a discontinued site) [10] and 1117 dapsone and 1118 vehicle recipients in study 2 [11].

The tolerability profile of dapsone 7.5% gel was generally similar to that of vehicle in studies 1 [10] and 2 [11], with adverse events considered to be treatment-related occurring in <5% of patients in each treatment group (2.9% of patients receiving dapsone vs. 3.3% of patients receiving vehicle in study 1; 4.0 vs. 3.4% in study 2); adverse events were rarely serious (<0.2% of patients in each treatment group in both studies) or the cause of discontinuation (<0.5% of patients in each treatment group in both studies). Where specified, the most common treatment-related adverse events in studies 1 [10] and 2 [11] involved the application site (namely erythema, exfoliation and pain in study 1; dryness, pain and pruritus in study 2). The incidence of these events was generally low (<2%) in dapsone and vehicle recipients.

These findings are generally supported by the pooled analysis of studies 1 and 2, in which the most frequent (incidence >1%) adverse events to occur in numerically more dapsone 7.5% gel than vehicle recipients included headache (1.6 vs. 1.2%), application-site dryness (1.2 vs. 1.0%), and application-site pruritus (1.1 vs. 0.6%) [12]. Notably, local stinging/burning, dryness, scaling, and erythema were generally mild in this analysis, with the majority of dapsone recipients scoring them as "none" on local dermal tolerability severity scales [12]. Similar tolerability scale findings were reported in each of the individual studies [10, 11]. There were no marked differences (within or between treatment groups) in the incidence of adverse events when data from the pooled analysis were assessed by age, sex, and race [13].

Phase I studies in patients with moderate acne applying once-daily dapsone 7.5% gel or twice-daily dapsone 5% gel demonstrated that both formulations were well tolerated [8]. Despite the higher concentration of the dapsone 7.5% gel, there were no clinically significant differences in the mean cumulative irritancy index (MCII) scores for dryness, scaling and erythema between dapsone 7.5 and 5% gel formulations. The average mean combined MCII scores across dapsone 7.5 and 5% gel formulations was zero; mean combined MCII scores for the upper chest, upper back, and shoulders were lower (indicative of better dermal tolerability) than those for the face [8].

The US prescribing information (PI) [6] contains warnings and precautions pertaining to certain adverse events that have occurred with dapsone formulations. Among these is methemoglobinemia, which has occurred (and led to hospitalization) with topical dapsone [14, 15]. Certain patients may be more susceptible to developing drug-induced methemoglobinemia, including those who already have methemoglobinemia (congenital or idiopathic), have G6PD deficiency, or use dapsone in combination with

methemoglobinemia-inducing drugs. In addition, hemolysis and hemolytic anemia have occurred with oral dapsone, with the risk increased in patients with G6PD deficiency; however, these events have not been clinically relevant with topical dapsone. Other serious adverse reactions that have occurred with oral dapsone include peripheral neuropathy, agranulocytosis and skin reactions, but these have not been seen with topical dapsone formulations in clinical trials. A local discoloration of the skin and facial hair may occur in patients applying dapsone gel followed by benzoyl peroxide; however, such effects are temporary. See Sect. 6 and local PI for further details.

## 6 Dosage and Administration of Dapsone 7.5% Gel

For the topical treatment of acne vulgaris in patients ≥12 years of age in the USA, a pea-sized amount of dapsone 7.5% gel should be applied to the entire face and then spread as a thin layer once daily; the gel must be rubbed into the skin gently and completely [6]. Dapsone gel may be applied topically in a thin layer to other affected areas once daily; however, it is not for ophthalmic, oral or intravaginal use. Treatment with dapsone 7.5% gel should be reassessed if no improvement occurs after 12 weeks of therapy [6]. Dapsone must be discontinued in the event of cyanosis (indicative of methemoglobinemia) or hemolytic anemia. Because of the hemolysis potential, the use of dapsone 7.5% gel should be avoided in patients receiving oral dapsone or antimalarial medications [6]. Dapsone 7.5% gel should be stored at room temperature; local PI should be consulted for details regarding drug interactions and special warnings and precautions relating to the use of dapsone 7.5% gel.

## 7 Place of Dapsone 7.5% Gel in the Management of Acne Vulgaris

There are currently many treatment options for acne [1], with the choice of treatment being dependant on patient-specific factors, such the severity of acne, site and extent of involvement, patient preference, comorbidities, drug-drug interactions, and the likelihood of adherence. Given the chronic nature and multifactorial pathogenesis of acne, long-term and combination therapy may be necessary for optimal outcomes [1]. Indeed, the American Academy of Dermatology (AAD) guidelines of care for the management of acne vulgaris recommend that topical combination therapy affecting different aspects of the pathogenesis of acne be used in the majority of patients, with consideration given to the compatibility of such agents [1].

The AAD guidelines [1] consider several therapies to be effective first-line treatment options for adolescents and young adults with acne vulgaris. Topical therapies, including benzoyl peroxide and retinoids are useful options as monotherapy and can be used in topical combination therapy with topical antibacterials for mild acne. Furthermore, a combination of topical agents may be used with or without oral antibacterials for moderate to severe acne [1].

Although antibacterials (topical and oral) are effective in the treatment of acne, monotherapy with these agents is not recommended due to the risk of development of bacterial resistance [1]. The addition of benzoyl peroxide to topical antibiotic regimens is recommended as it enhances efficacy and decreases the risk of bacterial resistance, although has potential limitations including concentration-dependant irritation, staining and bleaching of fabric, and an uncommonly occuring contact allergy [1]. Moreover, the use of systemic antibacterials remains limited by a short duration of therapy and the need for topical maintenance therapy [1]. Another treatment option is oral isotretinoin, used alone as an alternative treatment in moderate acne and as a first-line treatment in severe acne, but requiring careful monitoring of side effects (e.g. serum lipid profiles and liver function tests) [1]. Retinoids enhance the efficacy of any topical acne regimen offering anti-inflammatory, comedolytic, and precursor microcomedone lesion resolution [1]. However, their potential benefits are limited by side effects such as dryness, peeling, erythema, and irritation that occur with higher concentrations and frequent dosing of retinoids.

Many gaps still exist in the understanding of acne and its treatment. Evidence demonstrating the involvement of inflammation at all stages of acne pathogenesis (Sect. 1) and data from phase III clinical trials (such as those discussed in Sect. 4) indicate that agents with anti-inflammatory activity, such as dapsone 7.5% gel, are likely to be effective in the management of acne. In two well-designed phase III trials in patients aged ≥12 years with moderate acne, dapsone 7.5% gel improved acne severity and reduced lesion counts (both inflammatory and noninflammatory) relative to vehicle over 12 weeks of therapy (Sect. 4), with the improvements in inflammatory lesion counts being consistent with the known anti-inflammatory properties of the drug (Sect. 2). Moreover, its benefits over vehicle were seen as early as week 2 for inflammatory lesion counts, and from week 4 or 8 for other outcomes (Sect. 4). Results of pooled analyses were consistent with these findings (Sect. 4.1). All patients (except one) in these trials had a baseline GAAS severity of moderate (Sect. 4), which is more severe than that of

patients in dapsone 5% gel studies (in which ≈39% of patients had minimal or mild GAAS severity and ≈58% had moderate severity) [16], highlighting the robustness of these findings.

Dapsone 7.5% gel was generally well tolerated in these pivotal trials, with the majority of adverse events being administration-site related and of mild or moderate severity (Sect. 5). Although applied topically, many patients considered there to be no local dermal tolerability issues with using dapsone 7.5% gel (Sect. 5).

The current AAD guidelines preceded the FDA approval of dapsone 7.5% gel; however, they recommend topical therapy with twice-daily dapsone 5% gel as an alternative option for adolescents and young adults with mild acne, used alone, or in combination with topical retinoids in the presence of comedonal components [1]. The AAD guidelines also recommend the use of dapsone 5% gel for inflammatory acne, particularly in adult females with acne.

The Global Alliance to Improve Outcomes in Acne Group recognizes that adherence to acne therapies is poor and contributes to treatment failure, and that once-daily formulations are associated with better adherence than twice-daily regimens [17]. Additional evidence from studies of patient preferences of topical acne therapies, indicates that patients favor gel formulations that can be applied once daily with the fingers and stored at room temperature for up to 18 months [18]. The convenience of once-daily dapsone 7.5% gel may offer an adherence advantage over other topical agents requiring more frequent application, such as twice-daily formulations of erythromycin, combination erythromycin and benzoyl peroxide, azelaic acid and dapsone 5%. However, adherence to the dapsone 7.5% once-daily regimen has yet to be formally determined.

Given the chronic nature of acne, trials of dapsone 7.5% gel in acne beyond 12 weeks would be beneficial. Head-to-head comparisons of dapsone 7.5% gel with other topical acne therapies, both as monotherapy and in combination with other drugs, would likewise be of interest, particularly in terms of the effects of dapsone 7.5% on the quality of life of patients with moderate acne. Moreover, trials evaluating the efficacy of dapsone 7.5% in acne of other severities would also be welcome.

To conclude, dapsone 7.5% gel is an effective and well tolerated option for the topical treatment of acne vulgaris in patients aged ≥12 years, with the convenience of once-daily application.

| Data Selection Dapsone 7.5%: 156 records identified | |
|---|---|
| Duplicates removed | 1 |
| Excluded at initial screening (e.g. press releases; news reports; not relevant drug/indication) | 2 |
| Excluded during initial selection (e.g. preclinical study; review; case report; not randomized trial) | 0 |
| Excluded by author (e.g. not randomized trials; review; duplicate data; small patient number; phase I/II trials) | 137 |
| **Cited efficacy/tolerability articles** | 4 |
| **Cited articles not efficacy/tolerability** | 12 |
| **Search Strategy:** EMBASE, MEDLINE and PubMed from 1946 to present. Clinical trial registries/databases and websites were also searched for relevant data. Key words were Dapsone, Aczone, Gel, Topical, Acne. Records were limited to those in English language. Searches last updated 29 November 2016. | |

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**Compliance with Ethical Standards**

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