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Clocortolone Pivalate: A Topical Corticosteroid With a Unique Structure

Leon H. Kircik MD

Clinicians treating corticosteroid-responsive dermatoses, such as atopic dermatitis, contact dermatitis, other eczematous dermatoses, seborrheic dermatitis, and psoriasis have a number of treatment options. The selection of a topical corticosteroid (TCS) depends on several different factors, such as potency, formulation, dosage, cosmetic elegance, and cost considerations, including third-party coverage. Among these, clocortolone pivalate cream 0.1% (Cloderm® Cream; Promius Pharma, L.L.C., Bridgewater, NJ), which was introduced into the market more than 3 decades ago, has withstood the test of time and remains a versatile treatment option. It is an effective, midpotency (Class 4) TCS formulation with a favorable safety profile, including a low rate of contact sensitization (Category C). The formulation also has no generic equivalent, which makes legal substitution impossible.

As explored in the following pages, evidence shows that the unique molecular structure of clocortolone pivalate contributes to the skin penetration and the potency of the drug. All TCS molecular structures are based on hydrocortisone, and therefore, structural modifications influence efficacy, safety, and tolerability, as well as allergenicity. In the case of clocortolone pivalate, for example, halogenation at C-6 and C-9 appears to permit the drug to function like a midpotent corticosteroid while still maintaining a favorable safety profile.

The general perception in the dermatology community has been that halogenation is associated with an increased risk for adverse events, especially those involving skin, such as atrophy and striae. However, we now know that it is the location of the halogen atom and the type of the halogen atom that mediates safety rather than the halogenation itself; and therefore the simple presence of the halogen atoms does not increase the severe adverse events in clocortolone pivalate.[1] Moreover, with methylation at the C-16 position and esterification at the C-17 position, clocortolone pivalate belongs to Category C corticosteroids, with minimal risk of allergenicity.[2] Since contact sensitization to TCS may be very difficult to diagnose and confirm, and therefore is likely to be underdiagnosed, TCS-induced allergic contact dermatitis is a challenging problem for clinicians. Lastly, substitution of the pivalate group at C-21 increases lipid solubility of clocortolone pivalate. Clocortolone pivalate offers high lipid solubility, which seems to facilitate more rapid percutaneous absorption into skin, allowing access to the therapeutic target site without any apparent risk of increased adverse events based on results from several clinical trials.[3]

Phase 3 clinical trial data have demonstrated the efficacy and tolerability of clocortolone pivalate 0.1% cream in several steroid-responsive dermatoses. In studies for atopic dermatitis and other eczematous dermatoses, statistically significant improvement relative to placebo was seen at day 4.[4] In psoriasis trials, clocortolone pivalate 0.1% cream demonstrated superiority to vehicle by day 7, continuing at days 14, 21, and 28. This early onset of action will contribute to increased compliance in our patients. Also, in a study to assess the effects of clocortolone pivalate 0.1% cream on hypothalamic–pituitary–adrenal axis function, there was no evidence of adrenal suppression over the 21-day trial period, as measured by urinary 17-ketosteroids.[5] The use of clocortolone pivalate 0.1% cream in sensitive locations such as the face and intertriginous areas in clinical trials is another tribute to the excellent safety profile of this TCS.[6]

Finally, the emollient cream vehicle base may be dispensed in either a tube or a pump, offering both flexibility to prescribers and convenience to patients. The pump may be especially useful for ensuring that the patient uses an appropriate amount of medication. The vehicle base of clocortolone pivalate 0.1% cream is composed primarily of water and emollient ingredients (white petrolatum, mineral oil, and stearyl alcohol) and few preservatives.[7] In my practice, patients consistently report a high rate of satisfaction and cosmetic elegance with this product.

"The unique engineering of the clocortolone pivalate molecule balances potency with documented efficacy and a favorable safety profile."

As the accumulated clinical evidence and experience to be presented in the next several pages demonstrate, the unique engineering of the clocortolone pivalate molecule balances potency with documented efficacy and a favorable safety profile. Clocortolone pivalate 0.1% cream is a well-formulated and versatile therapeutic option to consider for many of our patients with steroid-responsive dermatoses.

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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

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ABSTRACT

Midpotency topical corticosteroids (TCSs) are frequently used for the treatment of common eczematous and inflammatory skin disorders in both adults and children. There are several commercially available products in this category, and many vehicles and formulations for the clinician to choose from. Clocortolone pivalate 0.1% cream is a midpotency TCS formulated in an emollient formulation that has been shown to be effective and well tolerated when used appropriately in the management of several corticosteroid-responsive dermatoses. This article discusses the physiochemical properties of the compound; the characteristics of its emollient cream formulation; the functions of individual excipients; and the efficacy, tolerability, and safety data supporting its use in adults and children, including for facial involvement.

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INTRODUCTION

Overview of Clinical Considerations and Product Selection

The rational selection of a topical corticosteroid (TCS) is affected by several factors that may be related to the compound, the disease state, the type of vehicle, and the individual components and characteristics of the formulation.[1-7] *Compound-related factors* include the individual corticosteroid compound and the concentration incorporated into the final formulation. *Disease-state-related factors* include the specific diagnosis, severity, and anatomic sites involved. The primary *vehicle-related factors* are 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. Lastly, *formulation-related factors* include specific excipients incorporated to exert certain properties (eg, penetration enhancement, humectancy, occlusivity, solubilization, spreadability, emolliency, product preservation) and active ingredient release characteristics. Collectively, all of these factors influence the efficacy, skin tolerability, and patient acceptability of a given TCS formulation.

The midpotency TCS group includes several compounds and formulations that are frequently prescribed for the treatment of common dermatologic disorders such as atopic dermatitis (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. With the exception of CPP and lichenified eczematous plaques, which sometimes warrant treatment with a high-potency or superhigh potency TCS, most of the dermatoses mentioned above respond favorably within a reasonable time frame to a midpotency TCS that is adaptable for application and does not cause local irritation or cutaneous allergy.[1,4,8] Several midpotency TCS formulations are available in the marketplace, including triamcinolone acetonide 0.1% cream and ointment, betamethasone valerate 0.1% cream and ointment, betamethasone valerate 0.12% foam, fluticasone propionate 0.05% cream and lotion, fluticasone propionate 0.005% ointment, hydrocortisone valerate 0.2% cream and ointment, hydrocortisone butyrate 0.1% cream and lotion, desoximetasone 0.05% cream, gel, and ointment, mometasone furoate 0.1% cream and solution, and clocortolone pivalate 0.1% cream.

This article provides a comprehensive review of clocortolone pivalate 0.1% (Cloderm® Cream; Promius Pharma, L.L.C., Bridgewater, NJ), which is a midpotency TCS emollient cream

approved by the US (FDA) Food and Drug Administration for the treatment of corticosteroid-responsive dermatoses (CRDs) that was first marketed in the United States in 1977.[5,10] This article discusses characteristics of the compound, the formulation, and the data on efficacy and safety, with an emphasis on clinical relevance and practical application.

Compound-Related Characteristics

Prior to the development of clocortolone pivalate 0.1% cream, the formulators sought to produce a medium-potency TCS that could be applied to eczematous, irritated, and/or inflamed skin in both adults and children without inducing further irritation or contact allergy. An important part of achieving their goal was to structurally modify the basic corticosteroid structural nucleus through the stepwise addition of specific molecules or side chains at different molecular positions designed 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] Several modifications were made to the basic corticosteroid structural nucleus during the development of clocortolone pivalate. Some examples include esterification at the C-21 position with substitution of a pivalate group, which increases lipophilicity and inherent potency, and decreases metabolic breakdown, resulting in prolonged tissue exposure and methylation at the C-16 position, which also increases lipophilicity and decreases allergenicity (Figure 1).[5,11] The outcome of achieving these objectives was the production of clocortolone pivalate 0.1% formulated in an emollient cream, which could be applied to the eczematous, inflamed, and irritated skin of adults and children with favorable efficacy and little to no risk of cutaneous irritation or contact allergy.

Although correlations between specific structure-activity characteristics of the clocortolone pivalate molecule and clinical outcomes have not been studied formally, evaluations of pharmacologic properties, efficacy data, and safety analyses substantiate that clocortolone pivalate 0.1% cream is a well-tolerated and effective midpotency TCS for the treatment of CRDs when used and monitored appropriately.[11,12] From a safety perspective, halogenation of a corticosteroid molecule does not automatically infer a higher risk of clinically significant corticosteroid-induced adverse effects, as evidenced by the large body of experience with clocortolone pivalate 0.1% cream captured in multiple clinical trials.[11,12] In addition, it is the position and nature of the halogen atoms in the structure of the molecule, and not halogenation itself, that mediates drug potency and side-effect potential.[5,11]

Formulation Components and Characteristics

The incorporation of clocortolone pivalate 0.1% into an emollient cream that spreads easily and is devoid of common irritants or allergens is advantageous when treating dermatoses that are inflamed and/or eczematous. The ease of spread is also helpful with application to larger body surface areas, especially in infants and children where, disorders such as AD and SD can be widespread.[1,4] In addition to the inherent anti-inflammatory effects of the clocortolone pivalate molecule, the emollient cream is simply designed with very few excipients, with some specifically incorporated to assist with the stratum corneum (SC) permeability barrier impairment and increased transepidermal water loss that are innately present with eczematous and inflammatory dermatoses.[11-16] The inclusion of these *barrier conscious excipients* provides adjunctive clinical benefit and reduces the potential for irritant contact reactions and secondary xerotic skin changes.[13-17]

> "Clocortolone pivalate 0.1% cream is a well-tolerated and effective midpotency topical corticosteroid for the treatment of corticosteroid-responsive dermatoses when used and monitored appropriately."

The basic functions of excipients that can be included in the base formulation of the TCS, which assist with the structural and functional integrity of the SC permeability barrier (*epidermal barrier*), are occlusivity and humectancy.[13-17] The individual ingredients of clocortolone pivalate 0.1% cream are depicted in Table 1, including comments that may be clinically relevant to a given ingredient. The overall formulation is an uncomplicated design. The 3 major excipients included in clocortolone pivalate 0.1% cream that have emollient properties and assist with the epidermal 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 excipients have been used in many skin care products over several decades with a very favorable track record of safety and acceptability, including mineral oil that has been applied to skin for cosmetic purposes since the late 1800s.[18] Stearyl alcohol is a commonly used fatty alcohol, which provides lubricant and emollient characteristics to skin and serves as both a nontoxic emulsifier and a slight thickening agent that assists in providing a "creamy" quality to the formulation.[19] Ultimately, these 3 excipients work collectively to assist the active ingredient (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 hydration and skin lipids provides adjunctive benefit.[4,14,20,21] It is equally important to avoid using ingredients that can elicit ACD.

TABLE 1.

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.
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Clocortolone pivalate 0.1% cream does not contain any fragrances or lanolin, both of which may be problematic in some patients, especially those with atopic skin.

It is important that any topical drug formulation adequately solubilizes, delivers, and releases the active ingredient so that it is available to penetrate through the SC and deeper into the skin to gain access to therapeutic target sites.[13] One important characteristic of clocortolone pivalate 0.1% cream is its effectiveness without penetration enhancers—such as propylene glycol in high concentrations and ethanol—being added to the formulation. As the addition of penetration enhancers frequently induces damage to the SC permeability barrier, which is already compromised by the skin disorder that is being treated, their absence in clocortolone pivalate 0.1% cream is advantageous, allowing for the incorporation of the active ingredient into an emollient cream that is "skin barrier friendly."[11]

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.

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 (<0.2%).[22,23]

Disease-Related Characteristics

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 actively treated with clocortolone pivalate 0.1% cream.[11,12] Overall, the efficacy and safety outcomes observed in these clinical trials were favorable. The results of these studies are summarized 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 in 147 study patients, especially those affected by SD and AD.[11] In this subset, the efficacy, tolerability, and safety outcomes did not differ significantly from the overall study results. 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. Concomitant or alternate use of nonsteroidal topical options can be incorporated based on the clinical situation and the type and severity of skin disease being treated.

Caution is also advised regarding avoidance of prolonged continuous application to the eyelids and intertriginous areas.

Other Relevant Considerations of Interest to Clinicians

Prolonged Duration of Therapy

A subset of study subjects with chronic eczematous dermatoses and psoriasis (n=27) were treated over more prolonged durations 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.

Use in Pediatric Patients

Pediatric patients in a broad range of ages (as young as 1 month) were treated with clocortolone pivalate 0.1% cream applied 3 times a day over a duration of ≤4 weeks (usually 2–3 weeks, except for psoriasis) in clinical trials.[11] Although there is no age restriction in the FDA-approved product labeling with clocortolone pivalate 0.1% cream, administration of a TCS to children should be limited to the least amount compatible with an effective therapeutic regimen.[10] TCSs can be absorbed in sufficient amounts to produce systemic effects when applied to an extensive body surface area, especially in children because of their larger skin surface to body weight ratio.[4,8,10,21]

Other Safety Considerations

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 (30 g twice daily) to subjects over 21 days with 12 hours of full-body occlusion each day, suppression of the hypothalamic–pituitary–adrenal axis was not observed using urinary 17-ketosteroid and serum cortisol levels at specified time points.[11] Other studies have shown that clocortolone pivalate 0.1% cream does not induce phototoxicity or photoallergy.[11]

CONCLUSION

Midpotency TCSs are an important part of the therapeutic armamentarium for the treatment of several CRDs. Many options exist in this category, many of which are predominantly available as generic formulations. This article discusses compound-related, vehicle/formulation-related, and disease-state-related information demonstrating that clocortolone pivalate 0.1% cream exhibits favorable pharmacologic properties, efficacy outcomes, and tolerability data, along with an emollient cream vehicle that is well designed for application to eczematous and inflamed skin.

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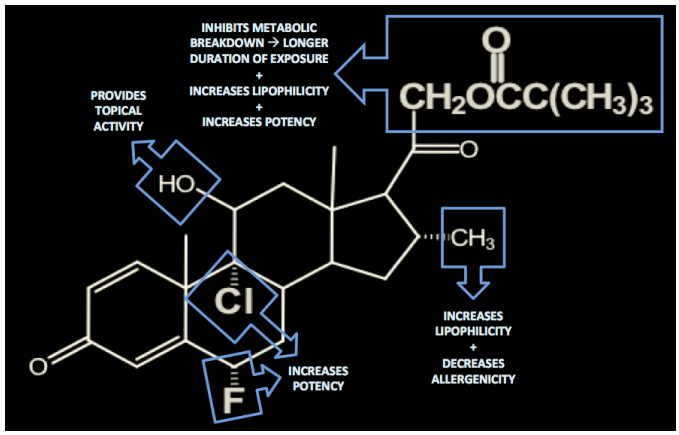
FIGURE 1. Chemical structure of clocortolone pivalate: molecular modifications and their associated effects.



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Clinical Case Studies

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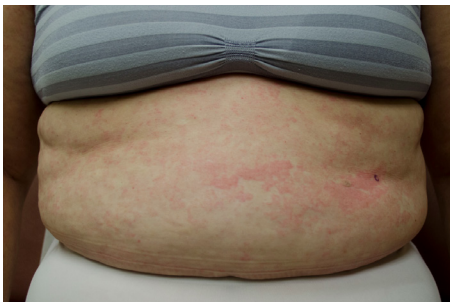
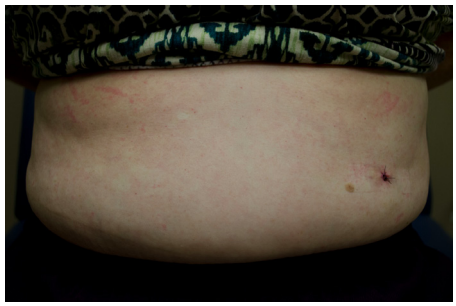
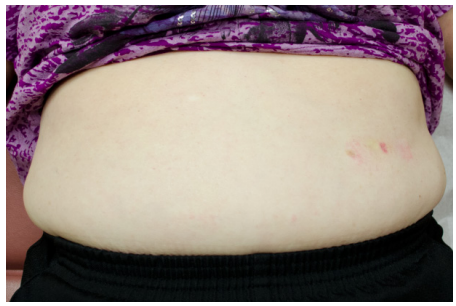
PATIENT 1. Drug reaction (chemotherapy).

Day 0: Pruritus 10
Day 3: Pruritus 0
Day 7: Pruritus 0

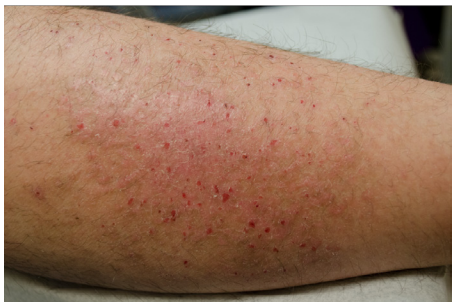
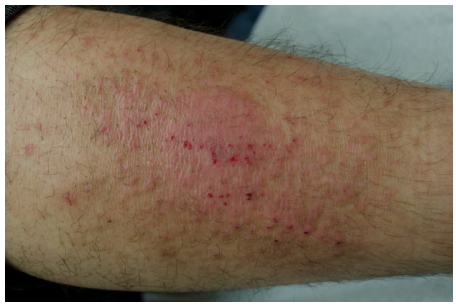
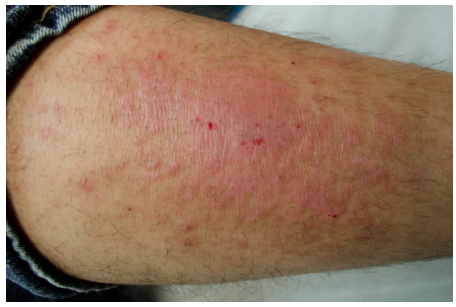
A 59-year-old female with a history of bilateral mastectomy. She had an intensely pruritic (10/10) rash on her abdomen and thighs that continued for 6 weeks after early discontinuation of chemotherapy. The patient had no improvement with diphenhydramine. *Diagnosis:* Drug eruption. *Treatment:* Cloderm® Cream 0.1% (Promius Pharma, L.L.C, Bridgewater, NJ), twice a day.

PATIENT 2. Atopic dermatitis and lichen simplex chronicus.

Day 0: Pruritus 8
Day 2: Pruritus 2
Day 7: Pruritus 0

A 45-year-old male with a 3-year history of pruritic rash on his right leg. He was given antibiotics by a generalist with no improvement. *Diagnosis*: Atopic dermatitis and lichen simplex chronicus. *Treatment*: Cloderm Cream 0.1 %, twice a day, and counseled to minimize scratching.

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