

## Psoriasis and the Pregnant Woman: What are the Key Considerations?

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### ABSTRACT

*Pregnancy is characterized by multiple physiologic changes. During the entire gestational period, both mother and infant are vulnerable to a variety of external and internal factors. Maternal disease, use of certain medications, drugs, alcohol, smoking, and radiation exposure can have devastating effects on the fetus. Pregnancy-related complications in women with psoriasis can be caused by both the disease and the treatment. The response of the maternal placenta to psoriasis-induced inflammation and comorbid conditions, such as obesity, hypertension, and depression, may also influence the pregnancy. Herein, we review the relationship between psoriasis and undesirable pregnancy outcomes.*

**Key words:** comorbidities, complications, drug therapy, pregnancy, psoriasis, risk factors

### Introduction

Pregnancy is a unique physiologic state characterized by an array of significant changes in the endocrine, vascular, and respiratory systems. These changes facilitate fetal growth and development and prepare the woman's body for labor and delivery. During the first trimester of pregnancy (weeks 0-13), the developing embryo undergoes organogenesis and is especially susceptible to injury from systemic maternal diseases, medications, drugs, alcohol, and smoking. During this period many pregnant women are often unaware that they are even pregnant, and therefore do not actively minimize risks to the fetus.<sup>1</sup> This may include women with chronic diseases, such as those with moderate to severe psoriasis, who require multiple drugs for treatment.

Psoriasis is an autoimmune inflammatory skin disease with manifestations resulting from a complex interplay between genetics and the environment. The incidence of psoriasis is bimodal, with one peak between the ages of 15-30 years and a second between 50-60 years.<sup>2,3</sup> The average age of diagnosis in women is 28, a prime age for pregnancy.<sup>3,4</sup> Annually, there are approximately 65,000-107,000 births to women with psoriasis, of whom 9,000-15,000 have moderate to severe disease.<sup>2</sup>

Psoriasis lesions are well-circumscribed, erythematous plaques with a fine silvery scale; they predominate on the scalp and extensor surfaces, yet can occur anywhere on the body; there may also be nail changes. The severity of the condition is determined

by two major criteria: 1) the extent of body surface area (BSA) involved and 2) the location of the lesions (for example, if psoriatic plaques are present on the palms and soles, it is considered severe, regardless of percentage of BSA involvement). In general, mild psoriasis occurs when lesions are limited to < 3% BSA, moderate psoriasis with 3-10% BSA, and severe psoriasis with >10% BSA. Quality of life issues for the patient also determine severity. While mild psoriasis can typically be controlled with topical treatments, moderate to severe psoriasis may require systemic therapy.

The management of psoriasis in pregnant women is challenging, since the physician and patient must balance teratogenic risks associated with certain drug therapies to potential adverse pregnancy outcomes from uncontrolled skin inflammation and excess cytokines inherent with the disease process. There is very little data detailing the effects of psoriasis on pregnancy outcomes.<sup>2,4-6</sup> Herein, we explore potential direct and indirect effects of psoriasis on pregnancy and the effects of pregnancy on psoriasis.

### Direct Effects of Psoriasis on Pregnancy

In general, inflammatory/autoimmune diseases such as rheumatoid arthritis, inflammatory bowel disease, systemic lupus erythematosus, and psoriasis have been shown to be associated with low birth weight (LBW), preterm birth, and abortions.<sup>5,7</sup> Autoimmune inflammation in psoriasis results from dysfunctional T helper cells with a concomitant amplification

of pro-inflammatory cytokines (most notably TNF-alpha, IL1 and IL6). Excess cytokines yield endothelial dysfunction with resulting systemic and placental vasculopathy through induction of platelet aggregation, intermittent vasospasm, and activation of the clotting system.<sup>5,8</sup> Placental vasculopathy has been postulated to contribute to LBW infants.<sup>5</sup> LBW is also a complication of preeclampsia, which is similarly associated with an activated inflammatory state and increased levels of the same cytokines seen in psoriasis (CRP, TNF-alpha and IL6).<sup>8-10</sup> There is conflicting data regarding the correlation between psoriasis during pregnancy and infant birth weight.<sup>5-7</sup> Yang et al studied 1,436 mothers with psoriasis compared to 11,704 mothers without psoriasis, and found that LBW was associated only with severe psoriasis (defined as any mother who had received photochemotherapy or systemic therapy within the 2 years prior to delivery).<sup>5</sup> In contrast, Cohen-Barak et al analyzed 68 pregnant women, but found that mothers with moderate to severe psoriasis were more likely to give birth to large infants when compared with controls.<sup>7</sup> This group found psoriasis to be associated with a higher risk for spontaneous and induced abortions, which is also seen in inflammatory conditions including rheumatoid arthritis and systemic lupus erythematosus.<sup>7</sup>

## Indirect Effects of Psoriasis on Pregnancy

### Comorbidity Induced Adverse Effects

The stress associated with chronic, relapsing diseases may affect mental health, increasing the tendency for alcohol misuse, depression, weight gain, and smoking. Psoriasis is also associated with higher rates of comorbid systemic conditions including diabetes mellitus (DM), cardiovascular disease (atherosclerosis, congestive heart failure, and myocardial infarction), obesity, and metabolic syndrome (consisting of obesity, high blood sugars, high triglyceride levels, low high-density lipoprotein, and hypertension). Obesity and hypertension have been shown to be at least twice as common in patients with psoriasis.<sup>4,11</sup> Pregnant women with psoriasis are more likely to be overweight/obese, depressed, smoke in their first trimester, and are also less likely to take prenatal vitamins or supplements.<sup>4</sup>

Both the comorbid conditions associated with psoriasis and the drugs used to treat them may be harmful to the developing fetus. Hypertension (HTN) is known to be associated with LBW secondary to placental insufficiency, perinatal mortality, and preterm delivery, in addition to increased risk for acute maternal morbidities.<sup>12</sup> The drugs commonly used to treat HTN, such as angiotensin-converting enzyme inhibitors and angiotensin receptor blockers, can be teratogenic.<sup>13,14</sup> DM is associated with increased neonatal mortality and multiple morbidities including, fetal macrosomia, post-natal hypoglycemia, and congenital malformations including transposition of the great vessels.<sup>15</sup> Furthermore, pregnancy has been shown to hasten the progression of DM; healthy women may even develop diabetes only during pregnancy, which is known as gestational DM.<sup>15</sup> Alcohol misuse may result in fetal alcohol syndrome and LBW. Maternal consequences of depression include inadequate weight gain, insufficient utilization of prenatal care, and increased substance abuse, whereas fetal consequences can include premature birth, LBW, decreased Apgar scores, and smaller head circumference.<sup>16</sup> Obesity has been associated with macrosomia,

low Apgar scores, and premature birth.<sup>4</sup> Smoking may increase the risk for oral clefts and reduced birth weight.<sup>4</sup>

### Treatment Induced Adverse Effects

Little evidence exists to delineate the effects of psoriatic medications on human pregnancy due to ethical implications associated with investigating potentially teratogenic medications.<sup>1</sup> General guidelines are based on retrospective data and on cases in which a woman may have used a questionable medicine without yet realizing she was pregnant. Mild psoriasis can usually be adequately treated with topical medications, while severe psoriasis may require systemic treatment. Limited amounts of topical preparations including corticosteroids, calcipotriene, coal tar, and anthralin appear to be safe. There is a low likelihood for significant systemic absorption with these topical preparations if used in conservative application patterns.<sup>1,5</sup> The risk for potential teratogenicity increases in a dose-dependant manner as systemic absorption increases. The factors that increase systemic absorption include prolonged duration of treatment, large amounts of medication applied, a compromised epidermal barrier, and occlusion.<sup>1</sup>

Systemic medications used for psoriasis unresponsive to topical therapies include acitretin, methotrexate, mycophenolate mofetil, and biologics such as adalimumab, alefacept, etanercept, infliximab, and ustekinumab. Most of the systemic antipsoriatic therapies are associated with significant toxic effects to the fetus and should be avoided during pregnancy. Acitretin (an oral retinoid) is strictly prohibited before or during pregnancy since it can cause a classic retinoid syndrome, consisting of well-characterized craniofacial, cardiac, thymic, and CNS malformations.<sup>1</sup> Furthermore, acitretin can linger for over 2 months after the last dose, so patients should stop this drug months before attempting to conceive.<sup>1</sup> Methotrexate is an anti-metabolite that is associated with a specific constellation of prenatal growth deformities, including growth retardation, large fontanelles, craniosynostosis, ocular hypertelorism, micrognathia, limb abnormalities, and developmental delay; these effects are dose-related. Mycophenolate mofetil interferes with DNA and RNA synthesis, and case reports indicate that it can cause microtia or anotia, cleft lip/palate and heart defects. Systemic corticosteroids are not commonly used for psoriasis; however, they remain the best available treatment for a rare condition, known as impetigo herpeticiformis, a form of pustular psoriasis seen in pregnancy.<sup>17</sup> The side-effects of systemic steroids have mostly been studied in pregnant patients with asthma and they include orofacial clefts, intrauterine growth restriction, and suppression of the hypothalamic-pituitary axis.<sup>1</sup> There is very limited data with regard to the biologics, but infliximab has been associated with congenital malformations in two infants and death in a third due to uncontrollable intracranial and pulmonary bleeding.<sup>1,18</sup>

Phototherapy with broad-band (290-320 nm) ultraviolet B (UVB) and narrow-band UVB (311-312 nm) appear to be safe during pregnancy.<sup>1</sup> The safety of systemic PUVA with psoralens is unknown, although mutagenic potential has been shown in rat studies; however, topical PUVA limited to small areas might be safe. Cyclosporin A in pregnant organ transplant recipients have failed to show an increased risk to the fetus<sup>1</sup> and may therefore be an option in pregnant psoriatic patients.

## Effects of Pregnancy on Psoriasis

Pregnancy may influence the severity of psoriasis.<sup>6,19</sup> In fact, psoriasis often improves during pregnancy. Boyd et al reported on a study of 90 women with psoriasis, who responded to a questionnaire regarding the condition of their psoriasis during pregnancy.<sup>6</sup> Seventy-seven percent of these women noticed a change in their psoriasis, the majority of whom (63%) experienced improvement; within 4 months of giving birth, however, 88% of the women subsequently developed a "post-partum flare" of their psoriasis. Similarly, Murase et al found that 55% of women noted improvement in their psoriasis during pregnancy and 65% experienced worsening of their psoriasis post-partum.<sup>19</sup> The patients with greater than 10% BSA who reported improvement during pregnancy noted that lesions decreased on average by 84%.<sup>19</sup> Furthermore, the authors found that estrogen, but not progesterone, was associated with changes in psoriasis; they attributed the improvement in psoriasis to the high ratio of estrogen to progesterone.<sup>19</sup> The authors hypothesized that the alterations in immunity (the immune response shifts from TH1 to TH2 dominance) due to hormonal changes in pregnancy, leads to the improvement in psoriasis, as previously shown in other TH1 mediated autoimmune diseases (i.e., rheumatoid arthritis and multiple sclerosis).<sup>19</sup> While the exact mechanism is still not understood, it appears that psoriasis is more likely to improve than worsen during pregnancy with a post-partum flare.

## Conclusions

The extent of the potential effects that psoriasis can have on pregnancy is variable. When possible, pregnant women should modify their behaviors and treatments to decrease any risk to themselves and their unborn children. Registries such as the International Psoriasis Council - project on pregnancy and psoriasis<sup>2</sup> and the OTIS Autoimmune Diseases in Pregnancy Project<sup>4</sup> are in the process of compiling more extensive data for this population. As data from these registries becomes more readily available, we will better understand the true implications of pregnancy on psoriasis and of psoriasis on pregnancy. Treatment plans can subsequently be developed that balance the risks from therapy versus the harmful effects of psoriasis and its associated comorbidities.

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# Newer Approaches in Topical Combination Therapy for Acne

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## ABSTRACT

*Acne vulgaris is a common chronic inflammatory cutaneous disease involving the pilosebaceous unit. Its pathophysiology is multifactorial and complex, including obstruction of the pilosebaceous unit due to increased sebum production, abnormal keratinization, proliferation of Propionibacterium acnes (P. acnes), and inflammation. Topical agents are the most commonly used therapy for acne. First generation topicals mainly consist of single agent retinoids, benzoyl peroxide (BPO) and antibacterials that target comedones, P. acnes, and inflammation. Novel topical therapies include combination products with advanced vehicle formulations that target multiple acne pathophysiologies and offer simplified treatment regimes. For example, the combination of clindamycin and tretinoin in a unique vehicle formulation allows for progressive follicle penetration and decreased irritation, resulting in increased efficacy. Furthermore, adapalene or clindamycin with BPO combinations target comedones, inflammation, and P. acnes synergistically. These newer combination products have the potential to increase both efficacy and patient adherence when compared with single agent treatment.*

**Key words:** acne vulgaris, adapalene, benzoyl peroxide, clindamycin, retinoid, topical combination therapies, tretinoin

## Introduction

Acne vulgaris is a common chronic inflammatory cutaneous disease involving the pilosebaceous unit. Acne is a common worldwide skin disease that affects about 85% of individuals between the ages of 12-24 years.<sup>1</sup> The pathophysiology includes androgen-mediated stimulation of sebaceous gland activity, abnormal keratinization leading to follicular plugging (comedo formation), proliferation of *P. acnes* within the follicle, and inflammation.<sup>2</sup> Genetic factors, stress, and possibly diet may influence the development of acne.<sup>2</sup> Acne can cause a considerable amount of emotional distress and physical discomfort, thus medical treatment must be accompanied by patient counseling and education, which can contribute to improved self-esteem and adherence to therapy.

## Treatment of Acne Vulgaris

Treatment is targeted to one or multiple pathogenic element(s). Topical therapies remain the most common and effective treatment option for mild to moderate acne and also for maintenance therapy for all levels of acne severity.<sup>1</sup> Retinoids (e.g., adapalene, tazarotene, tretinoin) act to reduce dyskeratosis at the pilosebaceous unit, inhibit the formation of microcomedones, and have mild anti-inflammatory effects.<sup>3</sup> Advanced vehicle formulations in the form of emollient cream and microsphere gel reduce irritation and enhance efficacy.<sup>4</sup> Antimicrobials (e.g., benzoyl peroxide (BPO), clindamycin, erythromycin, sodium sulfacetamide) have bactericidal or bacteriostatic action against *P. acnes*. Anti-inflammatory agents such as dapsone act through direct inhibition of leukocyte trafficking and the generation of chemical mediators of inflammation by leukocytes and/or potential interference with bacterial synthesis, thereby altering the levels and activity of *P. acnes*.<sup>5</sup>

Combination products (e.g., BPO + antibiotic, retinoid + antibiotic) target multiple pathogenic factors, which are

complementary and synergistic in mechanisms of action. It also simplifies the treatment regimen and reduces dosing frequency.<sup>3</sup> BPO + clindamycin combination products have been widely studied, a recent meta-analysis showed that BPO 2.5% + clindamycin is comparable to BPO 5%+ clindamycin in reducing acne lesion counts.<sup>6</sup> Investigators suggest that BPO 2.5% + clindamycin may in fact be more effective in treating non-inflammatory acne lesions possibly because of decreased irritation, thereby encouraging treatment follow-through by patients.<sup>6</sup> Furthermore, combination preparations were found to be superior in treating acne lesions compared with using either agent alone.<sup>6</sup>

The addition of BPO to topical antibiotics and retinoids in managing mild to moderate acne reduces the incidence of bacterial resistance. This bacteriostatic agent is efficacious against both nonresistant and resistant *P. acnes* strains. BPO acts by producing free-radical oxygen that oxidizes bacterial proteins and exerting a mild keratolytic effect on comedones. In more severe acne, when oral antibiotics are necessary, BPO may contribute to suppressing the emergence of resistant *P. acnes* strains.<sup>7</sup>

## Newer Fixed-dose Dual-agent Therapies

### Clindamycin Phosphate 1.2% + Tretinoin 0.025% Gel (Ziana®, Biacna™)

This fixed-dose combination gel was approved by the US FDA in November 2006 and sanctioned by Health Canada in December 2010 for the once-daily treatment of acne vulgaris in patients ≥12 years of age.<sup>8</sup> It combines the anti-inflammatory and antibacterial actions of clindamycin with the comedolytic and anticomedogenic actions of tretinoin<sup>5</sup> to target several mechanisms in the pathogenesis of acne. Multiple studies have demonstrated significantly greater reductions in comedones and inflammatory lesions by 12 weeks compared with either agent alone or vehicle (Table 1).

Study (12 weeks)	Comparative Treatments	Study Design	Major Results	Adverse Effects
Leyden et al. <sup>9</sup> n=2219	CTG vs. monotherapy with clindamycin, tretinoin or vehicle	Two randomized, double-blind, multicenter, active drug- and vehicle-controlled	CTG group showed superior efficacy in treating inflammatory and noninflammatory lesions compared with monotherapy or vehicle alone	Well tolerated overall; 87.6% of participants reported no adverse events
Yentzer et al. <sup>10</sup> n=21	CTG vs. application of two separate generic subcomponents	Single-blind, prospective, single center, randomized, controlled	CTG group showed a significant reduction in total lesions over length of study; both groups experienced improvement in mild to moderate acne	Treatment was well tolerated in both groups
Richter et al. <sup>11</sup> n=152	CTG vs. 0.025% tretinoin gel	Randomized, double-blind, multicenter	CTG was superior to tretinoin in papular and inflammatory lesions and in overall acne severity	Less burning reported with CTG
Zouboulis et al. <sup>12</sup> n=206	CTG vs. clindamycin lotion	Multicenter, single-blind, randomized, comparative	CTG was more effective at reducing acne lesions than clindamycin monotherapy	More erythema and desquamation reported with CTG

**Table 1:** Studies comparing combination clindamycin 1.0%-1.2%-tretinoin 0.025% gel (CTG) to monotherapy with clindamycin, tretinoin, or vehicle.<sup>13</sup> n = sample size of study population.

Recommended application is once-daily at bedtime (preferred) or morning (as the vehicle delivery formulation provides for the photostability of tretinoin).<sup>8</sup> Patients should be instructed to use only a pea-sized amount. The vehicle is an alcohol free aqueous gel containing a unique formulation of solubilized clindamycin phosphate and stable combinations of both solubilized and crystalline tretinoin.<sup>14</sup> The crystalline suspension allows for tretinoin to be released in a rate-controlled manner, thereby resulting in slower and progressive follicular penetration and increased tolerability.<sup>14</sup> The long-term efficacy and favorable safety profile was shown in a 52-week study, with the vast majority of participants not experiencing certain local cutaneous reactions, such as no itching (92%), no burning (91%), and no stinging (94%).<sup>15</sup> The most frequent adverse events were acne (29/442; 7%, usually a flare), sunburn (12/442; 3%), hypersensitivity (7/442; 2%), contact dermatitis (5/442; 1%), and application-site desquamation (3/442; 1%).<sup>15</sup> Common class-wide side-effects from topical retinoids can include peeling, redness, dryness, itching, and photosensitivity. Tretinoin increases the skin's sensitivity to UV light, therefore patients should be reminded to avoid excessive or unnecessary sun exposure and wear sunscreen and protective clothing daily. The contraindications include Crohn's, ulcerative colitis, colitis with previous antibiotic use, and use of concomitant erythromycin containing products; it has a US FDA pregnancy category C classification.<sup>8</sup>

### Adapalene (0.1%) + Benzoyl Peroxide (2.5%) Gel (Epiduo®, Tactuo™)

This combination gel was approved by the US FDA in January 2009 and approved by Health Canada in May 2011. It is the first fixed-dose retinoid-BPO treatment that has been developed as a convenient once-daily formulation. Adapalene has comedolytic, anticomedogenic, and anti-inflammatory properties and BPO is a

highly lipophilic oxidizing agent with bactericidal and keratolytic effects.<sup>16</sup> BPO lowers the incidence of bacterial resistance compared with other topical antibiotics and can be used for the long-term management of acne. The complementary modes of action address three pathophysiologic processes of acne: abnormal keratinization leading to follicular plugging (comedo formation), proliferation of the bacterium *P. acnes* within the follicle, and inflammation. Multiple studies have demonstrated significantly greater reductions in comedones and inflammatory lesion by 12 weeks compared with either agent alone or vehicle (Table 2).

Studies have shown that this adapalene + BPO combination has a comparable safety profile to adapalene monotherapy.<sup>18</sup> The long-term tolerability and safety of adapalene 0.1% + BPO 2.5% gel was evaluated in 452 acne subjects over 12 months, with 327 patients completing the study (72%).<sup>21</sup> No subjects discontinued due to lack of efficacy, while 2% discontinued due to adverse events. Overall, treatment was well tolerated with mean scores for local intolerance (comprising erythema, dryness, scaling, and burning/stinging) reported as mild or less in all study visits. The most common adverse event was dry skin (17%). The highest irritation scores were recorded in the first week and subsequently declined thereafter. Adapalene is stable when combined with BPO in the presence or absence of light.<sup>15</sup> It has been assigned a pregnancy category C rating.

### Patient Adherence

Acne is a chronic disease and poor medication adherence is a major contributor to treatment unresponsiveness.<sup>10</sup> Convenience and decreased complexity of treatment encourage patient adherence. Effective yet well tolerated treatment regimens offering simplified dosing suited to a patient's lifestyle are

Study (12 weeks)	Comparative Treatments	Study Design	Major Results	Adverse Effects
Gollnick et al. <sup>17</sup> n=1670	Adapalene-BPO vs. monotherapy of either drug alone and gel vehicle	Randomized, double-blind, controlled	Adapalene-BPO showed significantly greater efficacy than monotherapies	Well-tolerated, with comparable tolerability to adapalene monotherapy
Gold et al. <sup>18</sup> n=1429	Adapalene-BPO vs. monotherapy of either drug alone and gel vehicle	Multicenter, randomized, double-blind, parallel-group, active- and vehicle-controlled	Adapalene-BPO showed higher success rate and reduction of acne lesions than other groups	Comparable safety of adapalene-BPO to monotherapies and gel vehicle
Thiboutot et al. <sup>19</sup> n=517	Adapalene-BPO vs. monotherapy of either drug alone and gel vehicle	Randomized, double-blind, controlled	Adapalene-BPO was considerably more effective than monotherapies; significant reduction in lesion counts at 1 week	Similar adverse event frequency and tolerability profile for combination gel vs. adapalene monotherapy
Poulin et al. <sup>20</sup> n=243	Adapalene-BPO vs. vehicle	Multicenter, randomized, double-blind, controlled	Significantly higher lesion maintenance success rate for inflammatory and noninflammatory lesions with adapalene-BPO	Adapalene-BPO was safe and well-tolerated

**Table 2:** Studies comparing adapalene-BPO combination therapy to monotherapy with adapalene, BPO, and vehicle.<sup>13</sup>

more likely to optimize adherence and outcomes. Patients most commonly attribute frustration with the therapeutic regimen and forgetfulness as reasons for failure to use prescribed medication.<sup>22</sup>

## Conclusion

Successful topical treatment of acne depends on appropriate agent selection based on patient-specific acne severity and tolerance, adherence, and adequate follow-up. The advent of combinational therapeutic products provide increased efficacy by targeting multiple pathophysiologic processes. Additional advantages of using combination therapy include reduced complexity of treatment regimen and convenient once-daily dosing. The future of topical acne treatment holds the promise of more novel uses of conventional anti-acne agents formulated with advanced vehicle delivery systems that offer less side-effects, increased tolerance, dosing simplicity, and improved efficacy.

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| <a href="http://AcneGuide.ca">AcneGuide.ca</a>                   | <a href="http://BotoxFacts.ca">BotoxFacts.ca</a>         | <a href="http://ColdSores.ca">ColdSores.ca</a>                             | <a href="http://CosmeticProcedureGuide.ca">CosmeticProcedureGuide.ca</a> |
| <a href="http://DermatologyCare.ca">DermatologyCare.ca</a>       | <a href="http://EczemaGuide.ca">EczemaGuide.ca</a>       | <a href="http://FungalGuide.ca">FungalGuide.ca</a>                         | <a href="http://GenitalWarts.ca">GenitalWarts.ca</a>                     |
| <a href="http://HandEczema.ca">HandEczema.ca</a>                 | <a href="http://HerpesGuide.ca">HerpesGuide.ca</a>       | <a href="http://Lice.ca">Lice.ca</a>                                       | <a href="http://MildCleanser.ca">MildCleanser.ca</a>                     |
| <a href="http://MohsSurgery.ca">MohsSurgery.ca</a>               | <a href="http://PsoriasisGuide.ca">PsoriasisGuide.ca</a> | <a href="http://PsoriaticArthritisGuide.ca">PsoriaticArthritisGuide.ca</a> | <a href="http://RosaceaGuide.ca">RosaceaGuide.ca</a>                     |
| <a href="http://SkinCancerGuide.ca">SkinCancerGuide.ca</a>       | <a href="http://SkinCoverup.com">SkinCoverup.com</a>     | <a href="http://Sweating.ca">Sweating.ca</a>                               | <a href="http://StaphInfection.com">StaphInfection.com</a>               |
| <a href="http://UnwantedFacialHair.ca">UnwantedFacialHair.ca</a> |  |  |  |

## Medical professional sites:

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|--|--|--|--|
| <a href="http://Dermatologists.ca">Dermatologists.ca</a>       | <a href="http://PASItraining.com">PASItraining.com</a>           | <a href="http://SkinCareGuide.ca">SkinCareGuide.ca</a> | <a href="http://SkinPharmacies.ca">SkinPharmacies.ca</a> |
| <a href="http://SkinTherapyLetter.ca">SkinTherapyLetter.ca</a> | <a href="http://SkinTherapyLetter.com">SkinTherapyLetter.com</a> |  |  |

## Social networking sites for patients and health care professionals:

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| <a href="http://GenitalWartsPatients.com">GenitalWartsPatients.com</a> | <a href="http://PsoriasisPatients.com">PsoriasisPatients.com</a> |
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## Update on Drugs

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Name/Company	Approval Dates/Comments
<b>IncobotulinumtoxinA injection</b> <i>Xeomin</i> ® Merz Aesthetics	The US FDA has approved this injectable botulinum toxin type A in July 2011 for the temporary improvement in the appearance of moderate to severe glabellar lines produced by repeated muscular action of the corrugator supercili and procerus muscles in adult patients.
<b>Vemurafenib tablets</b> <i>Zelboraf</i> ™ <i>cobas</i> ® 4800 BRAF V600 Mutation Test Genentech/Roche Group Plexxikon/Daiichi Sankyo Group	The US FDA approved this oral, small molecule, kinase inhibitor in August 2011 for the treatment of metastatic or unresectable melanoma. Therapy is specifically indicated for patients with BRAFV600E mutation-positive melanoma. This BRAF enzyme inhibitor was approved with a companion diagnostic called the <i>cobas</i> ® 4800 BRAF V600 Mutation Test, which determines a patient's eligibility for treatment. Vemurafenib blocks the function of the V600E-mutated BRAF protein. The BRAF protein regulates cell growth, but is mutated in about 50% of patients with late-stage melanoma. Safety and efficacy were established in a single international trial of 675 patients with late-stage melanoma with the BRAFV600E mutation who had not received prior therapy. Patients who received vemurafenib had a 74% reduced risk of disease progression or death compared with those on chemotherapy (dacarbazine), median progression free survival was 5.3 months vs. 1.6 months, respectively. Common reported side-effects of vemurafenib include joint pain, rash, hair loss, tiredness, sunburn or sun sensitivity, nausea, itching, or warts.  <i>In June 2011, Roche announced that it was collaborating with Bristol-Myers Squibb to investigate combination therapy to improve outcomes with vemurafenib and ipilimumab (Yervoy™), an intravenously administered human monoclonal antibody that blocks a T-lymphocyte antigen (CTLA-4), which was FDA-approved in March 2011 for the treatment of metastatic melanoma.</i>
<b>Icatibant injection</b> <i>Firazyr</i> ® Shire Human Genetic Therapies	The US FDA approved this selective B2 bradykinin receptor antagonist for the treatment of acute attacks of hereditary angioedema (HAE) in adults ≥18 years of age. Upon recognition of an HAE attack, patients may self-administer through an injection in the abdominal area. In three clinical trials, the reported median time for onset of symptom relief was 2 hours compared with almost 20 hours with placebo. The most common reported side-effects were injection site reactions, fever, increased liver enzymes, dizziness, and rash.

### Drug News

In August 2011, the US FDA advised the public that chronic, high doses (400-800 mg/day) of the antifungal drug fluconazole may be associated with a rare and distinct set of birth defects in infants whose mothers received treatment during the first trimester of pregnancy. This risk does not appear to be linked with a single, low dose of fluconazole 150 mg used to treat vaginal yeast infection (candidiasis). As a result, the pregnancy category for fluconazole indications (other than vaginal candidiasis) has been changed from category C to category D; single dose fluconazole 150 mg used to treat vaginal candidiasis remains unchanged at category C. More information is available at: <http://www.fda.gov/Drugs/DrugSafety/ucm266030.htm>