Management of Chronic Hand Dermatitis: A Practical Guideline for the General Practitioner

M. Gooderham, MD, MSc, FRCP(C); M. Bourcier, MD, FRCP(C); G. de Gannes, MD, FRCP(C); G. Dhadwal, MD, FRCP(C), FAAD; S. Fahim, MD, FRCP(C); W. Gulliver, MD, FRCP(C); I. Landells, MD, FRCP(C); C. Lynde, MD, FRCP(C); A. Metelitsa, MD, FRCP(C); S. Nigen, MD, FRCP(C); Y. Poulin, MD, FRCP(C), FAAD; M. Pratt, MD, FRCP(C); N. H. Shear, BASc, MD, FRCP(C); S. Siddha, MD, FRCP(C); Z. Taher, MD, FRCP(C); R. Vender, MD, FRCP(C)

Introduction
Hand dermatitis (HD) can have a significant impact on quality of life of those affected. It may interfere with activities both at work and in the home and can be associated with social and psychological distress.1,2 The chronic form, chronic hand dermatitis (CHD) affects up to 10% of the population, which can have a considerable societal impact.2 Canadian Guidelines for the management of chronic hand dermatitis have been published to help guide management of this burdensome condition.3 This article provides helpful practical guidance for the general practitioner in the management of patients with HD.

Abbreviations: CHD – chronic hand dermatitis; ENT – ear, nose, and throat; HD – hand dermatitis; KOH – potassium hydroxide; QoL – quality of life; TCI – topical calcineurin inhibitors; TCS – topical corticosteroid(s)

Diagnosing HD - Important points to cover:
- Determine if the patient has eczema, or a childhood history of eczema (erythematous, scaling patches with some fissuring in typical locations).
- Ask about a personal or family history of atopy, including asthma, seasonal ENT allergies, nasal polyps.
- Ask about a history of psoriasis and comorbidities such as psoriatic arthritis.
- Does the patient have occupational exposures that could lead to allergic or irritant contact dermatitis?
- Has the patient had any recent exposure to irritants? Frequent handwashing?
- Do a skin scraping for fungal KOH and culture to rule out tinea manuum as needed.

Figure 1. Examples of hand dermatitis (HD)
Determining if HD is Acute or Chronic
• It is important to first differentiate between acute and chronic forms of HD, as the treatment options may vary.
• Acute HD lasts less than 3 months or occurs only once in a calendar year.
• CHD lasts for at least 3 months and/or patients experience at least 2 relapses in a calendar year.

Differential Diagnosis: Acute HD
• Dishydotric dermatitis (pompholyx)
• Acute allergic contact dermatitis
• Irritant contact dermatitis
• Tinea manuum

Differential Diagnosis: Chronic HD
• Allergic contact dermatitis
• Irritant contact dermatitis
• Psoriasis
• Tinea manuum
• Cutaneous T cell lymphoma
• Bowen’s disease

TIP: Could This Be Tinea?
• Check the feet for signs of *tinea pedis* and onychomycosis.
• Look for an active border suggestive of tinea.
• Take a skin scraping for KOH microscopy and culture.

TIP: Could This Be Psoriasis?
• Check the feet, scalp, elbows, knees, gluteal cleft and umbilicus for signs of psoriasis.
• Check the nails for signs of psoriasis: pitting, onycholysis, subungual hyperkeratosis, splinter hemorrhages, salmon patches (oil drops).

Prevention, Avoidance and Patient Education
• Every patient with HD, whether acute or chronic, should protect their hands and avoid irritants and exacerbating factors.
• Avoid wet work, frequent hand washing and alcohol-based hand sanitizers.
• Gloves should be worn to protect the hands: cotton gloves at home, or during the night; gel padded gloves for friction and protective gloves for wet work and irritant exposure.
• The following tips are provided for patients on what to use, what to avoid and helpful common practices.

Do | Don’t
--- | ---
• Moisturize hands regularly with an emollient | • Rub, scratch or pick at loose skin
• Wear gloves when possible to protect hands | • Wash hands or expose hands to water frequently (avoid wet work)
• Keep fingernails trimmed and clean | • Expose hands to irritants: liquid hand soaps, disinfectants, shampoos, hand sanitizers
• Follow the treatment plan |

Assessing and Encouraging Patient Adherence
• Ask patients to bring products and prescriptions to follow up appointments to assess usage.
• More frequent patient follow up visits improve adherence.
• Provide education on the disease, treatment options and potential side effects of therapy.
• Choose treatment in agreement with the patient.
• Suggest joining a support group or organization, such as the Eczema society of Canada (http://www.eczemahelp.ca/en/index.html).

Emollient Therapy
• All patients with HD should use a bland, rich emollient to help restore the skin barrier, and apply frequently throughout the day.
• Regular application may prevent itching and reduce the number of flares.
• For hyperkeratotic eczema, patients should use an emollient with keratolytic agent (salicylic acid 10-20% or urea 5-10%).
• Unscented petroleum jelly is inexpensive and helpful for many patients.
**Management of Acute HD**
- It is important to make a diagnosis of acute HD so that treatment can be started as quickly as possible to maximize the outcome and prevent chronic involvement.
- Patients with HD should be adequately counselled on prevention and avoidance strategies.
- Avoidance of irritants, potential allergens and regular use of emollients is essential.
- Early treatment includes control of flares with a potent or super-potent topical corticosteroid (TCS) applied twice daily. For example, clobetasol propionate 0.05% ointment applied twice daily is generally effective in acute flares.
- For less severe flares, consider betamethasone valerate 0.1% ointment applied twice daily until controlled.
- In more severe cases, systemic steroids (prednisone, intramuscular triamcinolone) should be considered. Prednisone starting at 40-50 mg orally once a day and tapering over three weeks is an effective treatment course.
- Avoid short courses of prednisone as the condition may flare again, so a tapering dose is advised.
- Look for signs of infection and treat concomitantly.
- Try to identify any allergen exposures and recommend avoidance. If allergy is suspected, the patient should be referred for patch testing.
- Once controlled, consider maintenance therapy with topical calcineurin inhibitors (TCIs), such as tacrolimus 0.1% ointment twice daily when necessary, or twice weekly as maintenance therapy.

**Management of Chronic HD**
- The treatment plan for CHD depends on whether it is mild, moderate or severe.

**Management of Mild CHD**
- Patients with mild CHD should be educated on proper prevention and avoidance strategies as outlined earlier.
- Regular emollient therapy should be used to restore and maintain the skin barrier.
- TCS therapy should be initiated with betamethasone valerate 0.1% ointment twice daily for 4-8 weeks.
- If not responding, adherence to the treatment plan should be assessed. Ask the patient to bring medication to follow up appointment to assess amount of product actually used.
- The patient can then be counselled on proper use of the product and provide support for ongoing management.
- If not responding with an adequate trial, a higher potency TCS, such as clobetasol propionate 0.05% ointment should be prescribed as next line therapy. Reassess after 2 weeks. If not responding to an adequate trial of a potent or super potent TCS, the patient should be considered to have moderate CHD.
Management of Moderate CHD

- In addition to regular use of emollients, patients with a diagnosis of moderate CHD should be given a 4-8 week trial of a moderate TCS, such as betamethasone valerate 0.1% ointment, or a super potent TCS, clobetasol propionate 0.05% ointment for a 2-week trial. If improved, the patient can continue this as necessary, for control of the condition.

- Another option is maintenance with a TCI, such as tacrolimus 0.1% ointment twice a day as needed, or twice weekly for maintenance. If not improved, reconsider the diagnosis and assess the patient for adherence.

- If a diagnosis of moderate CHD is confirmed, consider treating the patient with a course of phototherapy, if accessible. If unavailable or the patient does not respond, consider treating as severe CHD.

Safety Tip

When patients show signs of adverse effects to TCS, including atrophy or telangiectasias or they cannot tolerate topical steroid use, consider TCI (tacrolimus ointment 0.1%) as a non-steroid topical therapy option for treatment and maintenance.

Management of Severe CHD

- Patients who are diagnosed with severe CHD, patients with mild to moderate CHD who have failed an adequate trial on therapy, or patients who have a significant impact on the QoL, should be treated as having severe CHD.

- Treatment should be initiated with a potent or super-potent TCS, such as clobetasol propionate 0.05% ointment twice a day for 4-8 weeks (2 weeks on dorsal hands if super potent). If improved, patients may continue to use on an as needed basis, or switch to a TCI for ongoing maintenance therapy.

- Patients should be reassessed at 4-8 weeks. If they are not responding to therapy, consider adherence and review proper care.

- Treatment with oral alitretinoin (30 mg orally, once a day) is the next line of therapy based on best available evidence. Alitretinoin should be prescribed by those who are comfortable with prescribing retinoids.

- As with all retinoids, caution should be used in females of child bearing potential due to teratogenic potential. Monitoring of therapy with regular blood tests for hepatotoxicity and alterations in lipid profile is also recommended.

- If the patient responds to therapy, it should be continued for 3-6 months and reassessed at that time. Patients may discontinue therapy at this point, and continue with ongoing maintenance with topical therapy. If, in the future, they experience a flare, they can be retreated with alitretinoin.

- If a patient does not respond to 12 weeks of alitretinoin, they should be referred for confirmation of diagnosis and other treatment options, which would include treatment with immunosuppressive therapy such as cyclosporine, methotrexate, mycophenolate mofetil or azathioprine.

When to Refer

- Patients with CHD should be referred to a dermatologist when:
  - They may require patch testing
  - They are not responding to therapy
  - Condition is worsening instead of improving
  - Require phototherapy

*Ensure patient education and check compliance. Consider reassessment to rule out infection and infestation, or consider differential diagnosis.

Figure 5. Treatment algorithm for the management of moderate chronic hand dermatitis (HD). CHD – chronic hand dermatitis; TCS – topical corticosteroid

*Ensure patient education and check compliance. Consider reassessment to rule out infection and infestation, or consider differential diagnosis.

Figure 6. Treatment algorithm for the management of severe chronic hand dermatitis (HD). CHD – chronic hand dermatitis; TCS – topical corticosteroid
Table 1. Summary of evidence

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Generic Name (Trade Name)</th>
<th>Level of Evidence</th>
<th>Summary</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>A</td>
<td>Large scale, double blind RCTs showing superior efficacy compared to placebo in those refractory to TCS use</td>
</tr>
<tr>
<td></td>
<td></td>
<td>B</td>
<td>Small RCT showed low dose cyclosporine was as effective as betamethasone dipropionate</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Conclusion**

HD can have a significant burden on the patient with an impact on QoL. Early diagnosis of acute or chronic HD is important for optimal management. Other conditions such as tinea manus and psoriasis need to be ruled out and managed appropriately. Once a diagnosis of HD is confirmed, treatment depends on the severity of the disease. A treatment algorithm has been developed to assist the general practitioner to make a diagnosis and either refer or treat accordingly. Whichever treatment option is prescribed, all patients should be educated on emollient therapy, hand protection and avoidance of irritants or allergens, which may be contributing to their disease.

References

Apremilast in the Treatment of Psoriasis and Psoriatic Arthritis

Melinda Gooderham, MD, MSc, FRCPC1,3 and Kim Papp, MD, PhD, FRCPC2,3

1Skin Centre for Dermatology, Peterborough, ON, Canada
2K. Papp Clinical Research, Waterloo, ON, Canada
3Probity Medical Research, Waterloo, ON, Canada

Introduction
Phosphodiesterase 4 (PDE4) is a key enzyme in the regulation of immune responses of inflammatory diseases through degradation of the second messenger, cyclic adenosine 3’,5’-monophosphate (cAMP). Apremilast (APR), a selective PDE4 inhibitor, has been shown to reduce the production of pro-inflammatory cytokines by increasing intracellular levels of cAMP and promoting the production of anti-inflammatory cytokines. The efficacy and safety of APR in the treatment of psoriasis and psoriatic arthritis has been demonstrated in phase 2/3 studies and is reviewed here. Across all studies, treatment was generally well-tolerated with some mild gastrointestinal complaints that occurred early and resolved over time. Meaningful improvement of psoriasis and psoriatic arthritis including dactylitis and enthesitis were observed. Routine monitoring is not required given the absence of drug associated physiologic, biochemical, and haematological changes. APR proves to be a new promising systemic therapy for treating psoriatic disease.

Background
• Psoriasis is an immune mediated disease involving skin, joints, and possibly the bowel.1,4
• Recent clinical studies have shown precise blockade of phosphodiesterase 4 (PDE4) to be effective in the treatment of psoriasis5 and PsA.6
• PDE4 belongs to the phosphodiesterase family of enzymes involved in the breakdown of cyclic adenosine 3’,5’-monophosphate (cAMP).6,7
• Increase in cAMP leads to a cascade of cellular events resulting in a reduction of inflammatory mediators such as tumor necrosis factor (TNF)-alpha, interleukin (IL)-23, and IL-17, as well as increase in anti-inflammatory cytokines such as IL-10.8-10
• Inhibition of PDE4 leads to an increase in the intracellular cAMP concentration, thereby reducing the production of inflammatory mediators and increasing anti-inflammatory mediators.8,11

PDE4 Inhibitor in the Treatment of Psoriasis
• Apremilast (APR, CC-10004, Otezla™), a PDE4 inhibitor, has been shown to block the production of pro-inflammatory cytokines that play a major role in the pathogenesis of psoriasis.
• APR demonstrated a range of anti-inflammatory effects on a variety of cell lines in vitro,11 and biologic activity in a pilot study in humans.12
• APR has been evaluated in a number of phase 212-14 and phase 3 clinical trials (Efficacy and Safety Trial Evaluating the Effects of APR in Psoriasis [ESTEEM] 1 and 2 and LIBERATE), demonstrating efficacy in psoriasis15-17 and psoriatic arthritis (PsA).6,7,19-21

Apremilast Use in Psoriasis

Results from Phase 3 Studies in Plaque Psoriasis
• Efficacy and safety of APR 30 mg BID was evaluated in two phase 3 randomized, placebo-controlled studies ESTEEM 115 and ESTEEM 216 and compared with etanercept and placebo (PBO) in a phase 3b study (LIBERATE)17, the results of which are not described here.
• In ESTEEM1, 844 patients with plaque psoriasis (Psoriasis Area Severity Index (PASI) ≥12, Body Surface Area [BSA] ≥10%, static Physician’s Global Assessment [sPGA] ≥3) were randomized 2:1 to APR 30 mg BID (n=562) or PBO (n=282) for the first 16 weeks. See Figure 1 for study design after week 16.15
• In ESTEEM 2, 413 similar patients with psoriasis were randomized to PBO (n=138) or APR 30 mg BID (n=275) through Week 16. See Figure 1 for study design after Week 16.16

• Significant improvements with APR 30 mg BID were observed at Week 16 for PASI-75 (a reduction of ≥75% in PASI scores) and sPGA scores.
• In ESTEEM 1, significantly more patients in the APR group achieved PASI-75 (33.1%), PASI-50 (58.7%) and sPGA 0-1 (21.7%) vs. PBO (P<0.0001, all).15
• In ESTEEM 2, patients treated with APR achieved PASI-75 (28.8%), PASI-50 (55.5%) and sPGA 0-1 (20.4%) vs. PBO (P<0.0001, all).16
• For the subgroup of patients who received APR 30 mg BID from Day 0 and continued on therapy, with PASI-75 responders at Week 32, there was a mean percent change from baseline in PASI score of -80% at Week 52.15
• Improvements with APR 30 mg BID were also seen in nail, scalp and palmoplantar psoriasis as well as quality of life and pruritus.15,16
• Patients treated with APR 30 mg BID achieved a 50% improvement in the Nails Psoriasis Severity Index (NAPSI-75) response at Week 16 vs. PBO. In ESTEEM 1, 33.3% of APR patients achieved NAPSI-50 response vs. 14.9% PBO (P<0.0001),15 and in ESTEEM 2, 44.6% of APR patients achieved NAPSI-50 vs. 18.7% PBO (P<0.0001).16
• In the APR 30 mg BID group achieved significant scalp improvement, with ScPGA 0-1 (Clear-Minimal) at Week 16 vs. those in the PBO group. In ESTEEM 1, 46.5% APR vs. 17.5% PBO (P<0.0001),15 and in ESTEEM 2, 40.9% APR vs. 17.2% PBO (P<0.0001).16
• Palmoplantar psoriasis also improved. In ESTEEM 2, 65.4% of patients treated with APR 30 mg BID achieved PPPGA 0-1 (Clear-Minimal) vs. 31.3% of patients treated with PBO.16
• APR 30 mg BID was associated with an improvement in quality of life with significantly higher proportion of patients who achieved clinically important differences in the Dermatology Life Quality Index (DLQI) and pruritus VAS from baseline at Week 16.
• In ESTEEM 1, 70.2% of patients in the APR group achieved a clinically significant improvement in DLQI response vs. 33.5% with PBO (P<0.0001),15,22 and in ESTEEM 2, 70.8% of patients treated with APR achieved a significant DLQI response vs. 42.9% with PBO (P<0.0001).15
• For pruritus VAS, 70.6% of patients in ESTEEM 1 treated with APR achieved significant improvement vs. 33.7% with PBO (P<0.0001) in ESTEEM 1.22

Safety and Tolerability Profile
• APR demonstrated an acceptable safety profile and was generally well-tolerated for up to 52 weeks as most adverse events (AEs) were mild or moderate in severity.
Discontinuation rates for diarrhea and nausea were each <2% in the APR 30 mg BID group through Week 52. The most frequently reported AEs during the PBO-controlled period and APR-exposure period were diarrhea, upper respiratory tract infection (URTI), nausea, nasopharyngitis, tension headache, and headache. Serious AEs – including serious infections, malignancies, and cardiovascular events – and laboratory value changes were not significantly affected.

AEs in ≥5% reported during Weeks 0-16 and Weeks 0-52 in ESTEEM 1 are shown in Table 1. AEs reported during Weeks 0-16 in ESTEEM 2 are shown in Table 2.

**APR Use in Psoriatic Arthritis**

**Results from Phase 3 Studies in Psoriatic Arthritis**

- Efficacy and safety of APR were evaluated in four phase 3 trials in the Psoriatic Arthritis Long-term Assessment of Clinical Efficacy (PALACE) clinical program in patients with PsA. **Key inclusion criteria in PALACE 1,2 were adults with a documented diagnosis of PsA at baseline (duration ≥6 months; met the Classification Criteria for Psoriatic Arthritis [CASPAR] criteria), ≥3 swollen and ≥3 tender joints despite past or current disease-modifying antirheumatic drugs (DMARDs) and/or biologics. In PALACE 3, patients also had at least one psoriatic lesion ≥2 cm, and in PALACE 4, DMARD and/or biologics naïve patients were included. Study design for the PALACE clinical trial program is shown in Figure 3.**

- The results of a 24-week PBO-controlled phase of PALACE 1 have been published, as well as the 52-week period results. In PALACE 1, patients with active PsA (n=504) were randomized (1:1:1) to PBO, APR 20 mg BID or APR 30 mg BID. See Figure 3 for details.

- At Week 16, significantly more patients receiving APR 20 mg BID (30.4%; P=0.0166) and 30 mg BID (38.1%; P=0.0001) achieved an ACR20 response vs. PBO.

- Key inclusion criteria in PALACE 1,2 were adults with a documented diagnosis of PsA at baseline (duration ≥6 months; met the Classification Criteria for Psoriatic Arthritis [CASPAR] criteria), ≥3 swollen and ≥3 tender joints despite past or current disease-modifying antirheumatic drugs (DMARDs) and/or biologics. In PALACE 3, patients also had at least one psoriatic lesion ≥2 cm, and in PALACE 4, DMARD and/or biologics naïve patients were included. Study design for the PALACE clinical trial program is shown in Figure 3. The results of a 24-week PBO-controlled phase of PALACE 1 have been published, as well as the 52-week period results. In PALACE 1, patients with active PsA (n=504) were randomized (1:1:1) to PBO, APR 20 mg BID or APR 30 mg BID. See Figure 3 for details.

- At Week 16, significantly more patients receiving APR 20 mg BID (30.4%; P=0.0166) and 30 mg BID (38.1%; P=0.0001) achieved an ACR20 response vs. PBO.

- At Week 24, an ACR20 response of 45.3% was observed in patients treated with APR 30 mg BID independent of their response at Week 16.
At Week 52, ACR20 response was observed among patients receiving APR continuously for 52 weeks (n=254) in 63.0% (20 mg BID) and 54.6% (30 mg BID) of patients.7 ACR50 and ACR70 responses were observed in 24.8% and 15.4% of patients receiving APR 20 mg BID and 24.6% and 13.8% of patients receiving APR 30 mg BID, respectively.7

Patients treated with APR had a statistically significant improvement in physical function, as measured by changes from baseline in Health Assessment Questionnaire–Disability Index (HAQ-DI) score (P=0.0004 vs. PBO) and the 36-Item Short-Form Health Survey v2 Physical Functioning domain score (P=0.0001 vs. PBO).

Significant improvements were also seen in most ACR component scores, particularly swollen and tender joint counts and patient assessment of pain (P<0.0001 vs. PBO).6

In patients with enthesitis, the mean change from baseline in the Maastricht Ankylosing Spondylitis Enthesitis Score (MASES) was significantly higher for APR 30 mg BID vs. PBO (P=0.0334), and significantly greater proportions of patients receiving APR 20 mg BID (32.0%; P=0.0037) and 30 mg BID (33.6%; P=0.0013) achieved a MASES score of 0 at Week 24 vs. PBO (14.4%).6

In patients with dactylitis, mean change from baseline in dactylitis severity score was higher with APR vs. PBO. Greater proportions of patients with dactylitis achieved scores of 0 at Week 24 with APR 20 mg BID (50.9%), APR 30 mg BID (47.7%) vs. PBO (40.9%); these differences did not reach statistical significance at Week 24.6

At Week 52, in patients who received APR continuously from baseline, the median change in MASES was 100% with APR 20 mg BID.

### Table 1. Adverse events ≥5% any treatment group in ESTEEM 15

The APR-exposure period (Weeks 0-52) included all patients who received APR 30 mg BID, regardless of when treatment was initiated. Exposure-adjusted incidence rate (EAIR) per 100 patient-years is defined as 100 times the number (n) of patients reporting the event divided by patient years within the phase (up to the first event start date for patients reporting the event).15

<table>
<thead>
<tr>
<th>Patients (%)</th>
<th>Placebo n=282</th>
<th>Apremilast 30 mg BID n=560</th>
<th>Apremilast 30 mg BID n=804</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhea</td>
<td>7.1</td>
<td>18.8</td>
<td>18.7</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>7.4</td>
<td>10.2</td>
<td>17.8</td>
</tr>
<tr>
<td>Nausea</td>
<td>6.7</td>
<td>15.7</td>
<td>15.3</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>8.2</td>
<td>7.3</td>
<td>13.4</td>
</tr>
<tr>
<td>Tension headache</td>
<td>4.3</td>
<td>7.3</td>
<td>9.6</td>
</tr>
<tr>
<td>Headache</td>
<td>4.6</td>
<td>5.5</td>
<td>6.5</td>
</tr>
</tbody>
</table>

### Table 2. Adverse events ≥5% any treatment group in ESTEEM 2

<table>
<thead>
<tr>
<th>Patients (%)</th>
<th>Placebo n=136</th>
<th>Apremilast 30 mg BID n=272</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>6.6</td>
<td>18.4</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>5.9</td>
<td>15.8</td>
</tr>
<tr>
<td>Vomiting</td>
<td>3.7</td>
<td>5.1</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>4.4</td>
<td>7.4</td>
</tr>
<tr>
<td>Tension headache</td>
<td>1.5</td>
<td>7.4</td>
</tr>
<tr>
<td>Headache</td>
<td>0.7</td>
<td>6.3</td>
</tr>
<tr>
<td>Psoriasis</td>
<td>5.1</td>
<td>1.5</td>
</tr>
</tbody>
</table>

**Figure 3.** PALACE Study Design6,19-21

Note: Plasma samples for the biomarker assay were obtained at baseline and Weeks 4, 16, 24, and 40.

*All doses were titrated over the first week of treatment.

$Patients whose swollen and tender joint counts had not improved by ≥20% at Week 16 were considered non-responders and were required to be re-randomized (1:1) to APR 20 mg BID or 30 mg BID if they were initially randomized to PBO. APR-treated patients continued on their initial APR dose.

‡At Week 24, all remaining PBO patients were re-randomized to APR 20 mg BID or 30 mg BID.
Dosing pack. Over the first week is recommended and is available in a convenient 30 mg PO BID. However, an initial titrated dose from 10 mg to 30 mg intolerance, or contraindication to a prior disease-modifying arthritis in adult patients who have had an inadequate response, or in combination with methotrexate, for the treatment of active systemic therapy. It is also indicated for psoriatic arthritis either alone moderate to severe disease who are candidates for phototherapy or indicated for the treatment of plaque psoriasis in adult patients with Apremilast was approved by Health Canada in November, 2014.  It is Approval and Indications

Warning and Precautions: Data from Studies in Psoriasis and PsA

Weight Decrease
- During the controlled period of the trials, weight decrease between 5%-10% of baseline body weight was reported in 12% of psoriasis and 10% of PsA patients treated with APR 30 mg BID vs. 3-5% treated with PBO. Weight decrease of ≥10% of body weight occurred in 2% of patients treated with APR 30 mg BID vs. 1% in the PBO group.
- It is recommended that patients treated with APR should have their weight monitored regularly. Depression
- While treatment with APR was associated with a risk of depression, data from the clinical trials do not suggest an increase in depression nor suicidal ideation in subjects treated with APR vs. PBO.

Drug Interactions
- Co-administration with cytochrome P450 enzyme inducers (e.g., rifampin, phenobarbital, carbamazepine, phenytoin) resulted in a reduction of systemic exposure of APR, which may result in a loss of its efficacy and is not recommended.

Approval and Indications
Apremilast was approved by Health Canada in November, 2014. It is indicated for the treatment of plaque psoriasis in adult patients with moderate to severe disease who are candidates for phototherapy or systemic therapy. It is also indicated for psoriatic arthritis either alone or in combination with methotrexate, for the treatment of active arthritis in adult patients who have had an inadequate response, intolerance, or contraindication to a prior disease-modifying anti-rheumatic drug (DMARD). The recommended daily dosing is 30 mg PO BID. However, an initial titrated dose from 10 mg to 30 mg over the first week is recommended and is available in a convenient dosing pack.

References
22. Armstrong AW, et al. [Poster P1691]. Presented at: the 23rd Congress of the European Academy of Dermatology and Venereology; October 8-12, 2014; Amsterdam, the Netherlands.
23. Gooderham M, et al. [Poster P1688]. Presented at the 23rd Congress of the European Academy of Dermatology and Venereology; October 8-12, 2014; Amsterdam, the Netherlands.

Conclusion
Treatment with APR demonstrated efficacy in reducing the severity of moderate to severe plaque psoriasis and improving signs, symptoms and physical function in PsA. APR demonstrated an acceptable safety profile and was well-tolerated with generally mild GI complaints occurring early in the course of the treatment and resolving with time, and there was no requirement for laboratory monitoring. Based on these results, APR should be considered as a therapeutic option in the treatment of plaque psoriasis and PsA.

Acknowledgement
The authors gratefully acknowledge the medical editorial support from Flora Krasnoshtein in preparing the original manuscript.

Table 3. Adverse events ≥5% any treatment group in PALACE 1

<table>
<thead>
<tr>
<th>Patients (%)</th>
<th>Placebo-Controlled Period Weeks 0-24</th>
<th>Apremilast</th>
<th>Apremilast-Exposure Period Weeks 0-52</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo</td>
<td>Apremilast</td>
<td>Placebo</td>
</tr>
<tr>
<td>n=168</td>
<td>20 mg</td>
<td>30 mg</td>
<td>n=168</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>2.4</td>
<td>11.3</td>
<td>19.0</td>
</tr>
<tr>
<td>Nausea</td>
<td>6.5</td>
<td>9.5</td>
<td>18.5</td>
</tr>
<tr>
<td>Headache</td>
<td>4.8</td>
<td>10.1</td>
<td>10.7</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>3.6</td>
<td>6.0</td>
<td>4.2</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>3.0</td>
<td>3.6</td>
<td>4.8</td>
</tr>
</tbody>
</table>

BID and 66.7% with APR 30 mg BID, and a MASES score of 0 was observed in 50.7% (35/69) of patients receiving APR 20 mg BID and 38.2% (34/89) receiving APR 30 mg BID.
- AEIs in the PALACE 1 trial were similar to the psoriasis studies with gastrointestinal, mild or moderate in severity, occurred early, self-limited, did not recur, and inefinitely led to discontinuation (<2.5%) through Week 24.
- No imbalance in major adverse cardiac events, serious or opportunistic infections, malignancies or laboratory abnormalities was observed.
- For an overview of AEIs occurring in ≥5% of PALACE 1 see Table 3.

Warning and Precautions: Data from Studies in Psoriasis and PsA

Weight Decrease
- During the controlled period of the trials, weight decrease between 5%-10% of baseline body weight was reported in 12% of psoriasis and 10% of PsA patients treated with APR 30 mg BID vs. 3-5% treated with PBO. Weight decrease of ≥10% of body weight occurred in 2% of patients treated with APR 30 mg BID vs. 1% in the PBO group.
- It is recommended that patients treated with APR should have their weight monitored regularly.

Depression
- While treatment with APR was associated with a risk of depression, data from the clinical trials do not suggest an increase in depression nor suicidal ideation in subjects treated with APR vs. PBO.

Drug Interactions
- Co-administration with cytochrome P450 enzyme inducers (e.g., rifampin, phenobarbital, carbamazepine, phenytoin) resulted in a reduction of systemic exposure of APR, which may result in a loss of its efficacy and is not recommended.

www.SkinTherapyLetter.ca • Skin Therapy Letter • Family Practice Edition • Volume 11, Number 1 • October 2016
Actikerall™ (5-Fluorouracil 0.5% and Salicylic Acid 10%) Topical Solution for Patient-directed Treatment of Actinic Keratoses

Harrison P. Nguyen, BA1,2 and Jason K. Rivers, MD, FRCP, FAAD3,4
1MD/MBA/MPH Candidate at Yale University, New Haven, CT, USA; 2Baylor College of Medicine, Houston, TX, USA
3Department of Dermatology and Skin Science, University of British Columbia, Vancouver, BC, Canada
4Pacific Dermaesthetics, Vancouver, BC, Canada

Introduction
Actinic keratosis (AK), a common cutaneous lesion with the potential to transform into squamous cell carcinoma, has traditionally been treated with ablative and/or surgical procedures. Recently, a topical formulation combining 0.5% 5-fluorouracil with 10% salicylic acid (5-FU-SA) was introduced in Europe under the trade name Actikerall™ for the treatment of grade I/II AK. In a single randomized phase III trial, 5-FU-SA was shown to be superior to diclofenac 3% gel in hyaluronic acid, as measured by the histological clearance of one defined lesion (72% vs. 59.1%) and by complete clinical clearance (55.4% vs. 32.0%). 5-FU-SA should be applied once daily to a total area of up to 25 cm², which may include the lesion(s) and a small area of surrounding skin (rim of healthy skin should not exceed 0.5 cm), for up to 12 weeks. The most commonly reported side effects are local inflammation and pruritus at the application site, and no serious adverse effects have been reported to date. Now commercially available in Canada, 5-FU-SA represents a patient-applied therapeutic option for the treatment of both overt and subclinical AK.

Background
• Actinic keratosis (AK) is a lesion considered to be on a continuum with squamous cell carcinoma (SCC).1 6
• Invasive disease occurs in up to 10% of cases over time, which highlights the need for early recognition and adequate treatment of all AK, including subclinical lesions.7
• Although many AK never progress to SCC, their treatment has been recommended to preempt this eventuality.
• Treatment options can generally be stratified based on whether only discrete lesions are treated, or whether subclinical lesions are also targeted, which is referred to as field-directed therapy.
• Lesion-directed therapy has historically consisted of ablative and/or surgical procedures. However, several topical agents have emerged as attractive alternatives in the treatment of AK.
• Examples of topical agents available in Canada include 5-fluorouracil (5-FU), imiquimod (2.5%, 3.75%, and 5% formulations), diclofenac 3%, methylaminolevulinate/aminolevulinic acid (for photodynamic therapy), and ingenol mebutate.8
• In one controlled clinical trial, topical 5-FU applied to AK resulted in a 96% clearance after 4 weeks of twice daily application.9 However, high rates of severe localized tissue reactions with 5-FU have led to reduced patient compliance, and this, in part, may explain why the long-term clearance of AK in clinical practice is around 50%.4
• This problem has resulted in a search for therapeutic agents less likely to induce skin irritation.10
• In 2011, a topical formulation combining 0.5% 5-FU with 10% salicylic acid (5-FU-SA) was introduced to the European market under the trade name Actikerall™ for the topical treatment of grade 1/2 AK (slightly palpable and/or moderately thick hyperkeratotic lesions) in immunocompetent adult patients.11,12 This preparation is not novel as the same agent has been used in Europe for more than 30 years in the treatment of plantar warts (Verrumal®).

In this brief review, we present some of the clinical data to support the use of 5-FU-SA in patient-directed* management of AK and we summarize the salient information that the provider should be aware of when prescribing this product.

Evidence from Clinical Trials
• The primary evidence used to support the efficacy of 5-FU-SA in the treatment of AK comes from a single randomized, multi-center, phase 3 trial.13 The study included 470 patients with histologically diagnosed AK on the face, forehead, or bald scalp. Subjects were randomly assigned to 5-FU-SA, diclofenac 3% gel in hyaluronic acid (diclofenac HA), or placebo (5-FU-SA vehicle). Treatment was continued until either complete resolution of the lesions was evident, or for a maximum of 12 weeks.
• Subjects were instructed to apply their assigned intervention directly to their lesions – once daily for the 5-FU-SA and vehicle groups and twice daily for the diclofenac group.
• The primary outcome – histological clearance of one defined lesion within 8 weeks of treatment cessation – was achieved in 72.0%, 59.1%, and 44.8% of patients treated with low-dose 5-FU-SA, diclofenac and placebo, respectively.
• In addition to the histological data, the rate of complete clinical clearance was also highest in the study group (55.4% vs. 32.0% and 15.1% for 5-FU-SA, diclofenac HA, and vehicle groups, respectively).13 Similar to the temporary lesion increase associated with other topical therapies, an ephemeral increase in mean lesion area was observed only in patients treated with 5-FU-SA at week 2.
• However, by the end of the treatment period, reduction in mean lesion area was more evident in the study medication group compared to the comparator and placebo groups.
• In a more recent non-interventional study, a reduction in number and size of AK after 0.5% 5-FU-SA therapy was observed even after a short period of use: target results were achieved in approximately half of patients within 6 weeks of treatment commencement.15
• Another study assessed the efficacy of low-dose 5-FU-SA versus cryosurgery in patients with grade II/III hyperkeratotic AK.16 In this open labelled, randomized trial, patients with histologically confirmed AK received either a 6-week course of once daily topical 5-FU-SA applied directly to lesions or up to two cryosurgical treatments spaced 3 weeks apart.
• 5-FU-SA achieved greater histological clearance as measured by mean lesion area and lower recurrence of lesions compared to cryosurgery at the 6-month follow-up.

Adverse Effects
• In the phase 3 mentioned above13, about 95% of patients in the study medication group reported treatment-emergent adverse effects (TEAEs), with local inflammation and pruritus at the application site being the most common.

*Health Canada has elected to classify Actikerall™ as neither lesion-directed nor field-directed. This was done to support the individual needs of patients; the locational distribution of a patient’s lesions will dictate whether a lesion-directed versus a field-directed approach is preferred.
Approximately 60% of patients in the vehicle group also reported application site burning, suggesting the etiology of this sensation was likely related to dimethyl sulfoxide, which facilitates tissue absorption and is a known irritant present in the 5-FU-SA excipients. For patients who have difficulty tolerating the side effects, dosing can be reduced from daily applications to treatment three times a week. In spite of the relatively high rate of TEAEs, patients have reported a high level of satisfaction with the use of low-dose 5-FU-SA. No serious adverse effects directly related to 5-FU-SA treatment, including usage as Verrumal® for warts, have been reported in either clinical studies or post-marketing surveillance.

**Dosage and Administration**

- Actikerall™ is a transparent, colorless to slightly orange-white solution that is packaged in 25 mL glass bottles, accompanied by a nylon brush that allows for easy application. It is recommended for application once daily to a total area of up to 25 cm², which may include the lesion(s) and a small area of surrounding skin (rim of healthy skin should not exceed 0.5 cm), for up to 12 weeks (Table 1).
- If the lesions are located in areas with thin epidermis, the solution may be applied less frequently (e.g., 3 times per week).
- The solution should be allowed to dry on the skin but prior to re-application on subsequent days, the existing film should be peeled off, which can be facilitated by using warm water.

**Drug Profile for Actikerall™**

<table>
<thead>
<tr>
<th>Form/centre</th>
<th>Solution/0.5% fluorouracil and 10% salicylic acid</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nonmedicinal ingredients</td>
<td>Dimethyl sulfoxide, ethanol, ethyl acetate, pyroxyline, poly(butyl methacrylate, methyl methacrylate)</td>
</tr>
</tbody>
</table>

| Dosing and administration | Apply to AK in an area of up to 25 cm² once daily until the lesions have completely cleared or for up to a maximum of 12 weeks. Apply directly to lesions and up to 0.5 cm rim of healthy surrounding skin. |
| Contraindications | Hypersensitivity to fluorouracil, capetcitabine, or salicylates; contact with the eyes or mucous membranes; pregnant or in the lactation period; renal insufficiency; should not be used in conjunction with brivudine, sorivudine and analogues; known dihydropyrimidine dehydrogenase deficiency |

| Table 1. Summary of drug information |

- A significant reduction in lesions is usually seen within 6 weeks of starting treatment, and patients most likely to benefit from the full 12-week course are those who have failed previous treatments with other modalities.
- Patients should be advised that lesions may continue to regress for up to 8 weeks after cessation of therapy.
- 5-FU-SA is contraindicated for use during lactation or pregnancy. Other contraindications include renal insufficiency and concurrent usage of brivudine, sorivudine, or similar analogues. Of note, although these agents are structurally similar to acyclovir, which does not inhibit dihydropyrimidine dehydrogenase to any significant extent and is therefore safe to administer concurrently with 5-FU-SA.
- Additionally, instances of phenytoin toxicity related to the concurrent use of topical 5-FU-SA have been reported, so these patients should be tested at monthly intervals for plasma levels of phenytoin when this combination of therapies exists. 5-FU-SA should not be applied on bleeding lesions and has not been evaluated for the treatment of recurrent lesions.
- Patients should be educated on FU-SA’s flammability, propensity to desiccate quickly (the bottle needs to be closed tightly after use and it should be discarded if crystallization occurs), and ability to cause permanent stains on textiles and acrylics.

**Conclusion**

5-FU-SA represents a new addition to our treatment of AK, especially for individuals who want to avoid the pain or potential consequences associated with destructive therapy for isolated lesions. An emerging role for 5-FU-SA may be in combination therapy with other agents that have been unsuccessful in clearing hyperkeratotic lesions in the treatment zone.

**References**
