Pimecrolimus is an immunomodulating medication that inhibits production of inflammatory cytokines in the skin and this compound was specifically developed for the treatment of inflammatory skin diseases. Phase II and III clinical trials with the topical formulation of pimecrolimus (Elidel® cream, Novartis) have shown that it is safe and effective for use in patients with atopic dermatitis (AD). The US FDA recently approved Elidel® for use in patients ≥2 years of age with mild-to-moderate atopic dermatitis (AD).

**Key Words:** pimecrolimus, immunosuppressant, atopic dermatitis

Pimecrolimus (formerly SDZ ASM 981) is a natural macrolide product derived from the fungus Streptomyces hygroscopicus var. ascomyceticus. The topical formulation of pimecrolimus (Elidel® cream, Novartis) is one of a new class of non-steroidal topical immunosuppressant medications. When applied topically, it has cutaneous anti-inflammatory activity and appears to be minimally absorbed into the circulation. Safety and efficacy of pimecrolimus 1% cream have been established in several well-controlled clinical trials involving children and adults with AD. This medication was approved by the US FDA for use in adults and children (≥2 years) with mild-to-moderate AD in December 2001, and is now widely available. The product is currently undergoing regulatory review in Europe and Canada.

**Mechanism of Action**

The mechanism of action is closely related to that of cyclosporine, an immunosuppressant medication useful in some inflammatory skin disorders refractory to standard therapy. Oral cyclosporine is quite effective but has significant toxicities. Unfortunately, it has been found in trials to be ineffective topically. Efforts have been directed toward the development of new topical compounds with potent anti-inflammatory activity similar to cyclosporine, but without the systemic side effects. Topical tacrolimus and later, pimecrolimus, represent the first generation of this type of product. When applied topically, both medications selectively target inflammation in the skin without impairing systemic immune responses. In the early development phase of pimecrolimus, more than 400 ascomycin derivatives were synthesized and their characteristics explored in pre-clinical studies; SDZ ASM-981 was chosen for development because of its favorable safety profile and cutaneous efficacy.

Pimecrolimus binds with high affinity to the T-cell receptor macrophilin 12, which leads to inhibition of calcineurin, a protein phosphatase required for activation of the T-cell. As a result, T-cell activation is inhibited, and transcription and release of pro-inflammatory cytokines is prevented. Additionally, pimecrolimus decreases mast cell production of pro-inflammatory cytokines (e.g., TNF-alpha) and IgE induced pro-inflammatory mediators (e.g., histamine). The ability of pimecrolimus to inhibit the activation of multiple cell lines and cytokines may account for its ability to effectively reduce inflammation.

In animal models, both topical and systemic pimecrolimus are highly effective against skin inflammation. However, in contrast to tacrolimus, oral pimecrolimus is a poor systemic immune suppressant, reducing the likelihood of systemic toxicity.

**Drug Interactions**

Potential interactions between pimecrolimus and other drugs have not been systematically evaluated. Systemic interactions are unlikely due to the low levels of pimecrolimus found in the blood after topical application, but cannot be ruled out based on data gathered to date.
Studies with human liver microsomes indicate that pimecrolimus is metabolized \emph{in vitro} by the CYP3A family of P450 enzymes. It appears to be eliminated almost completely in the bile. FDA labeling suggests that concomitant administration of known CYP3A inhibitors in patients with widespread disease be undertaken with caution.

**Indications**

To date, pimecrolimus has primarily been studied for use in AD, which is a chronic, highly pruritic inflammatory skin disorder and the most common chronic skin disease in childhood. The disease may be associated with significant morbidity and can have a significant impact on quality of life for patients and families. Additionally, research has shown that patients are often not satisfied with prescribed therapy.

Until recently, topical treatment of AD has been limited to the use of corticosteroids. Patients who experienced side-effects from long-term use of the agents, or patients who were refractory to therapy had no other effective alternatives for topical treatment. Pimecrolimus and tacrolimus represent novel treatment options for this subset of patients.

Phase II and III trials of pimecrolimus have documented its safety and efficacy for AD treatment (summarized in Table 1). Although a few preliminary studies have been conducted using pimecrolimus to treat psoriasis and irritant hand dermatitis, its use has not yet been studied extensively for other skin conditions.

Pimecrolimus has also been studied for treatment of psoriasis and has demonstrated disease improvement when used under occlusion. A study of pimecrolimus for chronic irritant hand dermatitis found that the cream safely and effectively ameliorated the signs and symptoms of the disease after 6 weeks of therapy. Based on the studies to date, it is likely that pimecrolimus will be studied for a wide variety of inflammatory skin disorders in the future.

**AD Clinical Trials**

The efficacy and safety of pimecrolimus in patients with AD was shown in 1998, in a small, randomized, blinded, placebo controlled trial. In 34 adult patients, pimecrolimus 1% cream proved to be superior to placebo, and no clinically significant adverse events were reported.

Another larger, phase III, multi-center, blinded, randomized dose-finding trial also suggested efficacy and safety of pimecrolimus. This study evaluated 260 patients who were randomized to receive either 0.05%, 0.2%, 0.6%, 1% pimecrolimus, vehicle or betamethasone valerate 0.1% cream twice daily for 3 weeks. The 0.2%, 0.6% and 1% pimecrolimus creams were found to be more effective than vehicle, with 1% being the most effective. Betamethasone valerate was more effective than all concentrations of pimecrolimus. Pimecrolimus-related adverse events included burning and a feeling of warmth in the 0.6% and 1% groups (42.9% and 48.9%, respectively, vs. 34.9% with vehicle). Based on these findings, the 1% cream was chosen for further study in phase III trials.

Subsequently, 2 large, phase III, multi-center, randomized, controlled trials comparing pimecrolimus to vehicle were conducted in pediatric patients (aged 2-18 years) with AD. These two studies were of identical design, allowing for pooling of the results. Four hundred three patients were enrolled and both groups received treatment twice daily for 6 weeks. Efficacy was evaluated primarily by the Investigators Global Assessment (IGA), which uses a 6-point scale ranging from clear to very severe disease. The majority of patients studied had moderate disease. Treatment success was defined as achieving an IGA of 0-1 (clear to almost clear) during the study. At the first study visit (day 8), 12% of pimecrolimus patients achieved this, as compared to only 2.2% of vehicle patients (p<0.05). At the final study evaluation (day 43), 34.8% of pimecrolimus-treated patients were clear to almost clear, as opposed to only 18.4% of vehicle-treated patients (p<0.05).

<table>
<thead>
<tr>
<th>Design</th>
<th>Sample Size</th>
<th>Regimen</th>
<th>Inclusion</th>
<th>Primary Endpoint</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multicenter, randomized, blinded, controlled, dose-finding Phase II(^1)</td>
<td>n=260</td>
<td>Elidel® 0.05%, Elidel® 0.2%, Elidel® 0.6%, Elidel® 0.6%, Vehicle, or Betamethasone valerate b.i.d. for 6 weeks</td>
<td>Adult patients, moderate AD</td>
<td>Hanifin score (a numeric score based on signs and symptoms of AD)</td>
<td>Elidel® 0.2%, 0.6% and 1% were more effective than vehicle, with 1% the most effective. Betamethasone valerate was more effective than all concentrations of Elidel®</td>
</tr>
<tr>
<td>Multicenter, randomized, blinded, controlled Phase III (2 identical trials with pooled results)(^2)</td>
<td>n=403</td>
<td>Elidel® 1% or Vehicle b.i.d. for 6 weeks</td>
<td>Patients 1-17 years of age, mild-to-moderate AD</td>
<td>Physician's Global Evaluation</td>
<td>35% of Elidel® patients were clear or almost clear at end of study vs. 18% vehicle (p&lt;0.05).</td>
</tr>
<tr>
<td>Multicenter, randomized, controlled Phase III(^3)</td>
<td>n=186</td>
<td>Elidel® 1% or Vehicle b.i.d. for 6 weeks</td>
<td>Infants 3-23 months of age, mild-to-moderate AD</td>
<td>Physician's Global Evaluation</td>
<td>By first visit, 17% of Elidel® blinded, patients were clear or almost clear vs. 9.5% in vehicle (p=0.174). By final visit, 54.5% of Elidel® patients vs. 23.8% vehicle (p&lt;0.001) achieved this rating.</td>
</tr>
</tbody>
</table>

Table 1: Review of clinical trial data.
Pimecrolimus was also significantly more effective than vehicle at all visits for all secondary efficacy assessments studied (pruritus score and Eczema Area and Severity Index Score (EASI)). The incidence of adverse events was similar in both groups. The authors concluded that pimecrolimus 1% cream is safe and effective in children ≥2 years of age with mild-to-moderate AD.12

Another multi-center, randomized, controlled clinical trial was conducted, which compared pimecrolimus to vehicle in 186 children from 3-23 months of age. The design of this study was virtually identical to that of the two trials described previously. Patients applied medication twice daily for 6 weeks. The majority of the infants had moderate disease at study entry. By day 8, 17% of pimecrolimus-treated patients were clear or almost clear, compared with 9.5% in the placebo group (p = 0.174). By day 43 this increased to 54.5% of patients in the pimecrolimus group who were clear or almost clear and 23.8% of vehicle-treated patients (p<0.001). For all secondary efficacy parameters, pimecrolimus was significantly more effective than placebo. The incidence of adverse events was similar between the two groups. The authors concluded that pimecrolimus is safe and effective in infants aged 3-23 months with mild-to-moderate AD.13

Recently, a unique trial was conducted in pediatric patients aged 1-17 years, which suggested that pimecrolimus may be safe and effective maintenance therapy for preventing AD flares. The results also suggested a steroid-sparing effect in patients treated with pimecrolimus.14

**Pharmacokinetics**

Pharmacokinetic studies of pimecrolimus have been conducted with both adult and pediatric patients as young as 3 months of age. Measured blood concentrations of pimecrolimus were consistently low in both children and adults (99% had <2ng/ml) regardless of age, extent of body surface area (BSA) treated or duration of therapy. The majority of the readings were below the limit of quantification, even in the youngest patients. Over 12 months of treatment, there was no accumulation of the drug over time.15

**Adverse Effects**

Pimecrolimus cream is well tolerated when applied topically. Adverse effects have generally been limited to local irritation such as warmth, burning and pruritus. Unlike with topical corticosteroids, there has been no atrophy or adrenal axis suppression seen with Elidel®.

A significant concern exists related to local immunosuppression with topical application of tacrolimus and pimecrolimus. These agents inhibit T-cell activation and could therefore theoretically put patients at risk for conditions occurring more often in patients with T-cell suppression, namely skin cancer and viral infections. Incidence of these infections in completed trials was similar in the placebo and treated groups, but longer term data is needed to confirm that no association exists.

**Conclusions**

In summary, pimecrolimus cream is one of a new class of anti-inflammatory medications that have a unique mechanism of action derived from inhibition of pro-inflammatory cytokines in the skin. It has been shown to be safe and effective in several randomized, controlled trials in patients with AD. Long term data is limited to 1 year of use and ongoing studies to assess long term safety are appropriate. Based on the information gathered to date, it is likely that in the future, pimecrolimus will be used extensively for AD and a variety of other inflammatory skin conditions.

**References**

Psoriasis is a common dermatosis affecting 1-3% of the North American population. In children it is also very common, representing 4.1% of all childhood skin conditions, and usually occurring after 10 years of age; but 10% occur before age 10, and 2% before 2 years. This disorder causes significant morbidity, social embarrassment, and financial burden.

**Childhood Psoriasis**

In infants, psoriasis often starts in the diaper area, but a confident diagnosis at this stage is often difficult. Childhood psoriasis tends to be more extensive and severe than that seen in adults. However, systemic antipsoriatic modalities may have devastating and potentially irreversible side-effects that limit their use in children. Thus topical therapies are generally preferred in the pediatric population.

It is important to keep in mind that children are not simply small adults. There is a need for child and parental education, compliance, and cooperation. This is why, while being treated, children with psoriasis should be followed closely. Successful psoriasis treatment is a life-long task requiring major contributions from the family and physician, and failure to treat has been shown to have an adverse effect on quality of life in children.

There are five forms of psoriasis: plaque psoriasis, guttate psoriasis, pustular psoriasis, inverse psoriasis and erythrodermic psoriasis. In children, the most common types of psoriasis are the guttate and chronic plaque types. Psoriatic arthritis is seen in approximately 6% of children and adults.

Signs and symptoms of psoriasis include erythema, scaling, skin thickening, and pruritus. A thorough physical examination should include assessment of joints, scalp, elbows, knees, nails, palms, and soles of the feet.

**Triggers**

Triggers of psoriasis include comorbid inflammatory diseases (e.g., Crohn’s disease, HIV); emotional stress; withdrawal of systemic corticosteroids; preceding streptococcal infections in the case of guttate psoriasis; climate (northern regions); drugs (e.g., lithium, antimalarials, systemic interferon, and beta-blockers); and physical trauma (e.g., pressure, friction, rubbing and scratching). Exacerbating triggers are different in children and adults, with infections and trauma being the most common triggers in children.

**Pathogenesis**

Psoriasis is a complex disorder that may undergo periods of waxing and waning, recurrence and regression, and involves variable body surface areas. Genetic studies have linked it to several chromosomal loci (HLA-Cw6, 17q25, 4q), and psoriasis is an immunologic disorder leading to secondary hyperproliferation of keratinocytes. The normal turnover rate of keratinocytes from the basal cell layer to the stratum corneum is 28-44 days, but in psoriasis it is reduced to 4 days. Abnormal keratinocyte differentiation and infiltration of inflammatory cells are also typical features. Treatments available are designed to counteract one or more of these features.

**Treatment Options**

Available treatment modalities target keratinocyte hyperproliferation, abnormal keratinocyte differentiation, and infiltration of inflammatory cells. Treatment options for children include:

1) **Topical treatments**, e.g., corticosteroids (mild, mid and high potency agents), keratolytics, anthralins, coal tars, vitamin D analogs, retinoids, ureas, and emollients. Many of these are available as ointments (cutaneous plaques), creams (intertriginous areas) and lotions (scalp) (see Table 1).

2) **Phototherapy** (e.g., UVB with topical adjuvant therapy, topical or systemic PUA in teenagers). Sunlight and phototherapy can be beneficial if multiple areas are affected, but care must be taken to apply sunscreen to all unaffected areas.

3) **Systemic therapies** for severe, or resistant conditions (e.g., methotrexate, cyclosporine, retinoids, dapsone, hydroxyurea).

**Topical Treatments**

Therapy should start with a combination of emollients, topical corticosteroids and calcipotriol, with or without the addition of tar, salicylic acid, and other topical agents. For severe or resistant forms systemic modalities should be implemented. The choice of therapeutic agent should be based upon the location and extent of the plaques, the resistance to previous modalities, the various side-effects (see Table 2), and the cost of treatment (see Table 3). As a rule of thumb, ointments are more effective than creams, which are in turn, better than lotions. Other factors influencing the decision include the age of the patient, type of psoriasis, and associated medical disorders.
**Drug**  |  **Mechanism of Action/Use**  
---|---  
**Topical Corticosteroids** |  
**Low-Potency** – desonide (Desocort®, Tridesilon®), hydrocortisone agents (Prevex HC®, Cortate®, Emo-Cort®), hydrocortisone valerate (Westcott®) | • anti-inflammatory, immunosuppressive, and antiproliferative properties  
• mild potency for delicate skin (face, genitals, and face)  
• mid potency for torso and extremities  
• high potency for recalcitrant plaques, palms, and soles.  
• b.i.d. or daily with other topicals (e.g., Tazorac®, Dovonex®)  
**Mid-Potency** – betamethasone valerate (Celestoderm®, Prevex B®, Betnovate®), triamcinolone acetonide (Kenalog®), mometasone furoate (Elocom®) |  
**High-Potency** – amcinonide (Cyclocort®), fluocinolone (Lidex®), desoximetasone (Topicort®), halcinonide (Halog®) |  
**Ultra-Potency** – halobetasol propionate (Ultravate®), clobetasol propionate (Dermovate®), betamethasone dipropionate (Diprolene®) |  
**Keratolytics** - salicylic acid (Keralyt®) or with Vaseline, urea agents (Uremol®), and lactic acid (Lac-Hydrin®, Epi-Lyt®) | • remove scales or hyperkeratosis  
• may be added to topical Corticosteroids (e.g., Nerisalic®, Diprosalic®)  
**Anthralins** such as Anthra-Derm®, Drithocreme®, Dritho-Scalp®, Micanol® | • inhibit cell growth, restores cell differentiation  
**Coal Tars** - Estar® gel, Balnetar®, Neutrogena® T/Gel, MG271, DHS Tar, Doak®, LCD, Target® | • antiproliferative, anti-inflammatory  
• useful in combination with UVB  
• shampoos effective for scalp lesions  
• may be added to topical emollients or steroids  
**Vitamin D Analogs** – calcipotriol (Dovonex®, Dovobet®) | • inhibit keratinocyte proliferation  
• promote keratinocyte differentiation  
• available in combination with steroids (Dovobet®)  
**Retinoids** - Tazarotene (Tazorac®), trans-retinoic acid (Retin-A®) | • mediate cell differentiation, cell proliferation  
• for longterm improvement and maintenance therapy  
**Ureas** — Uremol® 10, Uremol® 20 | • thins stratum corneum, removes scaling  
• enhances water binding  
• good for adjuvant therapy  
**Emollients** — petrolatum (Vaseline®), Eucerin®, Aveeno®, oilated bath, Lubriderm®, Moisturel®, Aquaphor® | • softens dry skin and relieves itching  
• adjunct to most other therapies  

| Table 1: Mechanisms of Action for Topical Psoriasis Medications |  
---|---  
**Topical Corticosteroids**  
Corticosteroid efficacy is related to potency and absorption into the skin. There are four potency levels: low, mid-, high and ultra. A mild potency corticosteroid should be used for delicate skin, e.g., on the face and genitals. Mid-potency corticosteroids should be used on the torso and extremities, and high potency corticosteroids should be used to treat recalcitrant plaques, as well as the palms and soles. In children, the least potent topical steroid that is effective should be used, and the strength tapered as the condition improves. When used chronically, or at high doses, they can cause skin atrophy, tachyphylaxis, acne, localized hypertrichosis, striae, telangiectasia, and purpura. The may also suppress the Hypothalamic-Pituitary-Adrenal axis.  
**Anthralins**  
Anthralins are effective in inhibiting the hyperproliferative growth observed in psoriasis. Although it is an effective agent, it is not an ideal drug because of irritating and staining properties. Regardless of these shortcomings, it is the treatment of choice (in the US) for plaque psoriasis. These agents also have the benefit of synergistic effects when used in combination with UVB therapy, and salicylic acids. Emollients or suitable corticosteroid may be applied after the anthralin treatment has been washed off to potentiate the desired clinical outcome. Common side-effects include brownish staining of the skin, erythema, irritancy, and contact dermatitis.  
**Coal Tar**  
Tar products have both anti-inflammatory as well as antiproliferative effects. Their benefits are synergistic in combination with steroids, emollients, and especially UVB treatment. Coal tar can also be used effectively as a shampoo for psoriatic scalp lesions. Side-effects include folliculitis, contact ...
Drug Local and Systemic Side-Effects

Topical Corticosteroids (at high dose and chronic use) • skin atrophy, tachyphylaxis, acne, localized hypertrichosis, striae, telangiectasia, purpura • may suppress the Hypothalamic-Pituitary-Adrenal axis

Keratolytics • local irritation, salicylate toxicity (if extensive use)

Anthralins • no systemic effects • stains hair, nails, and local irritation of the skin

Coal Tars • folliculitis, contact allergic dermatitis

Vitamin D Analogs • irritant dermatitis, hypercalcemia (high dose and extensive use)

Retinoids • local skin irritation, pruritus, photosensitivity • possibly teratogenic

Ureas • no major side-effects, local irritation

Emollients • may be greasy, sticky, difficult to maintain compliance

Table 2: Adverse Effects of Topical Psoriasis Medications

<table>
<thead>
<tr>
<th>Drug</th>
<th>Local and Systemic Side-Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Topical Corticosteroids</td>
<td>• skin atrophy, tachyphylaxis, acne, localized hypertrichosis, striae, telangiectasia, purpura</td>
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</tr>
<tr>
<td>Emollients</td>
<td>• may be greasy, sticky, difficult to maintain compliance</td>
</tr>
</tbody>
</table>

Retinoids

Tazarotene and Retin-A® are actively involved in mediating cell differentiation, and decreasing cell proliferation. They are nonsensitizing, nonphototoxic, and nonphotoallergenic. Application is once daily to affected areas only, with clearing occurring in 12 weeks. The most common side-effect is local skin irritation, although pruritis, and photosensitivity may be observed. These agents used orally are teratogenic, and potentially have similar effects at high doses topically.1,3,8,11,18,19

Ureas

Urea is aprotolytic at high concentrations. It is most useful when applied to thickened nails secondary to psoriasis. It has also been added to some topical glucocorticoid preparations and is useful in treating psoriatic plaques and ichthysis. The most common side-effect experienced by some patients is local irritation.3,8,18,19

Table 3: Cost (in USD) of topical psoriasis treatments.20,23

<table>
<thead>
<tr>
<th>Drug</th>
<th>Cost</th>
</tr>
</thead>
</table>
| Topical Corticosteroids       | • weak $\leq 7^*$  
|                               | • moderate $\leq 14^*$  
|                               | • strong $4 \leq 14^*$  |
| Keratolytics (Keralyt® gel)   | $\leq 7^{**}$                                                      |
| Anthralins (Anthranol®, Micanol®, Anthraforte®) | $7 - 17^{**}$                                      |
| Coal Tars - prices vary according to product and strength used; generic preparations available | $\leq 17^{**}$                                      |
| Vitamin D Analogs (Dovonex®)  | $17 - 34^{**}$                                                    |
| Retinoids                     | • Retin-A® $17 - 34^{**}$  
|                               | • Tazorac® $>70^{**}$                                             |
| Ureas (Uremol® 10, Uremol® 20) | $\leq 17^{**}$                                                  |
| Emollients (Over the counter) | $\leq 17^{**}$                                                  |

* Cost of 15g of topical steroids (includes drug cost only)  
** Cost of 50g or 50ml or 30-day supply — includes drug cost only (excluding topical steroids)
Emollients

Emollients are occlusive agents that make the skin soft and pliable by increasing hydration of the stratum corneum. They act to soften dry skin and relieve itching. Petroleum is probably the most occlusive and therefore the best emollient available. In terms of efficacy, the more occlusive a preparation is, the more effective it is. In order to be most effective, emollients should be applied to damp skin. There are no reported side-effects, but they may be greasy and sticky, and patients may find it difficult to maintain compliance.18,19

Cost of Psoriasis Topical Treatment

Competing therapies for the treatment of psoriasis have substantially different cost implications. Clearly, assessment of the cost and benefits of a treatment needs to consider all costs (direct and indirect) as well as objective measurement of benefit (decrease in morbidity) from the patient’s perspective. Topical corticosteroids vary in price from <$7 to >$34USD per month based on potency (cheaper for low potency) and vehicle (lotions more expensive than creams and ointment). The newest topical treatments (retinoids and Vitamin D analogues) can be extremely expensive with monthly costs exceeding $100. Other topical treatment options are comparable in price to the low potency steroids, although combination therapy is commonly used in resistant plaques and costs may become very high.18,20,21

Conclusion

The treatment of psoriasis in children differs from that in adults. It is important to emphasize educating the family, dealing with emotional aspects of the disease, and eliminating triggering factors. Since psoriasis is a common dermatosis that can adversely affect the lives of children, these patients’ treatment should be active and effective. It is important to point out to patients that psoriasis is not contagious, that the disease can disappear in some cases, and that the doctor is there to help manage the problem. There is no cure, and this disease bears an enormous emotional and financial cost upon children and their families.

References


## Update on Drugs

<table>
<thead>
<tr>
<th>Class</th>
<th>Name/Company</th>
<th>Approval Dates and Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Anti-inflammatory Agent</strong></td>
<td>Fluocinolone Acetonide, Hydroquinone, Tretinoin Tri-Luma&lt;sup&gt;®&lt;/sup&gt; Hill Dermaceuticals</td>
<td>The US FDA approved this anti-inflammatory agent in January 2002, for the short-term treatment of moderate-to-severe melasma of the face, combined with sun avoidance measures that include the use of sunscreens.</td>
</tr>
<tr>
<td><strong>Atopic Dermatitis Agent</strong></td>
<td>Pimecrolimus Elidel&lt;sup&gt;®&lt;/sup&gt; Novartis</td>
<td>The Danish Medicines Agency approved this non-steroid atopic dermatitis agent in March 2002, for patients from as young as 3 months of age through to adulthood. Denmark is the first country in Europe to approve this cream.</td>
</tr>
<tr>
<td><strong>Anti-acne Agent</strong></td>
<td>Clindamycin, Zinc Zindaclin&lt;sup&gt;™&lt;/sup&gt; Gel Access Pharmaceuticals</td>
<td>The UK Medicines Control Agency approved this ant-acne agent in Feb 2002, for the treatment of acne. Zindaclin™ is a clindamycin zinc complex in a gel formulation that has a prolonged residence in the skin, thereby reducing systemic absorption and its associated side-effects. Clinical studies demonstrated that once-daily dosing was equivalent to the twice per day application required by the market-leading clindamycin product.</td>
</tr>
<tr>
<td><strong>Antifungal Agent</strong></td>
<td>Voriconazole Vfend&lt;sup&gt;®&lt;/sup&gt; Pfizer</td>
<td>The European Commission of the European Union authorized marketing of both the oral and IV formulations of this antifungal agent in March 2002, for treatment in immunocompromised patients with progressive, possible life-threatening infections that include acute invasive aspergillosis; fluconazole-resistant invasive Candida; and serious fungal infections caused by Scedosporium spp. and Fusarium spp.</td>
</tr>
<tr>
<td><strong>Antiviral Agent</strong></td>
<td>Imiquimod Aldara&lt;sup&gt;®&lt;/sup&gt; 5% Cream 3M Pharmaceuticals</td>
<td>The US FDA approved a broader indication for this antiviral agent in March 2002, to include adolescents 12 years of age and older for treatment of external genital warts. It was previously approved for patients 18 years and older.</td>
</tr>
</tbody>
</table>

## Drug News

**Antifungal Agents**

Ten patients with moccasin tinea pedis, a hard-to-treat chronic foot fungus all recovered following treatment with Carmol 40<sup>®</sup> cream (40% urea, Bradley Pharmaceuticals) combined with ciclopirox cream. A larger study is planned to verify the findings. In vitro studies had shown synergy between Carmol 40<sup>®</sup> and ciclopirox, i.e., the two compounds alone significantly reduced fungus counts after three days, but completely eradicated the fungus within 6 hours when given together.

**Human Papilloma Virus**

According to a recent large-scale study of women in western Washington in the US, infection with HPV can be a serious risk factor for vaginal cancer. Like cervical and other anogenital cancers, vaginal cancer was found to be strongly associated with prior infection of this virus. The results, published in *Gynecologic Oncology*<sup>®</sup>, suggest that women with genital warts should be monitored for the development of multiple anogenital cancers.

* *Gynecological Oncol* 84(2):263-70 (2002 Feb).