

# Cumulative Irritation Potential of Adapalene 0.1% Cream and Gel Compared With Tazarotene Cream 0.05% and 0.1%

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*Despite the many beneficial effects of dermatologic applications, most of the current treatments for acne cause local irritation. The objective of this study was to compare the ability of the epidermis to tolerate adapalene 0.1% cream and gel and tazarotene cream in concentrations of 0.05% and 0.1%. A total of 30 subjects were enrolled in the study. The test products were applied under occlusive dressings at randomized sites on the upper back for approximately 24 hours, 4 times a week, and for 72 hours, once a week, for a period of 3 weeks. Skin reactions (erythema score plus other local reactions) at the product application sites were assessed 15 to 30 minutes after dressing removal.*

*Twenty-six subjects completed the study. A total of 16 subjects discontinued use of 1 or more of the test products because of irritation scores reaching severe or greater; all but one of these discontinuations were at sites treated with the tazarotene products.*

*The mean 21-day cumulative irritancy indices for adapalene 0.1% cream and gel were significantly lower ( $P=.05$ ) than those for tazarotene cream 0.05% and 0.1% and not notably higher than that of the negative control product.*

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Acne vulgaris is the most common dermatologic disorder, affecting approximately 85% of individuals at some time between the ages of 12 and 14 years.<sup>1</sup> Although acne is most prevalent in this age group, the disease is reported in 8% of adults between the ages of 25 and 34 years and in 3% of adults between the ages of 35 and 44 years. In the United States alone, more than 50 million people are estimated to be affected by some form of acne, with over 17 million experiencing acne vulgaris. Acne is the most common dermatologic disorder—almost always diagnosed by the subject—and counts for 20% of all dermatologic consultations.<sup>1</sup> Currently, there is no single topical antiacne medication that acts against all 4 of the major pathophysiologic features of acne: hyperkeratinization, sebum production, bacterial proliferation, and inflammation. Despite the many beneficial effects of dermatologic applications, retinoids and their derivatives cause local irritation, which is manifested as erythema and peeling of the stratum corneum.<sup>2</sup>

Adapalene, a naphthoic acid derivative with retinoid activity, is effective in the treatment of mild to moderate acne vulgaris. Adapalene gel 0.1%

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has been shown to be better tolerated than several tazarotene formulations.<sup>3-7</sup>

Tazarotene is a receptor-selective retinoid. It normalizes keratinocyte differentiation, reverses keratinocyte hyperproliferation, and has anti-inflammatory effects. Tazarotene cream 0.1% has shown potential for irritation, erythema, peeling, dryness, burning, and itching.<sup>8</sup> A new concentration of 0.05% of tazarotene cream recently was made available to limit these side effects to the level of those for the 0.1% concentration of adapalene cream and gel.

This present study was designed to compare the irritation potential of adapalene 0.1% cream and gel with 2 different concentrations of tazarotene cream, 0.05% and 0.1%. White petrolatum served as a negative control.

Cumulative irritancy assays currently are used to assess the irritation potential of topically applied materials. Potential irritation is caused by direct damage to the epidermal cells; no immunologic (allergic) mechanisms are involved.<sup>7</sup> Results from this standard assay are widely accepted to be indicators of irritation.<sup>9</sup>

## Methods

The study was conducted in accordance with the principles of the Declaration of Helsinki and its amendments and in compliance with good clinical practice. Before entering the study, approval from an independent review board was obtained, and all subjects provided written informed consent.

**Population**—Subjects of any gender and race, aged at least 18 years, and with Fitzpatrick phototype I to IV were included in the study.<sup>10</sup> Female subjects had to have a negative urine pregnancy test at the beginning of the study.

Subjects with a known history of atopic dermatitis, eczema, or psoriasis or with known sensitivities to any ingredients in the test products were excluded from the study.

In addition, subjects who did not conform to the washout period of between 1 and 12 weeks for topical and systemic medications (eg, oral corticosteroids, nonsteroidal anti-inflammatory drugs, salicylic acid >1 g/d, any oral retinoids) were excluded from the study.

**Study Design**—The design of this study is standard for the determination of the 21-day cumulative irritancy assay. The use of comparative treatments and a negative control product provided appropriate control in the study.

This was a single-center, active-controlled and negative-controlled, investigator-blinded, intra-individual comparison study, with randomized

Table 1.

## Classification of Irritation

Mean Cumulative Irritancy Index	Product Classification
<0.025	Nonirritating
0.025–1 (noninclusive)	Slightly irritating
>1–2 (noninclusive)	Moderately irritating
>2–3 (noninclusive)	Very irritating

Table 2.

## Demographics and Subject Disposition

	N=30
Age, y	
Mean ± SD	50.9 ± 13.0
Range	24–75
Gender, n (%)	
Female	27 (90.0)
Male	3 (10.0)
Race, n (%)	
White	26 (86.7)
Hispanic	4 (13.3)
No. of subjects who discontinued, n (%)	4 (13.3)
At subject's request	1 (3.3)
Lost to follow-up	2 (6.7)
Nonrespect of washout period	1 (3.3)
No. of subjects who completed, n (%)	26 (86.7)

applications of study products to healthy subjects meeting specific inclusion and exclusion criteria.

To ensure the completion of 25 subjects, a total of 30 subjects were selected. All subjects received repeated applications of each of the study products on the upper back under occlusive dressings for a period of 3 weeks. The primary parameter of interest was an assessment of cumulative product irritancy,

Table 3.

## Mean Cumulative Irritancy Index (MCII) by Tested Products

Study Products	MCII±SD	Differences			
		Adapalene Gel 0.1%	Tazarotene Cream 0.05%	Tazarotene Cream 0.1%	White Petrolatum
Adapalene cream 0.1%	0.06±0.11	-0.12	-0.74*	-1.06*	0.03
Adapalene gel 0.1%	0.18±0.47		-0.62*	-0.94*	0.15
Tazarotene cream 0.05%	0.80±0.54			-0.33*	0.77*
Tazarotene cream 0.1%	1.12±0.54				1.09*
White petrolatum	0.03±0.05				

\* $P \leq 0.01$ .

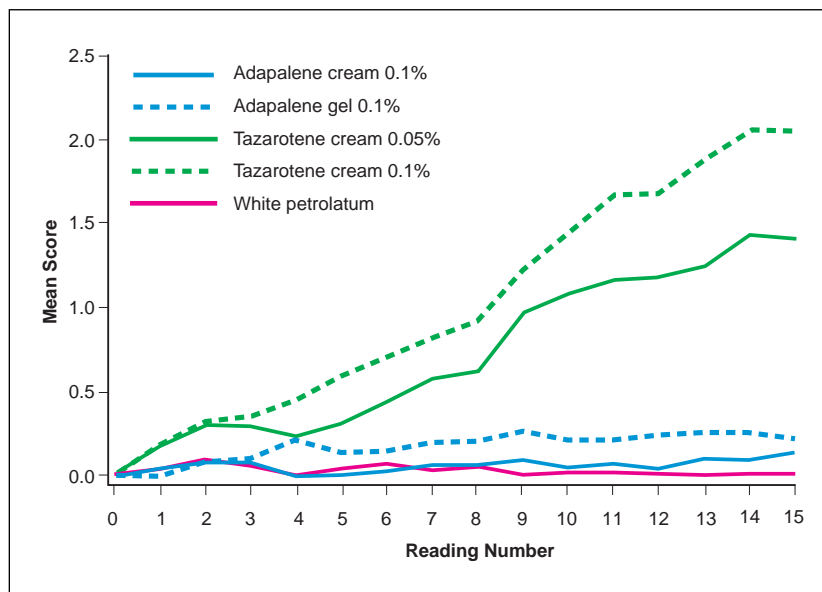


Figure 1. Mean individual treatment score for local tolerance by reading number.

based on visual grading of erythema and other local skin reactions at the application sites.

At each visit, following the initial dressing application, skin reactions were assessed 15 to 30 minutes after removal of the product. When an erythema reaction related to a product received a score of 3 (severe) at 1 or more sites, product applications at the incriminated sites were discontinued. Likewise, if an irritation reaction related to the adhesive prohibited dressing at a particular site, all product applications at the incriminated sites were discontinued, and the

scores were carried forward to the end of the study.

**Test Products**—Product applications were performed at the investigational site. Five zones, each with a surface of about 4 cm<sup>2</sup> in diameter, were selected on the upper back of each subject, avoiding any moles, hairs, or nonflat areas. On initiation, each of the products was applied randomly to one of the zones on the upper back according to a predefined randomization schedule.

All efforts were made to keep the evaluator blinded to the identification of the products applied. Thus, the individual applying and removing the product was different from the individual evaluating the sites. The randomization list was kept from the evaluator.

Each zone was delineated with a cutaneous marker. The zones were designated by the numbers 1, 2, 3, 4, and 5 on one side of the spine. About 0.2 g of each product (adapalene 0.1% cream or gel, tazarotene cream 0.05% or 0.1%, and white petrolatum) was applied, under an occlusive dressing (large Finn Chambers, a system that protects skin from rubbing against clothing), by a qualified member of the study site to its designated zone.

Dressings were applied at each visit and removed at the subsequent visit, approximately

24 hours later. Those applied on Friday were left on for 72 hours over the weekend and removed the following Monday.

Furthermore, subjects were asked to avoid exposure to the sun, including sunbathing or other excessive exposure or UV radiation (eg, tanning parlors); to avoid using any cosmetics on the study zone; and to avoid bathing or showering the upper back.

**Clinical Evaluation**—Evaluation visits took place every day except weekends. Each treated site on each subject’s back was assessed for erythema and other local cutaneous irritation before the initial treatment application and again at every study visit, approximately 15 to 30 minutes after dressing removal and before the following application.

Erythema was graded on a scale of 0 to 3, with 0 being no reaction and 3 being severe. In the case of severe irritation (an erythema score of 3) at a clinical evaluation or as described by the subject for any zone, product applications at the incriminated sites were discontinued and no longer scored.

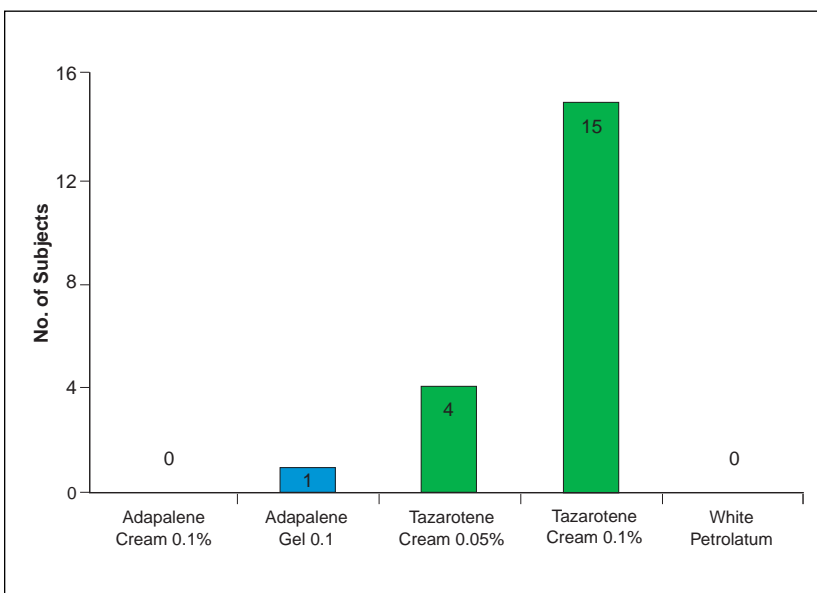
Other local cutaneous irritation reported throughout the study included edema, papules, vesiculation, blisters, pustules, hyperpigmentation, weeping or oozing, and spreading of reaction beyond the test area evaluated.

When an irritation reaction related to the adhesive prohibited dressing at a particular site, all product applications at the treated sites were discontinued, and the scores were carried forward to the end of the study. Safety was monitored through each individual’s report of adverse events.

**Statistical Analysis**—Twenty-five subjects were considered an accepted sample size to evaluate the irritation potential of topical products that had already been tested in large populations. To account for possible dropouts, at least 30 subjects had to be enrolled to ensure the completion of 25 subjects. To allow a balanced design, this number is a multiple of the number of test products.



**Figure 2.** Example of reactions to test products after 9 days of application.



**Figure 3.** Number of subjects who discontinued because of the occlusive dressing during the course of the study.

For evaluating the cutaneous tolerance, a cumulative irritancy index (CII) was calculated for each treatment and for each subject, as follows: CII equals the sum of irritation score and the number of readings. Classification of mean CII (MCII) is provided in Table 1.

To calculate the CII, a baseline score (day 0) was excluded from the calculation. When an irritation reaction was rated as 3 (severe) at any site, product applications at the incriminated sites were discontinued, and a score of 3 was imputed to the remaining readings (last observation carried forward). If

product application was discontinued at a site because of a cause other than product irritation (eg, adhesive irritation), product applications at all sites were discontinued, and the last reading of each site was carried forward. If a subject missed a scheduled visit, the scores from the following visit were assigned to the missed visit.

CIIIs were averaged across subjects to obtain an MCII for each treatment. CIIIs were submitted to an analysis of variance with effects for subject, zone, and formulation. To adjust for multiple comparisons, MCIIIs were compared and formulations classified using the Tukey multiple comparisons procedure performed at the 1% and 5% significance levels. There was a maximum of 15 readings in the study.

## Results

**Population**—Of the 30 subjects enrolled in the study, 26 (86.7%) completed the study. Table 2 shows demographics and subject disposition.

All female subjects of childbearing potential had to have a negative urine pregnancy test on enrollment in the study. No subjects had a medical history that precluded him or her from study participation.

Subjects received 15 applications of all study products for a period of 3 weeks. Exceptions to the full protocol-specified treatment regimen were 4 subjects who discontinued the study prematurely and 16 who discontinued treatment at specific application sites because of product-related irritation.

The MCIIIs ranged from approximately 0.06 to 1.12 for the 4 active test products. Detailed results are provided in Table 3 and Figure 1. Figure 2 shows an example of typical irritation with tazarotene after 9 days of application.

**Test Products**—Both adapalene products and the white petrolatum were significantly less irritating than the tazarotene products ( $P=.05$  and  $P=.01$ , respectively). Tazarotene cream 0.1%, as well as being significantly more irritating than the adapalene products and the negative control, was significantly more irritating than tazarotene cream 0.05% ( $P=.05$ ).

Individual reactions to the test products ranged from “no reaction” to “severe erythema with weeping or oozing.” Reactions to white petrolatum did not exceed “mild erythema,” and reactions to adapalene cream 0.1% did not exceed “moderate erythema,” which was experienced by one subject. The most severe reaction observed in response to treatment with adapalene gel 0.1% was “severe

erythema,” seen in one subject; dressing was discontinued in this subject because of this reaction.

Dressing with tazarotene cream 0.05% was discontinued in 4 subjects, and tazarotene cream 0.1% was discontinued in 15 subjects because of limiting reactions. No subjects in the adapalene cream 0.1% group were discontinued because of limiting reactions (Figure 3). No treatment-related adverse events were reported during the study.

## Conclusion

The present 21-day cumulative irritancy assay showed that adapalene 0.1% cream and gel were significantly less irritating than tazarotene cream in concentrations of 0.05% and 0.1% ( $P=.05$ ).

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## REFERENCES

1. Leyden JL. A review of the use of combination therapies for the treatment of acne vulgaris. *J Am Acad Dermatol*. 2003;49(suppl 3):S200-S210.
2. Kim BH, Lee YS, Kang KS. The mechanism of retinoid-induced irritation and its application to anti-irritant development. *Toxicol Lett*. 2003;146:65-73.
3. Verschoore M, Langner A, Wolska H, et al. Vehicle controlled study of CD 271 lotion in the topical treatment of acne vulgaris. *J Invest Dermatol*. 1993;100:221A.
4. Verschoore M, Langner A, Wolska H, et al. Efficacy and safety of CD 271 alcoholic gels in the topical treatment of acne vulgaris. *Br J Dermatol*. 1991;124:368-371.
5. Bernard BA. Adapalene, a new chemical entity with retinoid activity. *Skin Pharmacol*. 1993;6(suppl 1):61-69.
6. Brand B, Gilbert R, Baker MD, et al. Cumulative irritancy comparison of adapalene gel 0.1% versus other retinoid products when applied in combination with topical antimicrobial agents. *J Am Acad Dermatol*. 2003;49(suppl 3):S227-S232.
7. Greenspan A, Loesche C, Vendetti N, et al. Cumulative irritation comparison of adapalene gel and solution with 2 tazarotene gels and 3 tretinoin formulations. *Cutis*. 2003;72:76-81.
8. Guenther LC. Optimizing treatment with topical tazarotene. *Am J Clin Dermatol*. 2003;4:197-202.
9. Berger RS, Bowman JP. A reappraisal of the 21-day cumulative irritation test in man. *J Toxicol Cutan Ocul Toxicol*. 1982;1:109-115.
10. Fitzpatrick TB, Eisen AZ, Wolff K, et al, eds. *Dermatology in General Medicine*. Vol 1. 4th ed. New York, NY: McGraw-Hill; 1993:1689-1716.