Actinoc 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 AKs. 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 cm$^2$, 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 common 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 AKs.

**Key words:** Actikerall, actinic keratosis, antineoplastic antimetabolite, drug combinations, immunosuppressive agents, keratolytic agents, salicylic acid, skin neoplasms, topical therapy
Evidence from Clinical Trials

The primary evidence used to support the efficacy of 5-FU-SA in the treatment of AKs comes from a single randomized, multicenter, phase III trial. 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) and treatment was continued until complete resolution of the lesions, or for a maximum of 12 weeks. Subjects were instructed to apply their assigned intervention directly to the 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. Of note, up to 25% of untreated AKs may regress spontaneously over a 1 year period, and therefore, this phenomenon does not fully explain the high rate of clearance noted in the aforementioned study’s placebo group.

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). 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 (355.9 mm², 345.7 mm², and 341.4 mm², respectively). In a more recent non-interventional study, the reduction in number and size of AKs 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.

Another study assessed the efficacy of low-dose 5-FU-SA versus cryosurgery in patients with grade II/III hyperkeratotic AKs. 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. Although the sample size (33 per treatment arm) was not powered to draw statistically significant conclusions, 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.

Non-invasive assessment using reflectance confocal microscopy and high-definition optical coherence tomography has provided insight into the in vivo pharmacodynamic changes induced by 5-FU-SA. In one study, AKs were assessed 2 weeks after the last treatment with 5-FU-SA, and the measurement of stratum corneum and epidermis thickness showed significant reduction in both clinical and subclinical lesions. Moreover, histological characteristics of AK – including scaling, detached corneocytes, atypical honeycombing, round nucleated cells in the spinosum granulosum, round vessels, and inflammatory cells were all markedly reduced in lesions treated with 5-FU-SA.

Unlike 5-FU alone, there have been no studies to assess 5-FU-SA’s ability to treat superficial basal cell carcinoma or Bowen’s disease.

Adverse Effects

In the first trial mentioned above, 7.4% (35/470) of patients withdrew from the study prematurely: 14 patients from the 5-FU-SA group, 16 patients from the diclofenac group, and 5 patients from the vehicle group. 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. 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 application to treatment 3 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.

Dosing and Administration

Actikerall™ is a transparent, colorless to slightly orange-white solution packaged in 25 mL glass bottles, accompanied by a nylon brush that allows for easy application. 5-FU-SA 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). However, if the patient has lesions in areas with thin epidermis, the solution may be applied less frequently (e.g., 3 times per week). To avoid excess application, the brush can be wiped on the neck of the bottle. 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/strength</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, pyroxylene, poly(butyl methacrylate, methyl methacrylate)</td>
</tr>
<tr>
<td>Dosing and administration</td>
<td>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.</td>
</tr>
<tr>
<td>Contraindications</td>
<td>Hypersensitivity to fluorouracil, capecitabine, 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</td>
</tr>
</tbody>
</table>

Table 1. Summary of drug information
As noted, significant reduction in the lesion count is usually observed within 6 weeks of starting treatment, and patients most likely to benefit from the full 12-week course are those who have failed previous therapy with other modalities. Patients should be advised that lesions may continue to regress for up to 8 weeks after cessation of therapy.

The use of 5-FU-SA in areas other than the face and scalp has only been reported in the setting of small case series. In one publication, two patients with multiple AKs on the dorsal aspect of the hands achieved complete clearance after sequential treatment with diclofenac 3% gel and 5-FU-SA. A notable observation has been a lower therapeutic response of AKs located on the upper extremities compared to lesions on the face and scalp. This finding has also been observed with photodynamic therapy, ingenol mebutate and other topical agents used to treat AKs. Although the reason for this observation remains poorly understood, one hypothesis is that increased skin thickness in the upper extremities restricts drug absorption, thus limiting its therapeutic efficacy.

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. The latter consideration is related to the ability of these agents to inhibit the enzyme dihydropyrimidine dehydrogenase, which plays a critical role in breakdown of fluorouracil. Of note, although these agents are structurally similar to acyclovir, the latter drug 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. With regards to user experience and safety, the patient should be educated on the solution’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.

Cipher Pharmaceuticals, which owns the rights to Actikerall™ in Canada, has indicated that each bottle will be sold for a wholesale price of $36.25. Commercial availability commenced in February 2016.

Conclusions

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

DSM-5 Update in Psychodermatology

Dominik Alex Nowak, HBSc, MD¹ and Se Mang Wong, MD, FRCPC²

¹School of Medicine, McMaster University, Hamilton, ON, Canada
²Department of Dermatology and Skin Science, University of British Columbia, Vancouver, BC, Canada

Conflicts of interest: None reported.

ABSTRACT

Up to a third of dermatology outpatients have a significant psychiatric issue complicating their skin complaint. Although the ideal would frequently involve psychiatric assessment, those with comorbid mental illness often refuse psychiatric referral. As a result, it is imperative that dermatologists be mindful of psychiatric comorbidity in their patients and comfortable with the fundamentals of psychodermatologic diagnosis and therapy. This update summarizes current concepts, relevance, and therapeutics in psychodermatology, including aspects pertinent to depression, anxiety, obsessive-compulsive, impulse-control, and delusional disorders as described in the Diagnostic and Statistical Manual of Mental Disorders 5th edition (DSM-5, published in 2013 by the American Psychiatric Association).

Key words: anxiety, delusional disorder, depression, dermatology, DSM-5, excoriation disorder, obsessive-compulsive disorder, parasitosis, psychiatry, psychodermatology, trichotillomania

Introduction

Mind and skin are intimately related. Up to a third of dermatology outpatients have a significant psychiatric issue complicating their skin complaint.¹ The dermatologist’s work is far from skin deep; often the most meaningful aspects of management involve success in resolving the psychosocial impact of cutaneous disease. Although the ideal management would frequently involve psychiatric assessment, those with comorbid mental illness often refuse psychiatric referral. As a result, it is imperative that dermatologists be mindful of psychiatric comorbidity in their patients and comfortable with the fundamentals of psychodermatologic diagnosis and therapy.

Categories of Psychodermatology

Psychodermatology covers a broad spectrum of diseases. The four main categories include psychophysiological disorders, primary psychiatric disorders, secondary psychiatric disorders, and cutaneous sensory disorders.²

Psychophysiological disorders are primary skin diseases modified by psychosomatic factors. These include psoriasis, atopic dermatitis, acne, and hyperhidrosis, all skin conditions that are known to worsen with stress or emotional triggers.³

Primary psychiatric diseases include those that are psychotic, delusional, or obsessive in nature. Examples include delusions of parasitosis, neurotic excoriations, trichotillomania, and factitious disorder. No primary skin lesions will exist in most cases, as skin changes within this category will commonly be self-induced. These patients often lack insight into their condition, and as a result they require tactful clinical care. Note that factitious disorder, which in dermatology involves self-induced or alleged skin pathology without external incentive, is sometimes described as dermatitis artefacta or factitious dermatitis. These terms misleadingly suggest underlying inflammation.

Secondary psychiatric disorders, on the other hand, are psychiatric disturbances caused by skin disease. Depression, anxiety, and social phobias from acne, psoriasis, or alopecia areata are some examples. The morbidity from these diseases is predominantly a consequence of their effect on mental state. As a result, their psychiatric sequelae are often responsive to successful dermatologic therapy.

Cutaneous sensory disorders, like those in the primary psychiatric category, will involve no primary skin changes. Patients may complain of itching, burning, pain, or stinging. Cutaneous sensory disorders may involve a neuropathic etiology.

Major Diagnoses

Several high-yield diagnoses exist within the intersection of dermatology and psychiatry. These include psychotic and delusional disorders, obsessive and impulse-control disorders, depressive disorders, anxiety disorders, and cutaneous sensory disorders. Unfortunately, randomized controlled trials for the specific management of psychocutaneous diseases are sporadic and low-powered when present. Where they are relevant and robust, we will therefore emphasize Canadian guidelines, especially those from the Canadian Network for Mood and Anxiety Treatments (CANMAT) series.⁴⁻⁶

As the following diagnoses can be found within any of the previously described categories, the clinical diagnosis and category remain separate judgments. Treatment should be aimed at the underlying psychopathology, regardless of whether it is primary, secondary, or merely exacerbating skin disease. Neurotic excoriations secondary to depression, psoriasis worsened by depression, and depression secondary to alopecia areata, for example, all warrant a similar therapeutic approach.

Depressive Disorders

Depression is common in our patient population. One review suggests about 30% of patients in the general dermatology practice will have some form of depression. This prevalence compares to 22% in general practice.⁷ A cross-sectional study identified 10% of 384 dermatology patients with major depression.⁸ For many skin conditions, the prevalence may be even higher. In an extensive 2014 systematic review, Dowlatshahi et al. found 19% of psoriasis patients studied met the Diagnostic
and Statistical Manual of Mental Disorders 4th edition (DSM-IV) criteria for major depression. More recently, a 2015 4994-patient European cross-sectional multicenter study of dermatology outpatients reported a 12.7% rate of suicidal ideation (compared to 8.3% in the hospital employees used as controls). Psoriasis had a 17.3% association with suicidal ideation, and two-thirds of these patients responded that their ideation was a direct consequence of their skin condition. Atopic dermatitis, alopecia, urticaria, pruritus, and vitiligo also correspond to lower mood. Degree of itch plays a role, and conversely depression may work to lessen the threshold for pruritus. There are concerns that systemic use of corticosteroids or isotretinoin may increase the risk for depression and suicide. Surprisingly, disease impact does not seem to correlate well with severity, and physicians tend to underestimate the psychological implications of cutaneous disorders.

The CANMAT guidelines for unipolar depression direct first-line therapeutics for major depressive disorder towards any of the second-generation anti-depressants. These include selective serotonin reuptake inhibitors (SSRIs) and selective norepinephrine reuptake inhibitors (SNRIs) such as escitalopram, sertraline, and venlafaxine. Due to tolerability and safety, tricyclic antidepressants (TCAs) are second-line. In depression, combined treatment with both medication and psychotherapy is superior to either alone.

**Anxiety Disorders**

Anxiety disorders are associated with typical physical symptoms and excessive worry over finances, relationships, career, and health. They frequently accompany depression, especially in psoriasis, acne, and atopic dermatitis. Although Dalgard et al. found clinical depression present in 10% of 3635 dermatology outpatients, clinical anxiety was present in 17%. Both acute and chronic anxiety can contribute to skin disease, this link being especially well-documented in the inflammatory dermatoses.

In cases of acute anxiety, benzodiazepine anxiolytics are first-line due to their rapid onset of action. For the chronic management of generalized anxiety disorder, nonetheless, the CANMAT guidelines suggest first-line therapy by means of SSRIs/SNRIs such as sertraline, paroxetine, escitalopram, duloxetine, and venlafaxine, or by means of other agents such as agomelatine and pregabalin. Although second-line agents include other medications such as buspirone and hydroxyzine, the SSRIs and SNRIs are especially useful when anxiety coexists with depression.

**Obsessive-Compulsive (OCD) and Impulse-Control Disorders**

A delineating interview question in the 2015 European Society for Dermatology and Psychiatry (ESDaP) position paper on self-inflicted lesions is the following: “How did these lesions occur?” If self-damage is not denied or kept secret by the patient, this points to an obsessive or compulsive etiology. In the ESDaP classification, insight is the dividing line between this group and the delusional etiologies of self-inflicted skin lesions. Indeed, patients with obsessive or impulsive disorders will often realize the irrational and inappropriate nature of their intrusive thoughts and persistent behaviors. The DSM-5, in contrast, allows for specifiers within the obsessive compulsive and related disorders – these include “good or fair insight,” “poor insight,” and “absent insight/delusional.”

Impulsive behaviors are usually isolated acts of aggression towards one’s self or others. The dermatologically-significant clinical presentations of the impulsive spectrum include cutting, burning, hitting, and scarring. Compulsive behaviors, on the other hand, are repetitive, often ritualistic, and time-consuming or problematic in work, school, or relationships. They are often associated with an obsessive ideation, as in OCD. The compulsive spectrum disorders present with a more chronic dermatologic picture. Persistent ideas, thoughts, or impulses lead to repetitive behaviors such as skin-picking, hair-pulling, or excessive washing. New in the DSM-5 are excoriation (skin-picking) disorder and trichotillomania (hair-pulling). Both are examples of compulsive behaviors. Excoriation disorder involves recurrent skin picking resulting in skin lesions, despite repeated attempts to discontinue the behavior. Excoriation disorder is commonly secondary to acne, traditionally called acne excoriée. Trichotillomania, on the other hand, involves recurrent hair pulling resulting in hair loss, again despite repeated attempts to discontinue. A variety of rituals may accompany trichotillomania, including cutting or shaving, scalp-rubbing, hair-biting, or hair-eating.

In either, Gupta and Gupta also describe the potential for dissociative features, especially when skin picking or hair pulling occurs without preceding tension or full awareness. These patients will deviate from the typical OCD presentation, and present with mindless, automatic picking or pulling without full awareness of the act. Dissociative features are significant as their presence indicates that treatment must go beyond the standard habit-reversal and SSRI therapy. Rather, patients with dissociative features often have a repressive or post-traumatic stress disorder component of their illness. They require stabilization, assessment of suicide risk, and direct referral to psychiatry.

Important to note is the DSM-5 “Obsessive-Compulsive and Related Disorder Due to Another Medical Condition” and specifier “with skin-picking symptoms.” Many dermatologic conditions, especially psoriasis, atopic dermatitis, and prurigo nodularis, can lead to a skin-picking disorder. Picking, in these cases, is often secondary to itch.

Nail biting (onychophagia), nail tearing (onychotillomania), and lip chewing are examples of the DSM-5 “Body-Focused Repetitive Behavior Disorder” within the obsessive and impulse-control disorders. Self-inflicted cheilitis can also occur from repetitive lip licking.

Body dysmorphic disorder (BDD) is also categorized as an obsessive disorder in the context of the DSM-5. It involves a preoccupation with a perceived physical flaw, and by repetitive behaviors surrounding this flaw. These actions can include excessive grooming, mirror-checking, or self-other comparison. In the DSM-5, BDD is no longer coded as a delusional disorder. As in the other obsessive-compulsive and related disorders, patients can have good insight, poor insight, or absent insight accompanied by delusional beliefs. The prevalence is significant, as BDD encompasses 9-15% of dermatology patients, in comparison to only 2.4% of US adults. Patients with BDD have a high proportion of suicidal ideation, and a quarter attempt suicide in their lifetime.
in brachioradial pruritus or postherpetic neuralgia. Formication, itching, burning, or pain. The causes are sometimes neurologic, as in parasitosis in an elegant 2015 paper. The clinical encounter with a patient suffering from delusions of parasitosis, formication in the cutaneous sensory disorders, patients may describe the sensation of bugs crawling on or under the skin, and can be caused by cocaine or amphetamine abuse (called the “cocaine bugs”). Although prolonged formication may sometimes precede delusional parasitosis, formication in itself is a cutaneous sensory rather than a delusional state.

**Psychotic and Delusional Disorders**

In dermatology, the psychotic and delusional disorders most commonly involve what has been historically called monosymptomatic hypochondriacal psychosis. Patients will have an “encapsulated” fixed, false belief and will usually lack any other major psychological disturbance. In contrast to obsessive or compulsive patients, these individuals will lack insight into their condition from the onset of their illness.

The most common psychotic disorder in dermatology involves delusions of parasitosis. Here, patients present with the fixed, false belief that their body is infested with a parasite despite the absence of any objective evidence to suggest infestation. They may pick, scrub, or otherwise self-injure, all in an attempt to rid themselves of this parasite. In the DSM-5, delusional parasitosis falls under the category of delusional disorder, somatic type. The DSM-5 no longer separates delusional disorder from shared delusional disorder, traditionally called folie à deux.

Other psychotic disorders in dermatology include delusions of bromosis, in which patients believe that their body emits a strong foul odor, and delusions of dysmorphosis, considered an extreme end of the BDD spectrum in the DSM-IV. Although the DSM-5 categorizes BDD as predominantly obsessive rather than delusional, in clinical reality the distinction between obsession without insight and true delusion is frequently unclear.

Standard treatment for the psychotic and delusional disorders involves antipsychotics such as pimozide, risperidone, and olanzapine. For delusional disorders, outcomes do not seem to vary between first and second-generation antipsychotics. The challenge, nonetheless, lies in building adequate rapport for the patient to willingly embrace treatment. Often these patients will have had visited many providers, frequently having their concerns dismissed. Empathy is the key, as confrontation can be a barrier to treatment. It is equally important, nonetheless, to avoid confirming the patient’s delusion. Expanding on the above, Patel and Koo suggest verbatim how dermatologists may approach the clinical encounter with a patient suffering from delusions of parasitosis in an elegant 2015 paper.

**Cutaneous Sensory Disorders**

In the cutaneous sensory disorders, patients may describe itching, burning, or pain. The causes are sometimes neurologic, as in brachioradial pruritus or postherpetic neuralgia. Formication, on the other hand, describes the sensation of bugs crawling on or under the skin, and can be caused by cocaine or amphetamine abuse (called the “cocaine bugs”). Although prolonged formication may sometimes precede delusional parasitosis, formication in itself is a cutaneous sensory rather than a delusional state.

**Nonpharmacologic Therapies**

Psychopharmacology is only one aspect of the ideal approach to psychodermatology. Cognitive behavioral therapy, for example, has shown excellent efficacy in specific disease states such as depression and OCD. Combined pharmacotherapy and psychotherapy is often superior to either alone, as the CANMAT guidelines suggest in acute major depressive disorder. Even though the combination is not yet evidence-based for many other psychopathologies, most psychiatrists will offer a combination of psychotherapy and medication. Other nonpharmacologic modalities are not disease specific, but nonetheless offer global stress reduction, direct psychophysiological effects, enhanced compliance, and as a result excellent symptom improvement. These include interpersonal therapy, bibliotherapy, relaxation training, behavioral activation, among others. Some have suggested that dermatologists align themselves with a skin-emotion specialist, be it a psychiatrist, psychologist, nurse practitioner, counselor, or social worker.

**Conclusion**

Empathy, expectation management, and cheerleading are aspects of the clinical encounter that can foster a positive therapeutic relationship with a patient presenting with a psychodermatological complaint. Dermatologists ought to be mindful of the potential for meaningful improvements in quality of life by addressing the psychiatric dimension of skin disease.

**References**

**Services**

**Update on Drugs**

<table>
<thead>
<tr>
<th>Name/Company</th>
<th>Approval Dates/Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Betamethasone dipropionate 0.05% spray Sernivo™</strong></td>
<td>Promius Pharma</td>
</tr>
<tr>
<td><strong>Dapsone 7.5% gel Aczone®</strong></td>
<td>Allergan plc.</td>
</tr>
<tr>
<td><strong>Calcipotriol + betamethasone dipropionate foam Enstilar®</strong></td>
<td>Leo Pharma</td>
</tr>
<tr>
<td><strong>Botulinum toxin type A for injection (incobotulinumtoxinA) Bocouture®</strong></td>
<td>Merz Pharma</td>
</tr>
<tr>
<td><strong>Ixekizumab SC injection Tilds®</strong></td>
<td>Eli Lilly and Company</td>
</tr>
<tr>
<td><strong>Infliximab-dyyb for IV infusion Inflectra™ Hospira/Celltrion</strong></td>
<td></td>
</tr>
<tr>
<td><strong>SD Cream Pruridexin™</strong></td>
<td>Adcremex™ Cipher Pharmaceuticals</td>
</tr>
</tbody>
</table>

**In February 2016, the US FDA approved this topical corticosteroid spray formulation containing betamethasone dipropionate 0.05% for the treatment of mild to moderate plaque psoriasis in patients 18 years of age or older.**

**In February 2016, the FDA granted marketing approval to dapsone 7.5% gel for the topical treatment of acne in patients 12 years of age and older. This once daily topical agent treats both inflammatory and non-inflammatory acne with a new concentration of dapsone.**

**In February 2016, Health Canada approved cobimetinib (MEK-inhibitor) for use in combination with vemurafenib (BRAF-inhibitor) as an oral treatment of patients with unresectable or metastatic melanoma with a BRAF V600 mutation. Combined inhibition of BRAF and MEK is thought to improve outcomes in melanoma by preventing or delaying the onset of resistance seen with BRAF inhibitor use alone.**

**The European regulatory authorities approved this formulation of botulinum toxin type A in March 2016 for the treatment of upper facial lines, including horizontal frown lines, lateral periorbital lines and glabellar frown lines. Bocouture® is the only neurotoxin approved in Europe for the simultaneous treatment of upper facial lines. It has been available in the UK since 2008 under the tradename Xeomin®, which is licensed for blepharospasm and cervical dystonia. Cosmetic use in the UK was granted in July 2010 and is marketed for this indication under the brand name Bocouture®.**

**Scientific approval in the EU of this fixed combination of calcipotriol/betamethasone dipropionate 50 µg/g / 0.5 mg/g was granted in March 2016 for the treatment of psoriasis vulgaris in patients 18 years of age or older.**

**The FDA approved ixekizumab injection 80 mg/mL in March 2016 for the treatment of moderate-to-severe plaque psoriasis in adult patients who are candidates for systemic therapy or phototherapy. This humanized monoclonal antibody specifically targets interleukin (IL)-17A, a protein that plays a role in driving the underlying inflammation in psoriasis.**

**In April 2016, the FDA approved Inflectra™ for multiple indications. Inflectra™ is biosimilar to Janssen Biotech’s Remicade® (infliximab), which was originally licensed in 1998. Approved uses include chronic severe plaque psoriasis, psoriatic arthritis, rheumatoid arthritis, ankylosing spondylitis, Crohn’s disease, and ulcerative colitis.**

**In April 2016, the Natural and Non-Prescription Health Products Directorate of Health Canada approved SD Cream and AD Cream. Additionally, European approval of Helicin® Pruritis SD Cream (Pruridexin®) was granted in March 2016 as a Class III medical device. In Canada, the SD Cream is a barrier-repair cream for the management and relief of the signs and symptoms of seborrheic dermatitis (e.g., erythema, scaling and pruritis). AD Cream is for the management and relief of the signs and symptoms of atopic and contact dermatitis (e.g., erythema, scaling and pruritis).**