Calcipotriol and Betamethasone Dipropionate (Dovobet®, Daivobet®): A New Formulation for the Treatment of Psoriasis

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ABSTRACT

A new compound product containing calcipotriol 50µg/gm and betamethasone dipropionate 0.5mg/gm (Dovobet®, LEO Pharma) in an ointment base was recently introduced in Canada for the treatment of psoriasis. Known as Daivobet® in Europe, it was introduced to the Danish market in 2001, and approved for marketing by the European Union. This compound has been shown to be more active than either agent used alone. The efficacy of once daily application was not shown to be different from that of twice daily use.

Key Words: psoriasis, calcipotriol, betamethasone dipropionate

Calcipotriol

Calcipotriol is safe and efficacious for the treatment of psoriasis when used alone, but has a slow onset of action, which works mainly by favoring keratinocyte differentiation. Skin irritation occurs in 10% to 15% of patients. Calcipotriol does not influence calcium homeostasis at dosages of 100gm per week or less.

Corticosteroids

Topical corticosteroids are efficacious in the treatment of psoriasis, working by inhibition of inflammatory processes. However, the risk of side-effects from corticosteroids increases with the potency of the steroid molecule and the duration of use.

The corticosteroid and the calcipotriol molecules work via different pathways in the treatment of psoriasis, and the anti-inflammatory properties of the corticosteroid reduce the potential skin irritation from calcipotriol. Using both of them simultaneously is a rational approach in the control of psoriasis.

Combining Calcipotriol and Corticosteroids

Using a combination of calcipotriol and a corticosteroid has been reported previously. In these trials, calcipotriol and the steroid were applied at different times of the day, in alternate weeks or in alternate days. All these trials demonstrated a higher speed of psoriasis improvement with the dual regimen. Most of them also showed a higher success rate and a better side-effect profile for the combination regimens.

Externoproporaneous compounding of calcipotriol with a corticosteroid is tempting. However this may rapidly lead to deleterious alterations of the active molecules. Calcipotriol needs a basic pH, whereas betamethasone dipropionate requires an acidic one. Satisfactory, stable mixing of these components that were previously considered unmixable was obtained by creating an entirely new vehicle. In this new vehicle, betamethasone dipropionate remains unchanged, as does the calcipotriol molecule, and demonstrates full antipsoriatic activity. At room temperature, the shelf life of this compound is 2 years.

Clinical Trials

A series of prospective, randomized, double-blind parallel group clinical trials involving about 6,000 psoriatic subjects was done to evaluate the comparative efficacy of
the new product versus its individual components. All these trials clearly showed that the new combination product was significantly more active than either agent used alone. Moreover, the results of once daily dosing were very similar to those seen with twice daily application.

In a trial by Douglas, et al, 1,106 patients were randomized to twice daily double-blind treatment with the combination (Dovobet*), betamethasone dipropionate and calcipotriol for 4 weeks. The mean decrease in PASI from baseline to the end of the double-blind phase was 74.4% for the Dovobet* group compared to 61.3% in the betamethasone group and 55.3% in the calcipotriol group. Patients then received twice daily calcipotriol, unblinded, for a further 4 weeks. Ninety two percent of the randomized patients entered the maintenance phase of the study. Although this phase was open, investigators and patients were still blinded to what treatment had been used before. At the end of the double-blind phase, the mean PASI in the combination to calcipotriol group was 2.5 and 3.6 at the end of the maintenance phase. The corresponding figures for the betamethasone to calcipotriol group were 3.9 and 4.1, and for the calcipotriol to calcipotriol group 4.4 and 3.7. Psoriasis was maintained under control following transfer to calcipotriol without any signs of rebound flare.

The results of three randomized, double-blind trials involving a total of 2,964 patients (including Douglas, et al’s 19) were recently presented.19-21 Table 1 summarizes the main data from these trials. After one month of treatment, the mean percentage reduction in the Psoriasis Area and Severity Index (PASI) was 68.6% for the once daily application of the product and 73.2-74.4% for the twice-daily use. In comparison, the decrease in the PASI score for betamethasone dipropionate used alone twice daily was 61.3-63.1%. The mean decrease in PASI score for calcipotriol used alone twice daily was 48.8-58.8%. As per the investigators’ assessments, 68-76.1% of patients achieved a 75-100% overall improvement for the twice daily application of the new compound. In comparison, 46.6-55.8% of the betamethasone dipropionate group, and 33.4-50.7% of the calcipotriol group achieved a 75-100% overall improvement.

Moreover, all trials showed a faster response in reducing the PASI score for the new product; major improvement was seen after only 1 week of treatment. For example, the results of a trial where the compound product was applied only once daily showed a mean reduction in PASI of 48.1% after only 1 week of treatment with the combination ointment, vs. 41.4% with betamethasone dipropionate applied twice daily, and 28.4% with calcipotriol applied twice daily.

<table>
<thead>
<tr>
<th>Number of randomized subjects</th>
<th>Douglas19</th>
<th>Papp20</th>
<th>Guenther21</th>
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<tr>
<td>Mean % reduction in PASI after 1 week:</td>
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<tr>
<td>Dovobet* b.i.d.</td>
<td>47.4%</td>
<td>48.1%</td>
<td>47.6%</td>
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<td>45.5%</td>
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<td>41.4%</td>
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<td>Calcipotriol b.i.d.</td>
<td>31%</td>
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<td>33.6%</td>
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<td>Vehicle b.i.d.</td>
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<td>21.5%</td>
<td>20%</td>
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<tr>
<td>Mean % decrease in PASI after 4 weeks:</td>
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<tr>
<td>Dovobet* b.i.d.</td>
<td>74.4%</td>
<td>73.2%</td>
<td>73.8%</td>
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<tr>
<td>Dovobet* once daily</td>
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<td>---</td>
<td>68.6%</td>
</tr>
<tr>
<td>Betamethasone dipropionate b.i.d.</td>
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<td>63.1%</td>
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<tr>
<td>Calcipotriol b.i.d.</td>
<td>55.3%</td>
<td>48.8%</td>
<td>58.8%</td>
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<tr>
<td>Vehicle b.i.d.</td>
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<td>28.8%</td>
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<td>% of subjects who achieved 75-100% of improvement (investigators’ assessment)</td>
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<td>Dovobet* b.i.d.</td>
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<td>73.5%</td>
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<td>63.3%</td>
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<td>38.9%</td>
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<tr>
<td>Vehicle</td>
<td>---</td>
<td>7.5%</td>
<td>9.2%</td>
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</table>

Table 1: Results from three comparison trials with Dovobet*: mean percentage change in Psoriasis Area and Severity Index after 1 week and after 4 weeks, and percentage of subjects who achieved 75-100% of improvement, by investigators’ assessment.
**Adverse Effects**

All trials demonstrated that the side-effects were lower in the groups receiving the new compound, compared with those receiving calcipotriol alone. All trials restricted the amount of ointment to be used to less than 100g/wk, and serum calcium was measured with no changes reported.\(^{18}\)

Skin irritation was reduced by combining betamethasone dipropionate with calcipotriol. Transferring patients to calcipotriol treatment was found to be safe and maintained the clinical control of the psoriasis.\(^{20,21}\)

**Conclusion**

The new formulation containing both calcipotriol and betamethasone dipropionate in an optimal vehicle leads to fast, effective results, and has less side-effects than calcipotriol used alone.

* registered trademark of LEO Pharmaceutical Products used under the licence by LEO Pharma Inc., Thornhill, Ontario, Canada.

**References**


The term “atopic dermatitis” was first used in the 1930s to denote the close association of this condition with the presence of respiratory allergies. Since the 1980s, the most frequently cited definition for atopic dermatitis (AD) is one by Hanifin and Rajka, who listed major and minor diagnostic criteria. However, a better understanding of the underlying pathophysiology of this condition has led some to argue that the criteria are due for re-evaluation.

The precise role of allergies in the pathogenesis of AD has been debated for the last half-century. Out of that debate came the belief that when allergens are involved in AD, they provoke immediate (IgE-mediated) hypersensitivity reactions, but in contrast, AD patients have a reduced susceptibility to allergic contact dermatitis (ACD). Are these beliefs supported by current evidence? If they are, what is the role of patch testing for children with AD?

**Patch Testing**

Patch testing has been reported to be an excellent evidence-based method for diagnosing ACD because it reproduces the identical disease using the putative offending allergen. Patients are generally tested with one of several available standard series of the most common allergens, sometimes augmented by other suspected allergens. After dilution in an appropriate vehicle, the allergens are applied to the skin of the back, either in metal chambers that are secured to the skin with tape, or in tapes that have been impregnated with the allergen.

In contrast, the technique of “atopy patch testing” (APT) is a questionable tool of clinical usefulness and may be best suited for use at a research level. This procedure relies on the epicutaneous application of aeroallergens by the usual patch test techniques applied to uninvolved skin. APT produces reactions in 30-50% of patients with AD, and there is considerable variation in their performance and interpretation. The allergens used, e.g., molds and dust mites, have not been standardized. However, Ring et al, who performed several hundred of these procedures found that the morphology of the reactions of aeroallergens in the APT or classic contact patch test allergens were similar.

It is important to distinguish between true allergic reactions, i.e., pruritic, erythematous, indurated and sometimes vesiculated lesions that persist for at least 5 days, from shorter-lived nonspecific irritant reactions that do not require an immunological response. This is particularly important in patients with active AD, whose skin is more susceptible to irritation and false-positive results, especially with metals. Another common error is to produce false-positive results by inadvertently testing two or more strong antigens too close together on the skin (“angry back syndrome”).

There is a growing consensus that patch testing is safe for children and that the same series of antigens and the same concentrations can be used in children as well as adults. Children have more limited skin surface areas available for testing, shorter histories of antigenic exposures (therefore a shorter list of the “usual suspects”), and are more likely than

<table>
<thead>
<tr>
<th>Allergen</th>
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<tr>
<td>Nickel</td>
<td>Jewelry</td>
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<tr>
<td>Mercury</td>
<td>Thimerosal preservative in vaccines</td>
</tr>
<tr>
<td>Uroshiol</td>
<td>Poison ivy, oak, sumac</td>
</tr>
<tr>
<td>Fragrances</td>
<td>Wide variety of consumer products</td>
</tr>
<tr>
<td>Topical preparations</td>
<td>Topical antibiotics, cosmetics</td>
</tr>
<tr>
<td>Carba mix et al</td>
<td>Wide variety of rubber products</td>
</tr>
<tr>
<td>Wool alcohols (lanolin)</td>
<td>Emollients and soaps</td>
</tr>
<tr>
<td>Resins</td>
<td>Nail polishes, permanent press clothing</td>
</tr>
</tbody>
</table>

Table 1: Most common allergens yielding positive patch tests in children.

**ABSTRACT**

Allergic contact dermatitis (ACD) is more frequent in the pediatric population and in children with atopic dermatitis (AD) than has hitherto been appreciated. Patch testing, which is mediated by different immune mechanisms than prick skin testing, is both safe and diagnostically useful for individuals with AD. It may help to identify exacerbating allergens, e.g., constituents of topical treatments in refractory AD and to formulate treatment plans that feature preventive avoidance of the offending allergens.

**Key Words:** atopic dermatitis, patch testing, contact dermatitis
adults to dislodge the patches. Hence, an abbreviated standard series is often sufficient. Some of the most common contact allergens relevant to children are listed in Table 1.

What Are The Most Common Allergens?
The “standard series” of antigens contained in various commercially available patch test kits include many of the most common allergens. The North American Contact Dermatitis Group,9 after testing several thousand adult patients, noted that the 20 screening antigens included in a popular patch test kit detected ACD in only 54% of the patients, and missed a large number of allergic reactions that were deemed to be clinically relevant.

Of the positive reactions seen in adolescents who were patch tested (n=1146), 20 of 24 contact allergens were identified. Positive tests were most common to nickel (8.6%) and fragrance mix (1.8%). Significantly, more girls than boys were sensitized to nickel, whereas no sex difference was found for the other allergens.10

A positive patch test for thimerosal, an organic mercurial that is widely used as a preservative in vaccines, eye drops and contact lens solutions, was reported in 5 infants with AD.11 Nummular eczema appeared on the trunk, limbs and face 2-10 days after routine vaccinations. However, it is generally thought that if different needles are used to aspirate and to inject the vaccine, sensitivity to thimerosal should not prevent the completion of the routine vaccination series.

Interestingly, several authors have reported that the reproducibility of patch testing can be strongly affected by the nature of the antigen. Nickel in particular has been noted to produce discordant results in trials that double-tested patients.11,12 One reason for the apparent reported discrepancies in the incidence of ACD may be that the current antigen preparations yield intrinsically variable results.

Is ACD Common In Children With AD?
In recent years, the prevailing belief that ACD was very uncommon in children has been challenged. In fact, the true incidence of contact allergy and ACD in children and adolescents is unknown, partly because most studies examined referral populations, rather than unselected populations. Furthermore, they did not consider the clinical relevance of the contact allergic reactions that were noted, nor did they include follow-up data.13 However, ACD accounts for approximately 13.3%-23.3% of all the dermatitis seen in childhood.14-17

ACD has been observed in children under 3 years of age9 and even in neonates.7 In a large series of pediatric patients referred for patch testing to evaluate a variety of problems, the prevalence of positive patch test results is in the neighborhood of 40%.18 As previously noted, the standard series of allergens may miss a great many ACD patients, which may have contributed to the perception that it is not common in children.

The literature is extremely mixed with regard to whether ACD is less common in children with AD than in others. AD is one of the most frequent diagnoses among children who are referred for patch testing.19 In one recently reported series of 100 children, 87% had positive patch test reactions, and of these, 44.8% had AD.20 However, children with AD were reported to be somewhat underrepresented in a population of referred children whose patch tests were positive.21

Conversely, some investigators noted that the incidence of positive patch tests is lower in children with AD than in non-atopic children22 or in children with other types of dermatitis.23 A study of 499 adults reported that patients with atopy were significantly less likely to have a positive patch test result with a standard series of antigens.24 In contrast, a study of 670 referred children reported that atopy was a predisposing factor for contact hypersensitivity. Of the 42% with positive patch tests, 77% were atopic.25 Another sample of 410 patients found that the atopic subgroup had a significantly higher incidence of positive patch test results, although atopy also correlated with a higher incidence of nonspecific irritant reactions as well.26

A more recent report of patch testing in 1,146 adolescents with or without AD showed one or more positive reactions in 15.2% of subjects studied. Significantly more girls (19.4%) than boys (10.3%) (< 0.001). Two or more positive reactions were seen in 14.9% of children. Of those with allergic contact dermatitis, 37% had a history of AD.10

Possible Mechanisms
Contact dermatitis can be of the irritant or the allergic types. The irritant type, which is more common, depends to some extent on disruption of the epidermal barrier, and is related to the concentration and the duration of exposure to the irritant. ACD, on the other hand, requires an initial exposure. On re-exposure, memory T-lymphocytes are activated and proceed to mediate the inflammatory processes that lead to the familiar clinical picture.19

The results of patch testing in AD patients can vary greatly, e.g., as previously mentioned, certain antigens are likely to yield discordant results. Patch testing invokes a delayed, T-lymphocyte-mediated immune response, and thus might be expected to yield different results from the prick skin test, which invokes immediate, antibody-mediated hypersensitivity. In a prospective open study of 33 children with AD who were tested for food allergens, there were discrepancies in the results given by patch-scratch testing, skin application food tests (SAFT), prick skin tests and delayed-type patch tests.27 Among 113 infants with atopic
eczema, cow’s milk oral challenge was positive in 54 infants. This response correlated with prick skin testing in 36 infants and with patch testing in 18. However, 26% of the allergic infants were detected only with patch testing.28

Moreover, patients with active dermatitis, including AD, may have an intrinsic hyperreactivity of inflammatory cells which is shared with patients who have allergic rhinitis without dermatitis. This lower threshold may predispose them to the nonspecific “conditioned hyperirritability” that is often seen.29 In turn, the microscopic breaches of the epidermal barrier associated with skin irritation may allow specific antigens to penetrate more effectively and eventually to provoke the delayed immune responses that underlie the positive patch test result.

**Recommendations: Should AD Patients Be Patch Tested?**

Regardless of whether ACD is more or less frequent among children with AD than among other children, the incidence of ACD among children with AD in these populations is in the range of 40%.30 Despite the differences in comparative findings, this substantial positive rate has led to a consensus among investigators that patch testing is a useful modality for children with AD. First, it helps to improve the accurate identification of allergens that may be exacerbating the condition. Second, one frequently finds that individuals with AD have a positive patch test reaction to constituents of frequently used topical treatments (such as antibiotics or emollients). Thus, patients whose AD is persistent or flares despite appropriate treatment should be patch tested. Third, systematic patch testing has been advocated for children with AD so that preventive avoidance (e.g., to perfumed cosmetics) can begin early and clinical exacerbations may be spared. Although the standard series and concentrations are safe for children, using an abbreviated series of antigens may be adequate.

**Made possible through an unrestricted educational grant from LEO Pharma, Inc.**

**References**

**DERMATOLOGY NEWS**

**Dermatologists Increase Their Use of Patch Testing in US**

The standard for diagnosing delayed-type hypersensitivity reactions of the skin is considered to be patch testing, and according to a survey published in the June issue of the *American Journal of Contact Dermatitis*, its use is on the rise.

E.M. Warshaw and D. Nelson from the Minneapolis VA Medical Center and the University of Minnesota surveyed one-third of US Fellows of the American Academy of Dermatology in 1997, and the responses were compared with a survey of dermatologists done in 1990. They reported that 83% of those responding use patch testing in their practice, which is a significant increase over those using this test in 1990 (P<.0001).

Fifty-two percent used a 48-hour, 96-hour patch test reading schedule, and 26% carried out a single reading after 48 hours or 72 hours. Seventy-four percent of the dermatologists who use this test reported that they use the T.R.U.E. test® (Allerdeml), which was approved in July 1995, by the US FDA. Many (46%) said they were patch testing more patients now than when the T.R.U.E. test® was not available. Forty-four percent use the T.R.U.E. test® because it is less time consuming for their staff. Only 11% of dermatologists who patch test also use photopatch testing.

*Source: Am J Contact Dermat 13(2):58-8 (2002 Jun).*

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**INDUSTRY NEWS**

**New Policy on Pharmacy Compounding Set by the US FDA**

A recent US Supreme Court decision invalidated the compounding provisions contained in the US FDA Modernization Act of 1997, because they contained unconstitutional restrictions on commercial speech. As a result, the US FDA issued new guidelines for pharmacists in June 2002, which were published on their website on June 4, 2002.

These new guidelines are not directed toward the traditional activity of extemporaneously compounding drugs when they are manipulated in a reasonable quantity upon receipt of a valid prescription from a licensed practitioner for one identifiable patient. These guidelines are instead directed at an increasing number of establishments with retail pharmacy licenses that are engaged in manufacturing and distributing these compounds in a manner that is clearly outside the bounds of traditional pharmacy practice.

Generally, the US FDA will continue to defer to state authorities with regard to less significant violations to the Act relating to pharmacy compounding of human drugs. However, when the scope and nature of a pharmacy’s activities raise the kinds of concerns that are normally associated with a drug manufacturer and result in significant violations of the new drug, adulterations, or misbranding provisions of the Act, then the FDA will seriously consider enforcement action. In order to determine whether such action is necessary, they will consider whether the pharmacy engages in any of the following acts:

1. Compounding drugs in anticipation of receiving prescriptions, except in very limited quantities.
2. Compounding drugs that were withdrawn or removed from the market for safety reasons.
3. Compounding finished drugs from bulk active ingredients that are not components of FDA approved drugs without an FDA sanctioned investigational new drug application (IND).
4. Receiving, storing, or using drug substances without first obtaining written assurance from the supplier that each lot of the drug substance has been made in an FDA-registered facility.
5. Receiving, storing, or using drug components that are not guaranteed.
6. Using commercial scale manufacturing or testing equipment.
7. Compounding drugs for third parties who resell to individual patients, or offering compounded drug products at wholesale cost to other state licensed persons or commercial entities for resale.
8. Compounding drug products that are commercially available in the marketplace or that are essentially copies of commercially available FDA-approved drug products.
9. Failing to operate in conformance with applicable state laws that regulate the practice of pharmacy.

FDA-initiated regulatory action may include issuing a warning letter, seizure, injunction, and/or prosecution.

*Source: US FDA Compliance Policy Guide, Sec. 460.200 Pharmacy Compounding*
**Update on Drugs**

<table>
<thead>
<tr>
<th>Class</th>
<th>Name/Company</th>
<th>Approval Dates and Comments</th>
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| **Antiacne Agent** | Tretinoin Gel Microsphere  
Retin-A® Micro 0.04%  
Ortho Neutrogena | The US FDA approved this lower dose formulation in May 2002, for the treatment of acne. This product is formulated with A.P Pharma’s Microsponge® technology. |
| **Immuno-modulatory Agents** | Cyclosporine capsules  
25mg, 100mg  
Apopex Corp. | The US FDA approved this generic immunosuppressant in May 2002. It is the generic equivalent of Novartis Pharmaceuticals’ Sandimmune®. |
| **Anticonvulsant Agent** | Gabapentin  
Neurontin®  
Pfizer | The US FDA approved this anticonvulsant agent in May 2002, for the management of post-herpetic neuralgia, or pain in the area affected by herpes zoster after the disease has been treated. Neurontin® is also indicated as an add-on treatment for partial epileptic seizures. |
| **OTC Product** | Docosanol 10% Cream  
Avian Pharmaceuticals/  
GlaxoSmithKline | The Korea Food and Drug Administration approved this cream in May 2002, as an OTC topical treatment for cold sores. Also in May, TPP Canada approved this product for marketing and an NDA was submitted to the Swedish regulatory authorities seeking marketing approval there. In the US and Canada it is known as Abreva®. |
| **Keratolytics** | Salicylic Acid 15%  
Trans-Ver-Sal®  
Wart Removal Patch  
Bradley Pharmaceuticals | The Swedish Medical Products Agency approved this product in June 2002, for the treatment and removal of warts. |

**Drug News**

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<td><strong>Antiacne Agent</strong></td>
<td>Connetics Corporation announced in May 2002, that it licensed exclusive rights to develop and commercialize Velac® gel (clindamycin 1% and tretinoin 0.025%) in the US and Canada, and has licensed non-exclusive rights in Mexico. Connetics plans to request a pre-IND meeting with US FDA officials. Pending the outcome of that meeting, current plans are to begin clinical trials early in 2003. Under the current development timeline, Connetics expects to file an NDA for this product with the US FDA during the second half of 2004.</td>
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<tr>
<td><strong>Photodynamic Therapy</strong></td>
<td>DUSA® announced in June 2002, that its marketing and development partner for Levulan® PDT (Schering AG, Germany and its US affiliate Berlex Laboratories) has served a notice of termination in accordance with the parties’ marketing, development and supply agreement. As a result, DUSA® will be reacquiring all rights granted under the agreement by the end of June 2003. These include product marketing, reimbursement, inventory management and distribution and regulatory compliance. During the 12-month transition period Berlex will continue to sell the Kerastick™. Levulan® PDT is currently indicated for the treatment of actinic keratoses of the face and scalp.</td>
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<tr>
<td><strong>Diagnostic Criteria</strong></td>
<td>Trichotillomania is a chronic psychiatric disorder that is sometimes difficult to diagnose. According to an article recently published in the <em>Journal of Cutaneous Pathology</em>, researchers evaluated 28 scalp biopsies from 26 patients revealed trichomalacia in 57% and pigmented casts in 46%. They suggest that together with clinical suspicion of trichotillomania, trichomalacia and pigmented casts are major criteria when coming to a diagnosis.</td>
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*J Cutan Pathol 29:207-14 (2002).*