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Clocortolone Pivalate 0.1% Cream: A New Way to Enhance Patient Access

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Understanding Generics

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As dermatologists, we are lucky to be in a specialty in which we can take care of our patients with mostly topical treatments, avoiding possible systemic adverse events that can accompany oral medications. On the other hand, the importance of vehicles that deliver the topical treatments to the skin is unfortunately underrated and misunderstood, mostly by non-dermatologists; the generic substitution of most of our prescriptions by pharmacists being the best proof of this misunderstanding. Unfortunately, the daily generic substitution of our prescriptions has become routine, and it is here to stay as the pressure for cost-saving efforts in medicine increases with the new health care environment.

Let's take a brief look at the generic approval process for oral drugs in the United States. A generic drug aims to match the branded product in terms of active ingredient and dosage form by bioequivalence to the Reference Listed Drug or Innovator (Branded Drug). Oral generic drugs have to show equivalent bioavailability through comparable plasma concentrations. This process for oral medications is as simple as it seems.

Now, let's take a detailed look at the generic approval process for topical drugs in the United States. The methods of demonstrating bioequivalence are more complicated for topicals than for oral medications because plasma concentrations are really not a good measure.

There are 3 different ways for a generic topical drug to meet the bioavailability criteria:

1. Bioequivalence waiver from the US Food and Drug Administration

2. Clinical bioequivalence for all non-corticosteroid topical drugs in a 3-arm study in which the generic product is tested against the reference drug and the vehicle

3. Bioequivalence by a vasoconstriction bioassay for all topical corticosteroid generics. This bioassay, known as the Stoughton and McKenzie Assay, measures the area under the effect curve which is related to the potency of that particular corticosteroid. The test is performed on the volar forearm of healthy volunteers by measuring the blanching effect of the generic topical corticosteroid over an established period of time with a chromameter.

The bioequivalence requires that the test product (generic) does not differ "significantly" from the reference product (innovator). This significance is defined as 20%. That translates to a 45% variability, which means one generic can vary by 45% from the innovator or from another generic.[1]

This generic approval process for topical corticosteroids, which are the most commonly used drugs in dermatology, poses several challenges: Our patients can receive a different generic each time they fill their prescription. It is not unusual for patients to tell us, "That salve was working really well, but it is just not working anymore." We immediately think about tachyphylaxis or non-adherence, but perhaps it is just that they received a generic this month with 45% less bioequivalence than the generic they received last month! Perhaps they received a generic that has an excipient in the vehicle to which they are allergic. Perhaps they received a generic that has no clinical efficacy, since vasoconstriction assay does not test for clinical efficacy at all and is performed on healthy skin. Perhaps they received a generic with a vehicle that just rubs off the skin without penetrating the stratum corneum at all. Perhaps they received a generic that needs to be dosed 3 times a day rather than twice a day, since vasoconstriction assay is a single application test. Or perhaps they received a generic with a vehicle full of irritants that impairs the epidermal barrier and increases

"For all of these reasons, I am worried about my patients' well-being every time I write a generic topical corticosteroid prescription."

transepidermal water loss, since vasoconstriction assay does not test application site reactions. For all of these reasons, I am worried about my patients' well-being every time I write a generic topical corticosteroid prescription.

However, we now have branded generics in which the manufacturers have begun producing their own authorized generics with the exact same excipients as in their original branded vehicles. Promius Pharma, one of the leaders in this field, recently brought to the market clocortolone pivalate 0.1% generic formulation, which is exactly the same as their original branded product. Another advantage is that this formulation is the only authorized generic formulation of clocortolone pivalate 0.1% cream on the market.[2]

The new trend of authorized exact same generics of unique products such as clocortolone pivalate 0.1% is a welcome addition to our treatment armamentarium and a great service to our patients, allowing me to prescribe this generic formulation without any of the above concerns.

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References

1. Leon H. Kircik MD, Joseph B. Bikowski MD, David E. Cohen MPH MD, Zoe Diana Draelos MD, Adelaide Hebert MD. Vehicles Matter. *Supplement to Practical Dermatology.* 2010;(12-14). http://bmctoday.net/vehiclesmatter/pdfs/0310.pdf Accessed May 19 2014.
2. Cloderm [package insert]. Bridgewater, New Jersey: Promius Pharma, LLC; 2011.

Transitioning From Brand to Generic With Topical Products and the Importance of Maintaining the Formulation and Therapeutic Profiles of the Original Product: Focus on Clocortolone Pivalate 0.1% Cream

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ABSTRACT

Topical corticosteroids (TCSs) are a major part of the foundation of treatment for a wide variety of eczematous and inflammatory skin disorders in both adults and children. Mid-potency TCSs represent an important category as they are often used to treat eczematous dermatoses, such as atopic dermatitis. The TCS product must effectively release the active ingredient and promote cutaneous penetration so that therapeutic activity can occur. As many topical products eventually become available as generic formulations, it is important to recognize that although the active ingredient and its concentration are the same, the vehicle excipients may differ significantly, occasionally leading to potential differences in irritancy, in allergenicity, in effects on epidermal permeability barrier function, and, possibly, in efficacy. Clocortolone pivalate 0.1% cream is a mid-potency TCS formulated in an emollient formulation that has been shown to be effective and well-tolerated in the management of several corticosteroid-responsive dermatoses. This article outlines the pharmacologic and clinical data achieved with the original brand formulation of clocortolone pivalate 0.1% cream, and discusses the establishment of an authorized generic formulation that is identical in formulation to the original brand.

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INTRODUCTION

Topical corticosteroids (TCSs) are an integral component of the therapeutic armamentarium of the dermatologist. These agents are commonly used to treat a wide variety of cutaneous disease states, such as atopic dermatitis (AD), nummular eczema, contact dermatitis, seborrheic dermatitis, psoriasis vulgaris, and stasis dermatitis. The selection of a TCS is influenced by the anticipated responsiveness and anatomic locations of the disease state involved, the potency of the TCS formulation, and the characteristics of the vehicle formulation.[1-7] The collective factors that ultimately dictate TCS selection by influencing the efficacy, skin tolerability, and patient acceptability of a given TCS formulation are listed as follows:

Compound-related factors: The individual corticosteroid compound and the concentration incorporated into the final formulation.

Disease-state related factors: The specific diagnosis, severity, and anatomic sites involved.

Vehicle-related factors: The general category, such as cream, lotion, ointment, gel, solution, or spray; and the aesthetic characteristics of the final product, especially as viewed by patients.

Formulation-related factors: Specific excipients incorporated to exert certain properties (ie, penetration enhancement, humectancy, occlusivity, solubilization, spreadability, emolliency, product preservation, etc.) and active ingredient release characteristics.

The mid-potency TCS category represents a group of commonly prescribed agents that are used to treat a wide variety of common dermatologic disorders such as AD, irritant contact dermatitis, allergic contact dermatitis (ACD), seborrheic dermatitis (SD), and psoriasis (including chronic plaque psoriasis [CPP] and inverse psoriasis); as well as other eczematous dermatoses such as nummular eczema, asteatotic eczema, and stasis dermatitis. In many cases, CPP and lichenified eczematous plaques warrant treatment with a high-potency or super-high potency TCS, at least initially. However, most of the cutaneous disorders mentioned above respond favorably within a reasonable time frame to a mid-potency TCS that is adaptable for application and does not cause local irritation or cutaneous allergy.[1,4,8-11]

Among the currently available mid-potency TCS formulations available in the marketplace in the United States, clocortolone pivalate 0.1% cream has been available solely as a brand TCS

since 1977. This formulation is supported by data demonstrating efficacy in patients treated for a variety of common corticosteroid-responsive dermatoses (CRD), an excellent safety profile, a vehicle design which includes excipients that assist in reducing epidermal barrier dysfunction, and an active ingredient that exhibits negligible potential for allergenicity.[9-12] Therefore, when considering the availability of a generic formulation of clocortolone pivalate 0.1% cream, it is important that the quality and characteristics of the original brand formulation be upheld. Unfortunately, this is not always the case with generic formulations as the vehicle constituents and characteristics sometimes differ from the original brand formulation. As a result, clinicians may assume that their patients are being treated with a TCS product that delivers the qualities they have become accustomed to, when in fact a generic formulation may be very different in its formulation design other than for the active ingredient and its concentration.

The Brand vs Generic Debate

When confronted with a clinical scenario in which a mid-potency TCS is desired, the clinician has several compounds and formulations to choose from and will often make the selection based on their familiarity with the efficacy and tolerability of a given compound and product, and the type of vehicle that is adaptable for application to the anatomic areas affected. Importantly, in many cases this familiarity is based on their prior use of a given brand name product that is a consistent formulation in terms of its components and physiochemical characteristics. Many generic mid-potency TCS formulations differ from the brand in the excipients they contain, which in some cases may alter the physiochemical, efficacy, and tolerability characteristics of the final product.[9-12]

The approval of a generic topical formulation is based on assumptions of efficacy and tolerability from pivotal trials completed with the original branded formulation. Therefore, assessment of the clinical performance, skin tolerability, and safety of a generic formulation is left up to clinicians based on outcomes they observe in their patients, assuming they are fully aware of which product the patient actually used. Occasionally, the altered characteristics of the generic formulation may be clinically relevant, with the generic formulation exhibiting a relative lack of efficacy, greater potential for skin irritancy, possible contact allergy due to a specific excipient not used in the brand formulation, or inferior aesthetic characteristics. However, there appear to be no clinically relevant differences in many cases between the use of generic formulations as compared to their respective original brand products. Due to the vast array of generic TCS formulations that are available for pharmacies to stock and dispense, the clinician is confronted with a self-imposed question regarding the physiochemical properties, pharmacokinetic profile, efficacy, tolerability, and safety of different generic TCS formulations that may be dispensed to a given patient.[9]

How can questions about potential differences between brand and generic products be resolved with some certainty? With clocortolone pivalate 0.1% cream, its manufacturer is providing an authorized generic formulation that is identical to the brand formulation of clocortolone pivalate 0.1% cream (Cloderm® Cream; Promius Pharma, LLC; Princeton, NJ), a mid-potency TCS emollient cream approved in the United States by the Food and Drug Administration in 1977 for the treatment of CRDs.[5,10] This article discusses characteristics of the clocortolone pivalate compound, the clocortolone pivalate 0.1% cream formulation, and the data on efficacy and safety, with an emphasis on clinical relevance and practical application. The comfort level for the clinician is that this specific generic formulation will provide the same TCS product as the brand formulation, thus delivering the results to which they are accustomed if they have prescribed clocortolone pivalate 0.1% cream in the past, and results supported by evidence from clinical trials and safety data with the original brand product.[10-13]

> "Clocortolone pivalate 0.1% cream is a mid-potency TCS formulated in an emollient formulation that has been shown to be effective and well-tolerated in the management of several corticosteroid-responsive dermatoses."

The following is a comprehensive profile of the data available with the original brand formulation of clocortolone pivalate 0.1% cream, which can then be applied with certainty to the authorized generic formulation that is the identical product.

Pharmacologic Profile

A major part of developing a TCS product is the selection of the active ingredient. With clocortolone pivalate, the molecular chemists structurally modified the basic corticosteroid structural nucleus through the step-wise addition of specific molecules or side chains at different molecular positions to enhance lipophilicity and cutaneous penetration, increase potency, and counter potential structural interferences with glucocorticosteroid-receptor (GR) binding and other modifications that enhance GR-binding affinity.[2,3,5,6,11] One example of a structural modification made to produce clocortolone pivalate is esterification at the C21 position with substitution of a pivalate group that increases lipophilicity and inherent potency and decreases metabolic breakdown, resulting in prolonged tissue exposure. Another is methylation at the C16 position, which also increases lipophilicity and decreases allergenicity.[5,11] The collective modifications resulted in clocortolone pivalate, which was then incorporated into an emollient cream vehicle. In ad-

dition, unlike other structural classes of TCS, the clocortolone pivalate molecule is associated with a very low rate of inherent allergenicity, a factor that is clinically relevant as TCS allergy is easily misdiagnosed. [8,9,13]

Formulation Characteristics and Vehicle Components

As mid-potency TCS are commonly used to treat eczematous dermatoses that are associated with marked increase in transepidermal water loss (TEWL) and decreased stratum corneum (SC) hydration, the emollient cream vehicle was designed to include very few excipients. Some excipients were selected specifically to help improve the SC permeability barrier that is impaired in many eczematous and inflammatory dermatoses.[11,12-18] The inclusion of "barrier friendly excipients," such as white petrolatum, mineral oil, and stearyl alcohol, provides adjunctive clinical benefit and may reduce the potential for irritant contact reactions and secondary xerotic skin changes.[13-18] The further rationale of incorporating vehicle components that can assist in reducing SC permeability barrier impairment is to counteract potential adverse sequelae that TCS application can have on the SC, which result primarily from a decrease in SC lipid synthesis at sites of application.[19]

The excipients included in both the original brand and authorized generic clocortolone pivalate 0.1% cream and their primary vehicle functions that are likely to be clinically relevant are listed in Table 1. The 3 major excipients included in the clocortolone pivalate 0.1% cream that have emollient properties and can enhance the functional integrity of the SC permeability barrier are white petrolatum (occlusive emollient), mineral oil (light non-vegetable oil occlusive emollient), and stearyl alcohol (long-chain fatty alcohol emollient).[10] All 3 of these agents are well established as vehicle excipients that have been used for decades in many skin-care products with a very favorable track record of skin tolerability and safety. Mineral oil has been applied to skin for cosmetic purposes since the late 1800s.[20] Stearyl alcohol is a commonly used fatty alcohol, which provides lubricant and emollient characteristics to skin and serves as both a non-toxic emulsifier and a slight thickening agent that assists in providing a "creamy" quality to the formulation.[21] Ultimately, these 3 excipients function collectively to assist clocortolone pivalate by promoting skin hydration at the sites of active skin disease whilst the clocortolone pivalate is functioning to reduce cutaneous inflammation caused by the skin disease itself. As a TCS is not to be conceptualized as a "moisturizer," patients are still encouraged to use a gentle cleanser and moisturizer or "barrier repair" formulation diffusely, especially those patients with AD, asteatotic eczema, and xerotic skin, where replenishment of SC lipids and increased hydration provide adjunctive benefit.[4,15-17,20-23] However, inclusion in a TCS formulation of excipients that enhance the SC permeability barrier helps to sustain its proper function in areas of eczematous dermatitis where the TCS is being applied. [19]

Another important characteristic of a TCS formulation is the avoidance of ingredients that can be allergenic or induce irritancy. Clocortolone pivalate 0.1% cream does not contain any fragrances or lanolin, both of which can be problematic in eczematous dermatitis, such as AD.[10,13,23] An additional advantage of clocortolone pivalate 0.1% cream is the absence of penetration enhancers, such as propylene glycol (in high concentrations) or ethanol, which can induce allergenicity, irritancy, and/or SC barrier impairment.[11,13,15] A final comment about cutaneous allergenicity is worthy of mention. The clocortolone pivalate molecule falls into TCS Category C within the classification system used to differentiate the potential for different TCSs to induce ACD.[8] This category exhibits the lowest potential risk for ACD induced by a topically applied corticosteroid compound (<0.2%).[24,25]

Importantly, all of the favorable characteristics demonstrated by the original brand of clocortolone pivalate 0.1% cream apply also to the authorized generic clocortolone pivalate 0.1% cream because the formulations are identical and produced by the same manufacturer.

Effects of Clocortolone 0.1% Cream on the Statum Corneum Permeability Barrier

A total of 18 healthy adult female subjects were enrolled in the treatment phase of a study that evaluated the effects of clocortolone pivalate 0.1% cream, hydrocortisone butyrate 0.1% lipocream (HB-LC), and hydrocortisone butyrate 0.1% lotion (HB-L) on both TEWL and skin hydration.[26] Each subject was instructed to stop the use of all topical products with effects on skin moisturization (ie, soaps, creams, lotions, sunscreens, insect repellants, etc.) on their upper extremities during a 3-day pre-conditioning period prior to testing. On day 1, four 5cm x 5cm sites (2 sites on each volar forearm) were identified and underwent "dry shaving" as a method to induce SC permeability barrier dysfunction. Both increased TEWL and decreased skin hydration have been shown to occur using this methodology. On day 2, baseline measurements for TEWL and corneometry were obtained using recognized instrumentation from each of the 4 dry-shaved volar forearm sites and 1 non-shaved, non-treated off-site located to the side of one volar forearm prior to treatment. Measurements were repeated 1 hour (± 10 minutes), 2 hours (± 15 minutes), and 4 hours (± 15 minutes) after each subject underwent application to a given test site of a defined amount of clocortolone pivalate 0.1% cream, HB-L, and HB-LC, with the fourth dry shaved skin site left untreated to serve as "damaged control skin." As noted above, a site of normal undamaged skin was also identified to serve as a "normal skin control." Before each set of measurements was taken, subjects were required to acclimate in the environmentally-controlled room for 30 to 45 minutes. The results of this study are depicted in Figure 1 and Figure 2, demonstrating, based on this assay, that clocortolone piva-

TABLE 1.

Physiochemical Functions in Skin and Clinical Considerations

Physiochemical Functions in Skin and Clinical Considerations		
Ingredient	**Function**	**Commentary**
White petrolatum[a,b]	Occlusive emollient	- Synthesis process patented in 1872 - Long track record of use in many topical products - Excellent safety profile - Not used as the sole occlusive agent; decreases greasiness; combined with other emollients in the formulation
Mineral oil[c,d] (light)	Occlusive emollient	- Applied for cosmetic purposes to skin since the late 1800s - Light non–vegetable oil produced as by-product of petroleum distillation - Effective emollient with improved skin hydration and reduced TEWL; imparts a smooth feeling to skin - Permeability barrier repair properties confirmed using several technologies, including Raman confocal microscopy - Shown to be noncomedogenic with grade used in topical products
Stearyl alcohol[a,b]	- Fatty alcohol emollient - Nontoxic emulsifier - Thickening agent	- Used in topical products for several decades - Excellent safety profile - Imparts lubricant and emollient properties - Adds to "creamy" quality of formulation
Polyoxyl 40 stearate[a]	- Surfactant - Emulsifying agent	Commonly used in topical products
Carbomer 934P[a]	- Thickening agent - Suspending agent - Emulsifying agent	- Used in many topical products - Excellent safety profile - Very good shelf-life; not supportive of microbial growth - High water-absorption capacity - Thickens and suspends for even distribution and "creamy" quality
Edetate disodium[a]	- Stabilizing agent - Chelating agent	- Used extensively in topical products - Favorable safety profile - Chelates metallic impurities in water and other exposures to prevent product deterioration and rancidity
Sodium hydroxide[a]	pH Stabilizer	- Low concentration; commonly used in topical formulations to balance pH

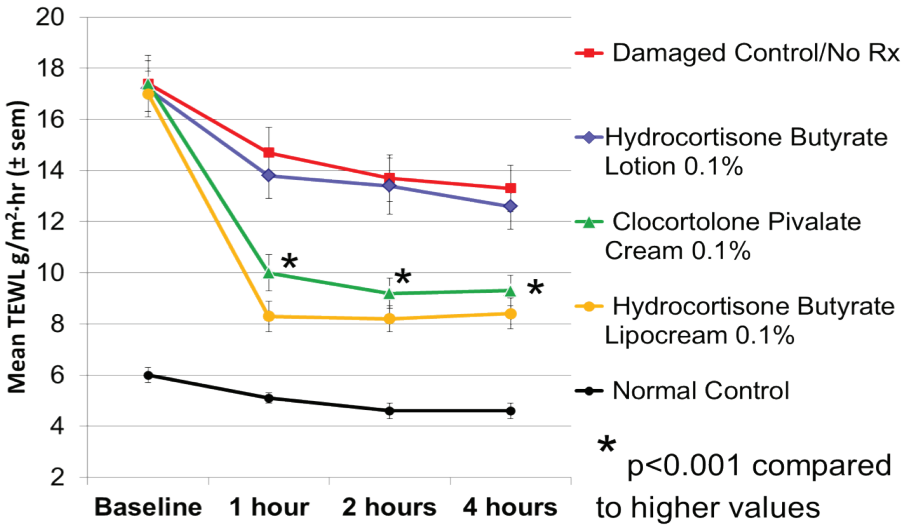
Methylparaben[e-h] Propylparaben	Preservatives	- Extensively used in many topical products for several years
		- Low rate of contact allergy compared with other commonly used preservatives
		  - Rate <1.1% based on patch testing (6,845 patients 1993-2006); referral bias likely means true rate is lower
		  - One of the lowest sensitization exposure quotients as compared with other preservatives
		  - Low rate (1.1%) of contact allergy among patients (n=1,927) with chronic eczema as compared with other preservatives in topical products (eg, thiomersal [11.3%], wood alcohols [4%], formaldehyde [2.5%], chloracetamide [1.6%], bronopol [1.9%], Kathon CG [1.4%])
		- Concerns regarding alleged estrogen-like hormonal effects of parabens and breast cancer risk not substantiated to date; no hormonal effects shown in humans at recommended amounts

TEWL, transepidermal water loss.
[a]*Ullmann's Encyclopedia of Industrial Chemistry*. New Jersey: Wiley-VCH; 2012. http://online.library.wiley.com/book/10.1002/14356007. Accessed December 6 2012.
[b]Del Rosso JQ. Moisturizers: function, formulation, and clinical applications. In: Draelos ZD, ed. *Cosmeceuticals*. Philadelphia: Saunders Elsevier; 2009:97-102.
[c]Rawlings AV, Lombard KJ. A review on the extensive skin benefits of mineral oil. *Int J Cosmet Sci*. 2012;34(6):511-518.
[d]DiNardo JC. Is mineral oil comedogenic? *J Cosmet Dermatol*. 2005;4(1):2-3.
[e]Castelain F, Castelain M. Parabens: a real hazard or a scare story? *Eur J Dermatol*. 2012 Nov 7. [Epub ahead of print].
[f]Chow ET, Avolio AM, Lee A, Nixon R. Frequency of positive patch test reactions to preservatives: The Australian experience. *Australas J Dermatol*. 2012 Oct 22. [Epub ahead of print].
[c]Schnuch A, Mildau G, Kratz EM, Uter W. Risk of sensitization to preservatives estimated on the basis of patch test data and exposure, according to a sample of 3541 leave-on products. *Contact Dermatitis*. 2011;65(3):167-174.
[h]Dastychová E, Necas M, Vasku V. Contact hypersensitivity to selected excipients of dermatological topical preparations and cosmetics in patients with chronic eczema. *Acta Dermatovenerol Alp Panonica Adriat*. 2008;17(2):61-68.

late 0.1% cream and HB-LC were comparable to each other, and superior to HB-L, in reducing TEWL, and that clocortolone pivalate 0.1% cream was superior to both HB-LC and HB-L in increasing skin hydration.[26]

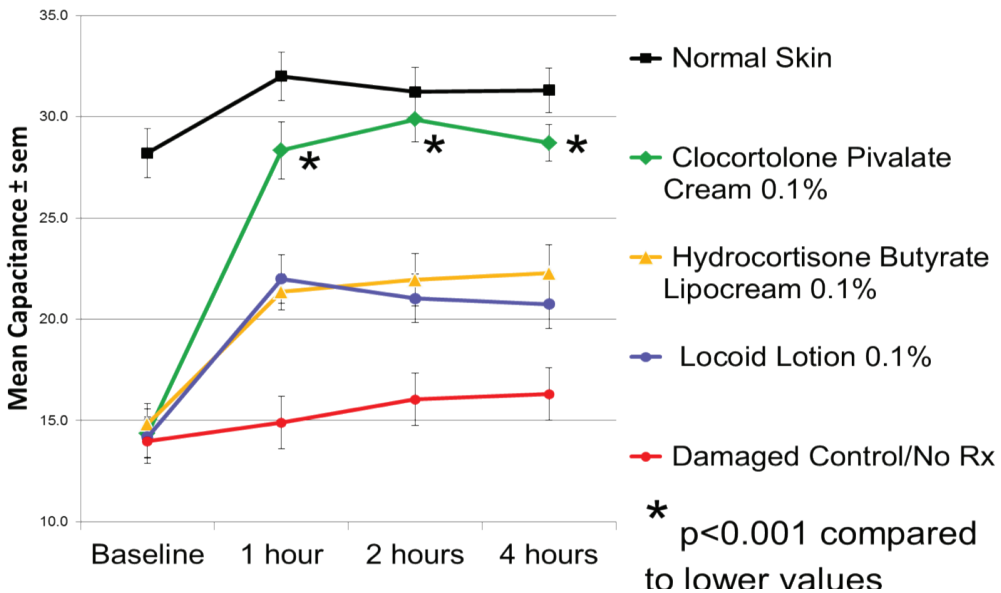
Although, it is not possible to directly quantify the correlation between the magnitude of these results and differences observed in the clinical setting, these results did demonstrate that clocortolone pivalate 0.1% cream exhibits the ability to enhance SC permeability barrier function by reducing TEWL and increasing hydration, supporting the careful selection of vehicle excipients that are "barrier friendly." Both the decrease in TEWL and increased skin hydration are advantageous when using a TCS product to treat eczematous and inflammatory der-

FIGURE 1. Effect on Transepidermal Water Loss over 4 Hours.Comparison of Clocortolone Pivalate 0.1% Cream,Hydrocortisone Butyrate 0.1% Lotion, and Hydrocortisone Butyrate 0.1% Lipocream



Clocortolone Pivalate and Hydrocortisone Butyrate Lipocream demonstrated similar TEWL reduction and both showed a significant difference to Hydrocortisone Butyrate Lotion.
Brand formulations use with all tested formulations.

FIGURE 2. Skin Hydration (Corneometry) over 4 Hours.Comparison of Clocortolone Pivalate 0.1% Cream,Hydrocortisone Butyrate 0.1% Lotion, and Hydrocortisone Butyrate 0.1% Lipocream.



Clocortolone Pivalate demonstrated superior skin hydration as compared to both hydrocortisone butyrate formulations.
Brand formulations use with all tested formulations.

matoses. Importantly, these findings were demonstrated with the clocortolone pivalate 0.1% cream containing the active TCS ingredient and not just with the cream vehicle alone. These results were confirmed in a second study of the same design.

Efficacy and Safety Data

Clocortolone pivalate 0.1% cream has been studied in multiple clinical trials for the treatment of a variety of CRDs. These trials were inclusive of 559 adult and pediatric patients who were ac-

TABLE 2.

Data on Clinical Response in Adult and Pediatric Patients Treated with Clocortolone Pivalate 0.1% Cream for Common Corticosteroid-Responsive Dermatoses[11,12]

Atopic dermatitis/ Eczematous dermatitis (n=209)	***Design*** - Six parallel, double-blind, randomized, placebo-controlled trials - Treated with clocortolone pivalate 0.1% cream (n=109) or vehicle (n=100) - Application 3 times daily - Duration of study 14 days ***Efficacy*** - Outcomes assessed at days 4, 7, and 14 (IGA rating of objective signs and subject assessment of symptomatology) - Good or excellent response by IGA in 41%, 56%, and 69% of subjects treated with clocortolone pivalate 0.1% cream at days 4, 7, and 14, respectively, compared with 27%, 41%, and 51% in vehicle-treated subjects at the same time points ***Tolerability/Safety*** - Dryness and/or skin irritation reported in 3.4% of subjects treated with clocortolone pivalate 0.1% cream - Dryness, skin irriation, or secondary infection in 10.4% of vehicle-treated subjects - No systemic reactions reported or observed
Psoriasis/ Contact dermatitis (n=139)	***Design*** - Two controlled trials enrolling patients with psoriasis or contact dermatitis - Randomized to be treated with clocortolone pivalate 0.1% cream or vehicle cream - Duration of treatment was 28 days for psoriasis and 21 days for contact dermatitis ***Efficacy*** - Good or excellent response by IGA in 44% in the group treated for psoriasis with clocortolone pivalate 0.1% cream (n=50) vs 24% in those treated with vehicle cream (n=50) ($P<.05$) - Good or excellent response by IGA in 87% in the group treated for contact dermatitis with clocortolone pivalate 0.1% cream (n=23) vs 50% in those treated with vehicle cream (n=16) ($P<.05$)
Pediatric patients (n=44) **Atopic dermatitis** **Eczematous dermatitis** **Psoriasis** **Contact dermatitis**	***Design*** - Treatment with clocortolone pivalate 0.1% cream or vehicle cream - Average age, 10 years (range, 3-14 years) ***Efficacy and Tolerability/Safety*** - Good or excellent response by IGA in 79% in the group treated for atopic dermatitis/eczematous dermatitis with clocortolone pivalate 0.1% cream (n=19) vs 55% in those treated with the vehicle cream (n=17) - Because of the low number of patients enrolled with psorisasis (n=7) and contact dermatitis (n=1), comparative data not available; 2/4 patients with psoriasis and 1/1 patient treated for contact dermatitis with clocortolone pivalate 0.1% cream demonstrated a good or excellent response - Tolerability and safety were excellent in both treatment groups
Facial dermatoses adult and pediatric patients (n=38) **Seborrheic dermatitis** **Atopic dermatitis** **Contact dermatitis** **Psoriasis**	***Design*** - Enrolled if inclusion criteria met and if aged <13 years or >19 years (avoid overlap with acne) - All subjects treated with clocortolone pivalate 0.1% cream applied 3 times daily for 21 days ***Efficacy*** - Subjects assessed by IGA at baseline and days 4, 7, 14, and 21, and also assessment of overall therapeutic response, which included rapidity of onset of clinical response and maximum degree of clearing; subject assessments of symptoms and tolerability; - 76% improved at end of study (day 21) and 68% with excellent or good overall therapeutic response ***Tolerability/Safety*** - Seven nonserious AEs (1 with mild transient application-site burning, 5 with mild acneiform eruption, 1 with folliculitis) - No major or serious AEs

AE, adverse event; IGA, Investigator's Global Assessment.

tively treated with clocortolone pivalate 0.1% cream.[11,12] Overall, the efficacy and safety outcomes observed in these clinical trials were favorable as depicted in Table 2.

Treatment of Facial Dermatoses

In clinical trials with clocortolone pivalate 0.1% cream, facial application over the designated study durations (range 2-4 weeks) was included for 147 study patients, especially those affected by SD and AD.[11] In this subset, the efficacy, tolerability, and safety outcomes were consistent with the overall results from the trial. The results of an analysis of patients with facial dermatoses who were treated with clocortolone pivalate 0.1% cream 3 times daily for 21 days are shown in Table 2. It is important that use of any TCS on the face be limited in duration through proper monitoring, with treatment-free periods interspersed as necessary if chronic administration is required for disease control. In addition, avoidance of prolonged continuous application to the eyelids and intertriginous areas is advised as a general caution with TCS use.

Additional Data of Clinical Relevance

A subset of study subjects with chronic eczematous dermatoses and psoriasis (n=27) were treated over more prolonged durations with clocortolone pivalate 0.1% cream at sites of active skin disease (mean 116.4 days).[11] No adverse reactions related to treatment were noted other than mild dryness in one patient. The use of any TCS to adequately manage a given skin disorder over prolonged durations of therapy warrants appropriate

monitoring by the clinician, with vigilance regarding potential local and systemic adverse reactions.

In cutaneous safety studies, the skin irritancy potential of clocortolone pivalate 0.1% cream was determined to be neglibible.[11] In one study (n=10) of extensive application of clocortolone pivalate 0.1% cream (30g twice daily) to subjects over 21 days with 12 hours of full body occlusion each day, suppression of the hypothalamic-pituitary-adrenal (HPA) axis was not observed using urinary 17-ketosteroid and serum cortisol levels at specified timepoints.[11] Other studies have shown that clocortolone pivalate 0.1% cream does not induce phototoxicity or photoallergy.[11]

SUMMARY

This article discusses compound-related properties, vehicle characteristics, and efficacy and safety data which demonstrate that clocortolone pivalate 0.1% cream exhibits favorable pharmacologic properties, efficacy outcomes, and tolerability data. In addition, the emollient cream vehicle is well-designed for application to eczematous and inflamed skin as supported both by clinical experience and by studies evaluating favorable effects on TEWL and skin hydration (corneometry). It is beneficial for clinicians to be aware that an authorized generic of clocortolone pivalate 0.1% cream has been made available from the same manufacturer as the original brand of clocortolone pivalate 0.1% cream, with both being identical in their formulation. This assures that substitution with this specific authorized generic of clocortolone pivalate 0.1% cream does not change what the patient is receiving as compared to the brand formulation of clocortolone pivalate 0.1% cream.

DISCUSSION

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REFERENCES

1. Del Rosso J, Friedlander SF. Corticosteroids: options in the era of steroid-sparing therapy. *J Am Acad Dermatol.* 2005;53(1 suppl 1):s50-s58.
2. Magnusson BM, Cross SE, Winckle G, Roberts MS. Percutaneous absorption of steroids: determination of in vitro permeability and tissue reservoir characteristics in human skin layers. *Skin Pharmacol Physiol.* 2006;19(6):336-342.
3. Katz M, Gans EH. Topical corticosteroids, structure-activity and the glucocorticoid receptor: discovery and development—a process of "planned serendipity". *J Pharm Sci.* 2008;97(8):2936-2947.
4. Hanifin JM, Cooper KD, Ho VC, et al. Guidelines of care for atopic dermatitis, developed in accordance with the American Academy of Dermatology (AAD)/American Academy of Dermatology Association "Administrative Regulations for Evidence-Based Clinical Practice Guidelines". *J Am Acad Dermatol.* 2004;50(3):391-404.
5. Bikowski J, Pillai R, Shroot B. The position not the presence of the halogen in corticosteroids influences potency and side effects. *J Drugs Dermatol.* 2006;5(2):125-130.
6. Buchwald P. Glucocorticoid receptor binding: a biphasic dependence on molecular size as revealed by the bilinear LinBiExp model. *Steroids.* 2008;73(2):193-208.
7. Sapp BR, Moss PE, Davis RL. Topical corticosteroids: considerations for appropriate use. *Am J Managed Care.* 1999;5(6):787-792.
8. Warner MR, Camisa C. Topical corticosteroids. In: Wolverton SE, ed. *Comprehensive Dermatologic Drug Therapy.* 2nd ed. Philadelphia: Saunders; 2007:595-624.
9. Del Rosso JQ, Kircik LH. Not all topical corticosteroids are created equal: optimizing therapeutic outcomes through better understanding of vehicle formulations, compound selection, and methods of application. *J Drugs Dermatol.* 2012;11(12):s5-s8.
10. Cloderm® Cream [package insert]. Bridgewater, NJ: Promius Pharma, LLC; 2011.
11. Del Rosso JQ, Kircik L. A comprehensive review of clocortolone pivalate 0.1% cream: structural development, formulation characteristics, and studies supporting treatment of corticosteroid-responsive dermatoses. *J Clin Aesthet Dermatol.* 2012;5(7):20-24.
12. Kircik LH, Del Rosso JQ. The treatment of inflammatory facial dermatoses with topical corticosteroids: focus on clocortolone pivalate 0.1% cream. *J Drugs Dermatol.* 2012;11(10):1194-1198
13. Del Rosso JQ, Kircik L. The role of a midpotency topical corticosteroid and the clinical relevance of formulation characteristics in the management of commonly encountered eczematous and inflammatory dermatoses in adults and children: focus on the pharmacologic properties of clocortolone pivalate 0.1% cream. *J Drugs Dermatol.* 2013 Feb;12(2):s5-s10.
14. Surber C, Tassopoulos T. Ointments, creams, and lotions used as topical drug delivery vehicles. In: Bronaugh RL, Maibaich HI, eds. *Topical Absorption of Dermatological Products.* New York: Marcel Dekker Inc; 2008.
15. Del Rosso JQ, Levin J. The clinical relevance of maintaining the functional integrity of the stratum corneum in both healthy and disease-affected skin. *J Clin Aesthet Dermatol.* 2011;4(9):22-42.
16. Del Rosso JQ. Understanding skin cleansers and moisturizers: the correlation of formulation science with the art of clinical use. *Cosmet Dermatol.* 2003;16:19-31.
17. Del Rosso JQ. Moisturizers: function, formulation, and clinical applications. In: Draelos ZD, ed. *Cosmeceuticals.* Philadelphia: Saunders Elsevier; 2009:97-102.
18. Johnson AW. Cosmeceuticals: function and the skin barrier. In: Draelos ZD, ed. *Cosmeceuticals.* Philadelphia: Saunders Elsevier; 2009:7-14.
19. Del Rosso JQ, Cash K. Topical corticosteroid application and the structural and functional integrity of the epidermal barrier. *J Clin Aesthet Dermatol.* 2013;6(11):20-27.
20. Rawlings AV, Lombard KJ. A review on the extensive skin benefits of mineral oil. *Int J Cosmet Sci.* 2012;34(6):511-518.
21. Noweck K, Grafahrend W. Fatty alcohols. In: *Ullmann's Encyclopedia of Industrial Chemistry.* New Jersey: Wiley-VCH; 2012.
22. Chamlin SL, Kao J, Frieden IJ, et al. Ceramide-dominant barrier repair lipids alleviate childhood atopic dermatitis: changes in barrier function provide a sensitive indicator of disease activity. *J Am Acad Dermatol.* 2002;47(2):198-208
23. Boguniewicz M. Conventional topical treatment of atopic dermatitis. In: Bieber T, Leung DYM, eds. *Atopic Dermatitis.* New York: Marcel Dekker Inc; 2002:453-477.
24. Browne F, Wilkinson SM. Effective prescribing in steroid allergy: controversies and cross-reactions. *Clin Dermatol.* 2011;29(3):287-294.
25. Baeck M, Marot L, Nicolas JF, Pilette C, Tennstedt D, Goossens A. Allergic hypersensitivity to topical and systemic corticosteroids: a review. *Allergy.* 2009;64(7):978-994.
26. Kircik L. A study to compare the occlusivity and moisturizing potential of three mid-potent topical steroid products using the skin trauma after razor Sshaving (STARS) bioassay. Poster presentation. Fall Clinical Dermatology, Las Vegas, Nevada, October 2013.

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