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# Dapsone Topical Gel for Acne

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**SUMMARY**

Indications: Dapsone gel is indicated for the topical treatment of acne vulgaris.

Dose: Dapsone should be applied to affected areas twice daily and gently rubbed into the acne areas until no medication remains visible.

Monitoring parameters: If no improvement is seen after 12 weeks of therapy, dapsone topical should be discontinued.

Pediatrics: The safety and efficacy in children younger than 12 years have not been established.

Pregnancy Category: C

Breastfeeding: Oral dapsone is secreted in breast milk and despite low systemic absorption of topical dapsone, systemic absorption of topical dapsone may occur. Use in lactating women should be done only if the potential benefit outweighs the risk.

Contraindications: None

Precautions and Warnings: Oral dapsone has dose-related hemolysis and hemolytic anemia and individuals with G6PD deficiency are more prone to hemolysis. No clinically relevant hemolysis or anemia was noted in patients treated with dapsone topical gel. If signs and symptoms of hemolytic anemia occur, dapsone topical gel should be discontinued. Peripheral neuropathy has been reported with oral dapsone therapy, but was not seen in clinical trials with dapsone topical gel. Oral dapsone therapy has been associated with skin reactions which have not been observed in clinical trials with dapsone topical gel.

Cost: The average wholesale price for a 30 gm tube of 5% topical dapsone gel is $142.80; a 60 gm tube is $297.50.

**Introduction:** Oral dapsone has been available for almost 60 years for the treatment of dermatitis herpetiformis and Hansen's disease. Historically, oral dapsone had been used to treat severe acne with doses of 25-300 mg daily; however, the use was limited by hematological reactions including dose-dependent hemolysis. Patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency are more sensitive to the hemolytic effects since the lack of G6PD can lead to hemolysis and hemoglobin breakdown. This limitation led to the development of topical dapsone therapy. Because of the risk associated with oral dapsone therapy, the initial FDA approval for topical dapsone in 2005 required screening of patients for G6PD deficiency prior to therapy initiation and monitoring of blood counts and reticulocytes in patients with a history of anemia. This requirement was removed in 2008 and the product (Aczone, Allergan Pharmaceuticals) was re-launched in 2009.[1]

Four primary factors interact to produce acne; sebum is produced by the sebaceous gland, *Propionibacterium acnes*, a gram positive anaerobe, colonizes the follicles, the keratinization process is altered and inflammatory mediators are released into the skin.[3] All factors lead to multiple sites for intervention in acne treatment. Acne is described as either inflammatory or noninflammatory, based on the types of lesions that are present and patients typically may present with multiple lesion types. Inflammatory lesions are described as papules or pustules while noninflammatory lesions are called comedones – either open comedo (blackheads) or closed comedo (whiteheads).

Guidelines for the management of acne focus on multimodal therapy, and therapeutic options are outlined in Appendix A on page 75.[3-5] A key point for the treatment options include that topical therapies are important since retinoids are useful for both comedonal and inflammatory acne. Benzoyl peroxide, in combination with clindamycin or erythromycin, helps to decrease bacterial resistance that may occur with antibiotic therapy alone (oral or topical). Other therapies such as salicylic acid or azelaic acid are options; however, their efficacy data are less robust. Topical dapsone was not included in the recommendations for therapy at this time.

## PHARMACOLOGY/PHARMACOKINETICS

Dapsone topical acts on neutrophils to interfere with message signaling by interrupting recruitment of more neutrophils to decrease the inflammatory cascade and to reduce the formation of neutrophil-generated destructive oxygen-bearing molecules that cause skin irritation.[6] It is also thought that the gel delivery system may enhance breakup of the sebum barrier of inflammation. While oral dapsone has antimicrobial activity, topical dapsone has not been tested *in vivo* for antimicrobial activity.

The pharmacokinetics of single-dose oral dapsone 100 mg were compared to topical dapsone twice daily for 2 weeks.[7] Topical dapsone achieves levels that are 100-fold less than oral dapsone. Low systemic availability is noted, with topical dapsone and the metabolites of dapsone (N-acetyl-dapsone) accounting for about 1% of systemic exposure. The long-term plasma dapsone and N-acetyl dapsone levels remain consistent from week 1 to week 52. Steady state is reached within 2 weeks and levels fall rapidly upon treatment cessation. The time to reach maximum serum concentrations ($T_{max}$) was 6 hours with topical dapsone, as compared to 3.8 hours for 100 mg oral dapsone. The maximum concentration

mg oral dapsone. The elimination half-life for topical dapsone is 42 hours. Dapsone is metabolized to an inactive metabolite, N-acetyl dapsone.

## CLINICAL TRIALS

Multiple scales to assess and evaluate acne are available and there is no consensus which scale best identifies effective/efficacious therapeutic interventions in acne management.[7] The Global Acne Assessment Scale (GAAS) was used in the majority of the dapsone topical studies. The 5-point scale is summarized below and the definition of success varies, but typically is defined as none or minimal acne at study endpoint. In most dapsone topical clinical trials, the definition of acne vulgaris was a minimum of 20 inflammatory lesions, primarily located on the face. The GAAS does not assess scarring, impact on quality of life and is investigator-rated, not patient-rated.

Draelos and colleagues reported the results from two randomized studies demonstrating the efficacy and safety of dapsone topical.[8] The multicenter, randomized, double-blind, vehicle-controlled, 12-week studies evaluated subjects age 12 or older with a diagnosis of acne vulgaris. Subjects needed between 20-50 papules or pustules and 20-100 comedones above the mandible line at baseline to be eligible for enrollment. Subjects were excluded if there was severe cystic acne, acne conglobata (severe nodular acne), concurrent use of topical drugs, any therapy that could impact acne, antibiotics or anti-inflammatory agents 4 weeks prior, systemic immunosuppressants that are known to impact acne, isotretinoin within past 3 months, allergy or sensitivity to dapsone, sulfa drugs, or excipients in gel, not on effective pregnancy deterrent or stable hormonal contraception. Subjects were evaluated at 2, 4, 6, 8, and 12 weeks using the GAAS, and assessing the number of total lesions, inflammatory lesions, and noninflammatory lesions. The primary efficacy endpoints were the proportion of patients that achieve success on GAAS and the mean percentage decrease from baseline in the number of lesions.

There were 1,506 subjects in the dapsone-treated group and 1,504 subjects in the vehicle-treated group. Approximately equal numbers of subjects discontinued the treatment in each group (15.9% dapsone-treated and 17.5% vehicle-treated). Few dapsone-treated subjects discontinued due to lack of efficacy (0.6%) or adverse events (0.4%). Most patients (58.4%) had moderate acne and 33.8% had mild acne at baseline. Dapsone-treated patients were more likely to have treatment success at 12 weeks ($p<.001$). Dapsone-treated patients had greater reductions in noninflammatory and total lesions at 12 weeks than vehicle-treated patients ($p<0.001$). Response was seen as early as 2 weeks and was significant for reduction in inflammatory lesions at week 4 ($p=0.008$). Overall success rates at week 12 are summarized in the table below.

**TABLE 1. GLOBAL ACNE ASSESSMENT SCALE**

| Score | Amount | Description |
|---|---|---|
| 0 | None | No evidence of facial acne vulgaris |
| 1 | Minimal | Few comedones are present; few papules/pustules may be present |
| 2 | Mild | Several to many comedones are present; a few papules/pustules are present |
| 3 | Moderate | Many comedones and papules/pustules are present; no nodulocystic lesions are allowed |
| 4 | Severe | Significant degree of inflammatory disease; papules/pustules are predominant feature; a few nodulocystic lesions may be present; comedones may be present. |

Adverse events were reported by 58.2% of dapsone-treated patients and 58.6% of vehicle-treated patients; most events were mild to moderate in intensity and did not result in therapy discontinuation. Most commonly reported events included dryness (20% dapsone, 18.9% vehicle), erythema (16.3% dapsone, 16.1% vehicle), burning (1.4% dapsone, 1.6% vehicle) and pruritus (1% dapsone, 1.3% vehicle). Other non-application site reactions included nasopharyngitis (4.8% dapsone, 6.3% vehicle), headache (3.1% dapsone, 3.3% vehicle), upper respiratory infection (3.2% dapsone, 2.9% vehicle) and pharyngitis (2.5% dapsone, 2.6% vehicle). No hematological laboratory abnormalities were noted in the trial.

The study only assessed the short-term efficacy of dapsone topical and only evaluated monotherapy. This study was listed in the package labeling; however, patients with minimal acne at baseline were not included in the analysis presented so numbers and success rates may differ.

The long-term safety of dapsone was reported by Lucky and colleagues; efficacy was also reported, but was not a primary study endpoint.[9] The multicenter, open-label non-comparative 12-month study assessed patients age 12 and older with a diagnosis of acne vulgaris. The exclusion criteria were similar to Draelos et al.[8] Assessments occurred at 1, 3, 4, 6, 9 and 12 months and included acne lesion counts, inflammatory lesions, noninflammatory lesions and total lesions. The primary analysis was safety; however, efficacy was evaluated as mean percent reduction from baseline in lesion counts. The study protocol allowed for courses of antibiotics or anti-inflammatory agents for short term use and if after 3 months, systemic or topical acne therapy was deemed necessary, add-on therapy was allowed and recorded as "prohibited concomitant medications."

There were 506 subjects enrolled in the intent-to-treat population and 340 (67.2%) completed the trial. There were 15.6% of subjects lost to follow-up and 0.8% discontinued the study due to lack of efficacy. A total of 111 subjects (22%) used prohibited concomitant medications during the evaluation period. Dapsone was well tolerated with 68% of patients experiencing an adverse event, with 9.5% of the events deemed related to dapsone

**TABLE 2. PERCENT OF PATIENTS ACHIEVING GAAS SUCCESS WEEK 12**

| | Study 1 | Study 2 | Combined results |
|---|---|---|---|
| Dapsone gel | 44.2%[a] | 36.9%[b] | 40.5%[a] |
| Vehicle gel | 35.9% | 29.8% | 32.8% |

[a]$p<.001$, [b]$p<.002$; Success defined as GAAS=0 or 1.

| TABLE 3. CHANGE IN LESION COUNTS | | |
|---|---|---|
| Mean Lesion Counts | Baseline (n=505) | 12 months (n=337) |
| Inflammatory lesion counts, n (SE) | 48.1 (1.4) | 18.4 (1)[a] |
| Noninflammatory lesion counts, n (SE) | 38.5 (1.9) | 25.1 (1.9)[b] |
| Total lesion counts, n (SE) | 86.6 (2.6) | 43.5 (2.5)[a] |
| SE= standard error. [a]p<0.001, [b]p<0.002 | | |

therapy. Dryness, rash, sunburn, burning and erythema were the most common adverse events reported by 2.9%, 2.5%, 2.3%, 1.6% and 1.6%, respectively. The reactions were reported as mild to moderate in intensity by 90% of the patients and study discontinuation due to reactions occurred with 10 patients overall and those reactions occurred early in the first few weeks of the study.

Efficacy as assessed by mean lesion counts over time is summarized in table 3 above. Inflammatory lesions were reduced by 58.2%, while noninflammatory lesions decreased by 19.5% and total lesions by 49%.

A post-hoc analysis assessed the patients that had "prohibited concomitant medications" use during the trial and their outcomes did not differ significantly from those without prohibited medication use. This study was primarily designed to evaluate long-term safety and, therefore, was open-label and did not have a comparison group.

As a subset of the overall randomized studies as reported by Draelos and Lucky, the safety and efficacy of dapsone therapy in adolescents (age 12-15 years) were reported by Raimer.[10] Of the 3,516 enrollees, there were 1,306 adolescent patients that were included in the pivotal trials and the safety trials as described above. Less than 2% of adolescents discontinued the studies due to lack of efficacy or tolerability. The percent reduction in acne lesions is summarized in table 4.

Success, as defined by a GAAS equal to 0 or 1 was achieved by 40.1% dapsone-treated adolescents compared to 28.2% vehicle-treated adolescents, p<.001. These results were similar to the adult population. Safety results were not different for adolescents, with application site reactions being reported by 2% of adolescents.

## ADVERSE EFFECTS

Piette et al evaluated 64 patients with a

dapsone for acne vulgaris to assess the hematologic safety of topical dapsone.[11] Subjects were treated with dapsone topical or vehicle for 12 weeks, followed by 12 weeks of the alternate therapy after a 2-week washout period. Plasma dapsone, N-acetyl dapsone concentrations, hemoglobin, bilirubin, reticulocyte counts, haptoglobin and lactate dehydrogenase levels were assessed at baseline, 2 weeks and 12 weeks for each treatment. The largest decrease in hemoglobin was 1.7 g/dL during vehicle treatment and 1.5 g/dL during dapsone treatment. Only 5% (3/56) of subjects had hemoglobin concentrations decrease below normal during both treatment phases. Overall, the mean decrease in hemoglobin from baseline was 0.32 g/dL after 2 weeks

| TABLE 4. PERCENT REDUCTION IN LESION COUNTS FROM BASELINE | | |
|---|---|---|
| Type of lesion | Dapsone gel | Vehicle gel |
| Inflammatory lesion | -44.9[a] | -36.8 |
| Noninflammatory lesion | -26.9[a] | -15.8 |
| Total lesion | -34.6[a] | -24.8 |
| [a]p<0.001 AVOVA using least squared method | | |

of dapsone therapy. No other laboratory changes occurred in the study to suggest clinically relevant hemolysis and no clinical signs or symptoms of hemolytic anemia were reported.

Local side effects included dryness (14%), erythema (9%), and oiliness/peeling (13%) and were reported as mild during the clinical trials.[1] Most reported the incidence of application site event as mild and similar local effects were reported in the vehicle-treated group. One patient noted facial swelling during a clinical trial with dapsone topical and discontinued therapy.

Systemic effects noted included psychiatric effects (suicide attempt, depression and tonic-clonic movements). In clinical trials, 9 of 2372 dapsone-treated patients compared to 3 of vehicle-treated patients reported depression. Psychosis was also reported by 2 of 2372 dapsone-treated patients and none in the vehicle-treated group.

## DRUG INTERACTIONS

When used in combination with oral trimethoprim/sulfamethoxazole (TMP-sulfa) double strength 160 mg/800 mg, the levels (based on area-under-the-curve concentrations) of dapsone and its metabolites increased by 40% (dapsone) and 20% (N-acetyl-dapsone); dapsone hydroxylamine was more than double the systemic exposure with TMP-sulfa.[12] The $T_{max}$ of dapsone and its metabolites remained unchanged with TMP-sulfa. The combination of oral TMP-sulfa and topical dapsone may increase the likelihood of hemolysis in patients with G6PD deficiency. Oral dapsone or antimalarial medications should not be used in combination with topical dapsone because of the increased potential for hemolytic reactions.

When dapsone gel is applied in combination with topical benzoyl peroxide, a temporary local yellow or orange discoloration of the skin and facial hair was reported by 7 of 95 subjects; the discoloration resolved in 4 to 57 days.[1]

## DOSING AND HOW SUPPLIED

Dapsone topical is formulated as an aqueous gel with each gram containing 50 mg of dapsone and is available in a 30 or 60 gram tube. Dapsone should be applied to affected areas twice daily and gently rubbed into the acne areas until no medication remains visible. If no improvement is seen after 12 weeks of therapy, dapsone topical should be discontinued.

Multiple options are available for the management of acne and are summarized in the table 5 on the next page. Each product is available in multiple formulations (cream, lotion, wash, gel, ointment, etc), various concentrations and container sizes. Products may last longer than one month, depending upon area of coverage so direct cost comparisons from product to product below may not apply.

## CONCLUSION

Allergan, the manufacturer of dapsone topical cream, recently was sent a warning letter from the FDA regarding advertisements that appeared to be false

or misleading because it overstated the efficacy and safety of dapsone topical gel.[12] The ad did not adequately address the drug interactions with benzoyl peroxide (temporary skin and hair discoloration) and overstated the efficacy which was not supported by clinical trials (stated that the drug "worked fast," with a substantial effect at 2 weeks).

Guidelines for acne management emphasize multimodal therapy. None of the guidelines specifically mention a role for dapsone, although it fits into the anti-inflammatory and antimicrobial category. Dermatologists are interested in the use of dapsone topical since it is an additional option for therapy; however, they have limited experience with its use at this time.

Dapsone is a new entity for the management of acne that is now available in a topical formulation to bypass the hematologic complications of oral dapsone therapy. The available clinical trials have all assessed dapsone topical as monotherapy only and potential interactions (positive or negative) with other topical acne formulations have not been investigated. Future data regarding combination with benzoyl peroxide and tretinoin products will be coming soon as per the manufacturer. Because of concerns about long-term oral antibiotic use and bacterial resistance, dapsone topical offers an alternative for those who have had suboptimal response with currently available therapies. It would likely be used in patients that have not tolerated benzoyl peroxide or the antimicrobial agents and would not replace tretinoin products. Multiple topical options are available for management of mild to moderate acne. Lack of comparative data with dapsone limits the therapy to patients who have not had success on other more cost effective treatment options. ●

**TABLE 5. TREATMENT OPTIONS FOR ACNE**

| Drug product | Specific product | Mechanism of action | Estimated AWP |
|---|---|---|---|
| salicylic acid | numerous OTC products | comedolytic | Varies by product, all relatively inexpensive |
| benzoyl peroxide | Brevoxyl 4% gel 42.5 grams | keratolytic effects, antimicrobial activity, anti-inflammatory, helps to decrease bacterial resistance in combination with antimicrobials | $89.25 |
| clindamycin/ benzoyl peroxide | Benzaclin 1%/5% gel 35 gram pump | antimicrobial activity, anti-inflammatory, helps to decrease bacterial resistance in combination with antimicrobials | $154.88 |
| erythromycin/ benzoyl peroxide | Benzamycin 3%/5% gel 46.6 grams | antimicrobial activity, anti-inflammatory, helps to decrease bacterial resistance in combination with antimicrobials | $217.16 |
| sulfacetamide sodium 10% | Klaron 10% lotion 118 mL | antimicrobial activity | $126.02 |
| tretinoin | 0.025% cream<br>0.05% cream<br>Retin A Micro 0.1% gel<br>45 grams | inhibit microcomedone, anti-inflammatory properties | $53.20<br>$78.86<br>$182.55 |
| adapalene | Differin 0.1% cream 45 grams | inhibit microcomedone, anti-inflammatory properties | $199.50 |
| azelaic acid | Azelex 20% cream 50 grams | comedolytic and antimicrobial activity | $179.68 |
| adapalene / benzoyl peroxide | EpiDuo 0.1%/2.5% gel 45 grams | inhibit microcomedone, anti-inflammatory properties, antimicrobial activity | $209.49 |
| tazarotene | Tazorac 0.1% cream/gel 30 grams<br>0.05% cream/gel 30 grams | inhibit microcomedone, anti-inflammatory properties | $145.80<br>$137.24 |
| dapsone | Aczone 5% gel 30 grams | anti-inflammatory properties | $142.80 |

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**REFERENCES**

1. Aczone Gel (dapsone). [package insert]. Irvine, CA: Allergan; Revised September 2008.
2. Thiboutot DM, Willmer J, Sharata H, et al. Pharmacokinetics of dapsone gel, 5% for the treatment of acne vulgaris. Clin Pharmacokinet 2007; 46:697-712.
3. Thiboutot D, Gollnick H, Bettoli V, et al. New insights into the management of acne: An update from the Global Alliance to Improve Outcomes in Acne Group. J Am Acad Dermatol 2009; 60(5, Suppl 1):S1-S50.
4. Strauss JS, Krowchuk DP, Leyden JJ, et al. Guidelines of care for acne vulgaris management. J Am Acad Dermatol 2007; 56:651-663.
5. Zaenglein AL, Thiboutot DM. Expert committee recommendations for acne management. Pediatrics 2006; 118:1188-1199.
6. Aczone Gel AMCP Formulary Dossier. Allergan Inc.; Revised October 2008.
7. Tan J. Current measures for the evaluation of acne severity. Expert Rev Dermatol 2008; 3:595-603.
8. Draelos Z, Carter E, Maloney JM, et al. Two randomized studies demonstrate the efficacy and safety of dapsone gel, 5% for the treatment of acne vulgaris. J Am Acad Dermatol 2007; 56:459 e1-e10.
9. Lucky A, Maloney JM, Roberts J, et al. Dapsone gel 5% for the treatment of acne vulgaris: safety and efficacy of long-term (1 year) treatment. J Drug Derm 2007; 6:981-987.
10. Raimer S, Maloney JM, Bourcier M, et al. Efficacy and safety of dapsone gel 5% for the treatment of acne vulgaris in adolescents. Cutis 2008; 81:171-178.
11. Pierre WW, Taylor S, Pariser D, et al. Hematologic safety of dapsone gel, 5%, for topical treatment of acne vulgaris. Arch Dermatol 2008; 144:1564-1570.
12. US Food and Drug Administration. Inspections, Compliance, Enforcement, and Criminal Investigations. Available at: http://www.fda.gov/ICECI/EnforcementActions/WarningLetters/ucm179769.htm. Accessed: August 17, 2009.

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