

# Clindamycin Phosphate 1.2%–Tretinoin 0.025% Gel: Vehicle Characteristics, Stability, and Tolerability

James Q. Del Rosso, DO; Waranush Jitpraphai, PhD; Sanjay Bhambri, DO; Saira Momin, DO

*An aqueous gel formulation containing solubilized clindamycin phosphate 1.2% and a stable combination of both solubilized and crystalline tretinoin 0.025% (clin/tret) has been evaluated in 3 pivotal phase 3 studies, among other studies including a 52-week trial. The pivotal studies enrolled 4550 participants 12 years and older with mild, moderate, and severe acne vulgaris. The combination clin/tret gel was effective in reducing both inflammatory and noninflammatory lesions and was well-tolerated. This article reviews important vehicle characteristics of the combination gel as well as formulation stability and tolerability data that are potentially clinically relevant.*

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**A**n aqueous gel formulation containing solubilized clindamycin phosphate 1.2% and a stable combination of both solubilized and crystalline tretinoin 0.025% (clin/tret) has been evaluated in 3 pivotal phase 3 studies, among other studies including a 52-week trial.<sup>1-3</sup> In the pivotal studies, 4550 participants 12 years and older with mild,

moderate, and severe acne vulgaris were enrolled.<sup>1,3</sup> The combination clin/tret gel was effective in reducing both inflammatory and noninflammatory lesions and was well-tolerated. In addition, the combination gel proved superior to either active component alone and to vehicle, regardless of acne severity.<sup>1,3</sup>

This article discusses specific vehicle characteristics of the clin/tret gel that appear to be clinically relevant, stability characteristics including results after exposure to UV light and/or benzoyl peroxide (BPO), and cutaneous tolerability.

## What are the vehicle characteristics of clin/tret gel?

The patented clin/tret vehicle is an aqueous-based, alcohol-free gel.<sup>1</sup> The clindamycin phosphate 1.2% is solubilized, equivalent to clindamycin 1%. The tretinoin is incorporated into the vehicle as a stable combination of 2 forms, with a portion solubilized and the remainder present as a crystalline form in suspension.<sup>1</sup> After skin application, the crystalline tretinoin must first solubilize on the skin surface, allowing for slower follicular penetration of tretinoin. It is believed that the rate of cutaneous delivery from solubilized tretinoin is more rapid than crystalline tretinoin, accounting for the favorable tolerability profile and low irritation potential of the clin/tret gel.<sup>1</sup>

The clin/tret gel uses a unique formulation approach, especially the incorporation of both solubilized and crystalline tretinoin. The particle size of tretinoin in the clin/tret formulation is tightly controlled during the manufacturing process, with the small size optimized to enhance follicular penetration.<sup>4</sup> The crystalline tretinoin component allows for slow dissolution and progressive cutaneous penetration. The vehicle characteristics of the clin/tret

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Drs. Del Rosso, Bhambri, and Momin are from Valley Hospital Medical Center, Las Vegas, Nevada. Dr. Jitpraphai is from Medicus Pharmaceutical Corporation, Scottsdale, Arizona. Dr. Del Rosso is a consultant, researcher, and speaker for Allergan, Inc; Coria Laboratories, Ltd; Galderma Laboratories, LP; Intendis, Inc; Medicus Pharmaceutical Corporation; OrthoNeutrogena; QLT Inc; Ranbaxy Laboratories, Ltd; SkinMedica, Inc; Stiefel Laboratories, Inc; Triax Pharmaceuticals; Unilever; and Warner Chilcott. Dr. Jitpraphai is an employee of Medicus Pharmaceutical Corporation. Drs. Bhambri and Momin report no conflict of interest.

Correspondence not available.

gel appear to correlate with its favorable tolerability profile, as reported in large controlled clinical trials, including a 52-week trial.<sup>1-3</sup>

### What are the stability characteristics of clin/tret gel?

Because topical acne therapies frequently are used in combination, it is important to know stability characteristics to avoid degradation of an active ingredient in a specific formulation when applied sequentially with or too closely in time after another topical agent. Conventional vehicle formulations of tretinoin are known to be degraded by BPO and also are photolabile.<sup>5</sup> Rapid degradation of an active ingredient such as tretinoin because of the effect of another topically applied agent may potentially correlate with decreased efficacy.

**Admixture Study With BPO**—Results obtained from an independent analytical laboratory evaluated the degradation profile of tretinoin in clin/tret gel when mixed in equal volume with BPO gel 6% over a 24-hour period after incubation at 35°C.<sup>6</sup> Tretinoin assays were obtained at baseline and at 2, 4, 6, 8, and 24 hours. Over the first 8 hours, 96.8% of the original label amount of tretinoin remained intact, with 79.8% still present after 24 hours (Table).<sup>6,7</sup> These data suggest that sequential application of clin/tret gel and BPO gel 6% would not result in rapid degradation of the tretinoin component of this specific formulation.

**Photostability**—The chemical stability of the combination of both the solubilized and crystalline tretinoin used in the clin/tret gel was evaluated using 2 Franz cell human skin penetration models under both light and dark conditions with a fixed-dose technique.<sup>6</sup> Human cadaver skin, freshly harvested within 48 hours of death, was used to perform the studies. The assays evaluated the amount of tretinoin absorbed; dermal, epidermal, and stratum corneum concentrations; and amount of tretinoin in surface wash. Total tretinoin recovery from the clin/tret gel reported as percentage of applied dose after 24 hours under both light and dark conditions was 89.8%±2.7% under light conditions and 116.4%±0.4% under dark conditions. Using the same assay design, evaluation of solubilized tretinoin as a control, using both 0.4% and 0.1% concentrations, remained fully stable under light conditions; however, total tretinoin recovery after 24 hours under dark conditions was 16.8%±1.6% and 25.6%±3.2%, respectively.<sup>6</sup>

**Additional Observations From Skin Penetration Analyses**—Additional important observations of potential clinical relevance were noted during analyses of data from skin penetration performed under a variety of conditions, including with or without UV light exposure (light or dark conditions) and

### Stability of Tretinoin in Admixture of Clin/Tret Gel and BPO Gel 6% Over 24 Hours<sup>6,7</sup>

Time, h	Tretinoin in Assay, % <sup>a</sup>
Baseline	101.6
2	101.6
4	99.2
6	98.4
8	96.8
24	79.8

Abbreviations: Clin/Tret, clindamycin phosphate 1.2%–tretinoin 0.025%; BPO, benzoyl peroxide.

<sup>a</sup>0.0125% (weight per weight) of tretinoin in the admixture based on labeled concentration in clin/tret gel.

with or without exposure to BPO gel 5% two hours after application of clin/tret gel. Tretinoin concentrations were assayed using high-performance liquid chromatography.<sup>6</sup>

Data from human cadaver skin penetration analyses performed over a 24-hour period indicate that tretinoin from the clin/tret gel formulation does not penetrate human skin. Penetration is slow, with a progressive rise in dermal and epidermal concentrations observed over time.<sup>6</sup>

Exposure to BPO 2 hours after application of clin/tret gel to human skin did not have an appreciable effect on tretinoin penetration under dark conditions. A slight increase in tretinoin penetration appeared to occur after BPO exposure under light conditions at 8 hours.<sup>6</sup>

Over 24 hours, mass balance accountability of tretinoin from the clin/tret gel ranged from 70% to 88% under light conditions and 103% to 108% under dark conditions, both without BPO exposure.<sup>6</sup> In the presence of BPO under light conditions, the recovery of tretinoin dropped to 12% at 24 hours compared with 61% at 24 hours with BPO under dark conditions. Total percentage recovery of tretinoin after exposure to BPO under dark conditions was sustained at 75% over the 4- to 12-hour measurement time points.<sup>6</sup>

### What potentially clinically relevant information may be obtained from clin/tret gel stability data?

Overall, the stability studies completed with clin/tret gel support that exposure to BPO, although associated

with some degradation of tretinoin over 24 hours, does not appreciably alter the percutaneous delivery of tretinoin. Total percentage recovery of tretinoin after exposure to BPO under dark conditions was sustained at 75% over the 4- to 12-hour measurement time points.<sup>6</sup> Exposure to both light conditions and BPO enhances the degradation of tretinoin. Stability results suggest that use of BPO and clin/tret gel does not require separation of application by 8 to 12 hours, which is what has been recommended with use of conventional formulations of tretinoin in combination with BPO.<sup>5</sup> Consistent with the methodology used in the clin/tret gel clinical trials, it is optimal to apply clin/tret gel in the evening; however, light exposure without simultaneous or near-simultaneous BPO exposure appears to exhibit negligible tretinoin degradation, potentially allowing for daytime application of clin/tret gel if preferred by the patient.

The clin/tret gel stability results provide flexibility based on individual patient needs directed at maximizing compliance. The stability data suggest that clin/tret gel may be applied in the evening or during the day, though evening application appears to be most optimal.

When a BPO-containing formulation is added to the clin/tret gel regimen, it is suggested that clin/tret gel be applied in the evening. Based on skin penetration assays using freshly harvested human cadaver skin, it does not appear that BPO use needs to be separated beyond 2 hours after application of clin/tret gel, with admixture data suggesting that BPO and clin/tret gel may be applied sequentially.

### **What are the tolerability characteristics of clin/tret gel?**

As discussed above, the incorporation of both solubilized and crystalline tretinoin in clin/tret gel appears to contribute to a highly favorable tolerability profile. Both the slow dissolution and cutaneous penetration of tretinoin from the crystalline form and the controlled tretinoin particle size are believed to be factors that correlate with the low skin irritation potential observed with clin/tret gel.<sup>1-3</sup>

In a 52-week open-label trial of participants using clin/tret gel (N=442) for treatment of acne vulgaris as monotherapy (78%) or in combination with other agents (22%), the overall discontinuation rate due to adverse reactions was less than 1% in participants treated for up to 6 months and 0% in participants treated for up to 12 months. Clin/tret gel was well-tolerated, with 91%, 94%, and 92% of participants reporting no burning, no stinging, and no pruritus, respectively.<sup>2</sup>

An evaluation of initial acne flares captured during phase 3 trials demonstrated that most participants did not experience such flares.<sup>8</sup> The subset of participants most likely to experience an initial flare of inflammatory acne lesions is the group with mild or moderate disease. The percentage of participants exhibiting a 10% or 20% increase in inflammatory acne lesions within the first 2 weeks of treatment was highest in participants receiving tretinoin gel 0.025% as monotherapy or vehicle. Participants treated with clin/tret gel demonstrated a 30% to 60% lower rate of increase in inflammatory acne lesions, comparable with the rate observed in participants treated with clindamycin phosphate gel 1.2% as monotherapy.<sup>8</sup>

In a randomized, investigator-blinded, split-face, 22-day, cutaneous tolerability study, participants applied clin/tret gel to one side of the face (n=45) and either tretinoin microsphere gel 0.1% (n=23) or adapalene gel 0.1% (n=22) to the other side of the face.<sup>9</sup> Participants applied a pea-sized amount of study drug on each side of the face once daily for 21 days, including the nasolabial (melolabial) folds, with application supervised by study personnel each Monday through Friday and unsupervised on weekends. Parameters for evaluation were daily investigator assessments of erythema and scaling and participant assessments of burning, stinging, and pruritus. Results from this study reported the cumulative erythema and scaling scores were greater from day 10 and day 7 through study end point, respectively, with tretinoin microsphere gel 0.1% (day 22, erythema >60, scaling >50) than with clin/tret gel (day 22, erythema <20, scaling <20). Additionally, the cumulative score for participant-assessed symptoms (burning, stinging, pruritus) was greater in the tretinoin microsphere gel 0.1% treatment group. There was a trend toward greater erythema, scaling, and participant-assessed symptomatology with adapalene gel 0.1% than with clin/tret gel; however, the differences between groups were not significant.<sup>9</sup>

### **What potentially clinically relevant information may be obtained from clin/tret gel tolerability data?**

The characteristics of the clin/tret gel formulation support the favorable tolerability profile observed in more than 2200 participants who were actively treated with clin/tret gel in clinical trials.<sup>1-3</sup> The low irritation potential of clin/tret gel is supported by a 52-week trial, with 91%, 94%, and 92% of participants reporting no burning, no stinging, and no pruritus, respectively, including participants using

clin/tret gel as monotherapy or in combination with other agents.<sup>1-4,8,9</sup>

Possible explanations for the more favorable tolerability profile of clin/tret gel compared with tretinoin microsphere gel 0.1% in the comparative, split-face, cutaneous tolerability study are the greater concentration of tretinoin in the latter formulation and the potential anti-inflammatory effects of clindamycin present in the clin/tret formulation.<sup>9</sup> As discussed above, vehicle characteristics of the clin/tret gel, including slow release and cutaneous penetration of tretinoin from the crystalline suspension, also are believed to play a role in reducing cutaneous irritation.

## REFERENCES

1. Schlessinger J, Menter A, Gold M, et al. Clinical safety and efficacy studies of a novel formulation combining 1.2% clindamycin phosphate and 0.025% tretinoin for the treatment of acne vulgaris. *J Drugs Dermatol*. 2007;6:607-615.
2. Leyden JJ, Wortzman M, Plott T. Safety of a novel gel formulation of 0.025% tretinoin and 1.2% clindamycin phosphate: results from a 52-week open-label study. Poster presented at: 31st Hawaii Dermatology Seminar; March 3-9, 2007; Maui, HI.
3. Leyden JJ, Plott T, Wortzman M. A novel gel formulation of 0.025% tretinoin and 1.2% clindamycin phosphate: efficacy in patients with mild, moderate, and severe baseline acne. Poster presented at: 31st Hawaii Dermatology Seminar; March 3-9, 2007; Maui, HI.
4. Plott RT. Unique aqueous formulation results in reduced risk of tretinoin-induced irritation bioassay. Poster presented at: 31st Hawaii Dermatology Seminar; March 3-9, 2007; Maui, HI.
5. Del Rosso JQ. Evaluation of a patented pad formulation of benzoyl peroxide in combination with a topical retinoid: chemical stability, efficacy, and tolerability. *Cosmet Dermatol*. 2006;19:93-97.
6. Del Rosso JQ, Bhambri S, Momin S. Clindamycin phosphate 1.2%/tretinoin 0.025% gel: vehicle characteristics, stability and tolerability. Poster presented at: Fall Clinical Dermatology Conference; October 18-21, 2007; Las Vegas, NV.
7. Data on file. Scottsdale, AZ: Medicis Pharmaceutical Corporation; 2007.
8. Leyden JJ, Plott T, Wortzman M. A novel gel formulation of tretinoin and clindamycin is not associated with retinoid induced flaring of inflammatory acne. Poster presented at: 31st Hawaii Dermatology Seminar; March 3-9, 2007; Maui, HI.
9. Leyden JJ, Plott T, Wortzman M. Comparison of facial tolerance of a novel gel formulation of 0.025% tretinoin and 1.2% clindamycin phosphate, 0.1% adapalene gel, and 0.1% tretinoin microsphere gel. Poster presented at: 31st Hawaii Dermatology Seminar; March 3-9, 2007; Maui, HI.