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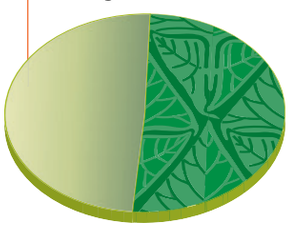
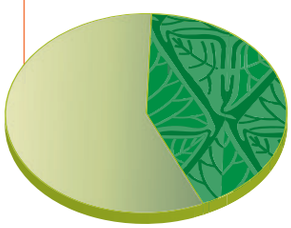
Percentage of adults with eczema who reported using alternative medicine



51%

Source: Jensen P. *Acta Derm Venereol.* 1990;70(5):421-424

Percentage of children **with atopic dermatitis** who have used alternative medicine



43%

Source: Hughes R, et al. *Pediatr Dermatol.* 2007;24(2):118-120

the Alternative

The lure of unconventional therapies may signal a therapeutic gap

By Ilya Petrou, M.D. | SENIOR STAFF CORRESPONDENT

THE FIELD of alternative medicine is increasing in popularity among dermatologists in the United States, as well as among their patients. Though conventional treatment approaches can be effective in quelling the symptoms associated with atopic dermatitis and other cutaneous diseases and conditions, "natural" remedies can also be of significant value in carefully selected patients.

Alternative medicine largely remains a frowned upon fringe field in medicine. According to Peter Lio, M.D., however, many dermatologists are increasingly showing an interest in alternative approaches and realize their potential healing benefits,

ALTERNATIVES see page 28

→ PRURITUS → CUTANEOUS ONCOLOGY → PERFORMANCE MEASUREMENT & OUTCOMES

→ RESEARCH TARGETS THREE KEY GAPS

By Lisa B. Samalonis | STAFF CORRESPONDENT

THE AMERICAN ACADEMY OF DERMATOLOGY (AAD) COUNCIL on Science and Research's Research Agenda work group has identified three key areas — pruritus, cutaneous oncology, and performance measurement and outcomes — to target in the future for continuing research in the dermatology specialty.

The group surveyed and met with key leaders in dermatology research, including physician stakeholders, patient advocacy groups, and industry representatives to determine several priority research areas and then set out to develop a plan for promoting and

RESEARCH see page 31

SEPT. 23, 2013

COMPLIANCE

Proactive steps can protect you, your practice from big financial hits

By Jeffrey Bendix | SENIOR EDITOR

THE FINAL "OMNIBUS" Health Insurance Portability and Accountability Act (HIPAA) rule announced earlier this year includes numerous provisions that, if violated, could result in a medical practice being fined thousands of dollars. Fortunately, there are steps doctors can take to ensure both that they are compliant with HIPAA and to protect themselves financially if they are not.

Although the original HIPAA legislation affects many aspects of medical practices, the primary focus of the Omnibus rule is on strengthening HIPAA's privacy and security protections for patients' protected health information (PHI). That's because the Omnibus rule revisions stem from the 2009 Health Information Technology for Economic and Clinical Health (HITECH) Act, explains Robert Tennant, M.A., senior policy adviser for the Medical Group Management Association-American College of Medical Practice Executives (MGMA-ACMPE).

"The HITECH Act was the same legislation that included the billions of

OMNIBUS see page 68

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NAFTIN Cream, 2% is indicated for the treatment of interdigital tinea pedis, tinea cruris, and tinea corporis caused by the organism *Trichophyton rubrum* in adult patients ≥18 years of age.

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ADVERSE REACTIONS

In clinical trials with NAFTIN Cream, 2%, the most common adverse reaction (≥1%) was pruritus.

WARNINGS AND PRECAUTIONS

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Please see brief summary of Full Prescribing Information on adjacent page(s).

References: 1. Data on file, Merz Pharmaceuticals. **2.** NAFTIN Cream, 2% [package insert]. Greensboro, NC: Merz Pharmaceuticals, LLC; January 2012. **3.** NAFTIN Gel, 2% [package insert]. Greensboro, NC: Merz Pharmaceuticals, LLC; June 2013. **4.** Brennan B, Leyden JJ. *J Am Acad Dermatol*. 1997;36(2 pt 1):S3-S8.

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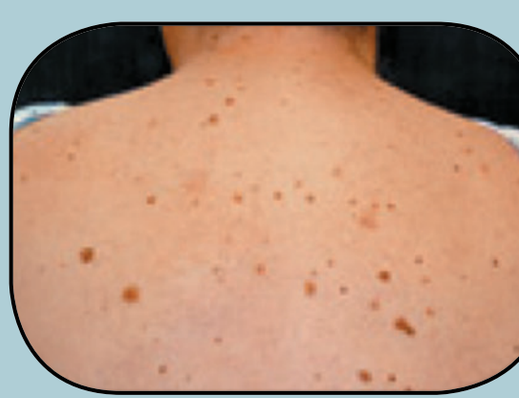
What's your diagnosis?

The mother of a 13-year-old boy was diagnosed with a malignant melanoma, and her mother died from disseminated melanoma two years ago. She has mapped 61 acquired moles on her son's trunk, face, and extremities, and many are large with fuzzy borders. She requests your immediate recommendations for management. What do you suggest? Tell us: facebook.com/dermatologytimes



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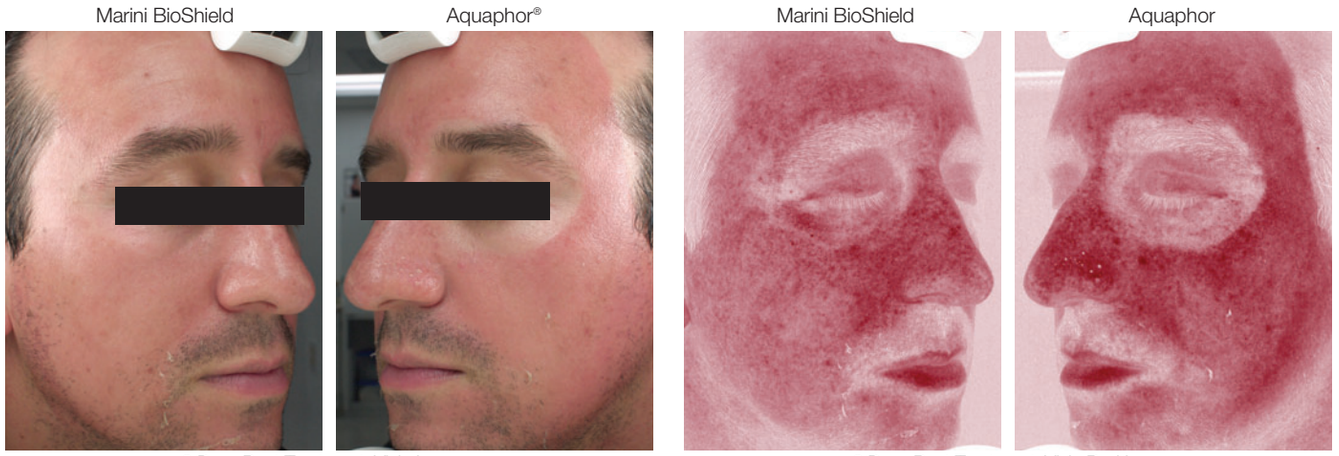

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Read more on the nuances of skin types beginning on page 47

Terrence Keaney, M.D., *is director of the Men's Center at the Washington Institute of Dermatologic Laser Surgery.*

Skin deep

Successful cosmetic outcomes result from recognizing gender and skin type differences

Successful cosmetic treatment of men with skin of color requires dermatologists to recognize their unique differences in anatomy and skin aging. Men of color are a particular challenge because the anatomical differences of both the male gender and skin of color need to be understood in order to provide a successful cosmetic outcome.

Biologic differences

Cutaneous gender differences are wide-ranging[1] and are primarily mediated by sex hormones. In men, the increase in androgens affects several functions of human skin and its appendages. Male skin, both epidermis and dermis, is thicker at all ages with the extent varying with anatomical region.[2]

The male facial anatomy is significantly different, as men have a larger and uniquely shaped skull. Men tend to have a large forehead with prominent supraorbital ridges,[3] wide glabella,[4] and a prominent protruding mandible. Men have increased skeletal muscle mass,[5] including facial mimetic muscles.[6] The subcutaneous adipose layer is thinner in men irrespective of age.[7]

The anatomical differences between genders result in differences in aging. Men have more severe facial rhytids[8] except in the perioral area.[9] The loss of subcutaneous adipose with age results in deeper expression lines in men because of the thicker skin and more prominent facial musculature, as opposed to the superficial rhytids that women tend to develop.

Facial aging in skin color is unique because the inherent pigmentation protects against photodamage and extrinsic aging.[10] Intrinsic aging predominates with volume loss from fat atrophy, gravity-induced soft tissue redistribution, and bony resorption.[11] Patients with skin of color are less likely to develop fine rhytids and solar lentigines than Caucasians.

Cosmetic procedures

Injection of botulinum toxin is the most common cosmetic procedure in men, with 363,018 injections performed in 2011.[12] Injection sites, technique and administered dose do not differ based on ethnicity, but do vary between genders.

When treating the male frontalis muscle, a flat injection technique is recommended to minimize brow arching and maintain the normal flat male eyebrow position. Extra caution is required when treating the inferior portion of the frontalis muscle to avoid eyebrow ptosis. More injections may be required to ensure complete and balanced treatment of the frontalis muscle due to the larger surface area of the male forehead.

Soft tissue augmentation with dermal fillers can be particularly effective in treating soft tissue redistribution seen in men with skin of color. Volume loss is a shared aging process seen in both the male gender and skin of color. Once again, the male facial anatomy dictates a unique injection technique.

Filler augmentation of the midface should focus on the centromedial cheeks to avoid creating wide lateral cheeks, which is a feminine characteristic. Enhancement of the lower face is also beneficial in men. The filler should be injected along the mandible to strengthen the jawline. Fillers can also be used to enhance the male forehead prominence by injecting into the bony sulcus over the eyebrows. The upper lip is generally avoided in men due to the risk of feminizing, and this is rarely a concern in skin of color patients because their lips tend to be fuller.

There is no "one size fits all" approach when evaluating a cosmetic patient. The gender of the patient and the color of their skin must be considered when choosing the appropriate procedure and technique. **DT**

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DAVID GOLDBERG, M.D., J.D., *is director of Skin Laser & Surgery Specialists of New York and New Jersey; director of laser research, Mount Sinai School of Medicine; and adjunct professor of law, Fordham Law School.*

Taking leave

Can a dermatologist be sued under the Family Medical Leave Act?

Dr. Derm has become very successful in his 20 years of practice. He now runs 16 offices with 82 employees — most of them full-time. Among his many coveted employees is his 37-year-old nursing clinical coordinator. She has worked with him for more than 10 years and oversees all of the many nurses and medical assistants in the office. Her role is of enormous importance to Dr. Derm and for this she is paid well.

Two years ago, the nurse notified Dr. Derm that she was pregnant and would be leaving the office to have her baby. She assured Dr. Derm that she will return to her position one month after delivery.

Dr. Derm knows that he cannot run the office without this nurse. He quickly finds a replacement and makes it clear to the replacement that he will rehire his nurse upon her return from maternity leave. Much to Dr. Derm's surprise, the temporary nurse turns out to be outstanding in her role as clinical coordinator. Because she is a new hire, she is also being paid 25 percent less than his long-time nurse.

On the 31st day post-delivery date, Dr. Derm realizes that his long-time nurse has not returned to work. He calls her home and cell phone repeated times over the next several weeks and is unable to reach her.

Back to work

Six weeks after the nurse left, Dr. Derm assumes she will not return. He offers the new nurse a permanent job. Both employer and employee are delighted. On day 64 post-maternity leave, his former nursing clinical coordinator returns to work, expecting her old job and salary. Dr. Derm responds by saying it is unreasonable to be gone almost three months and expect to come back to the same job and salary. He offers her a lesser job and lesser salary. If she does not take the job, she is told she will be terminated. She responds by demanding her old job and salary or she will sue Dr. Derm. Who is legally in the right?

The Department of Labor's Employment Standards Administration's wage and hour division administers and enforces the Family and Medical Leave Act (FMLA) for all private, state and local government employees, and some federal employees. The FMLA entitles eligible employees to take up to 12 work weeks of unpaid, job-protected leave in a 12-month period for specified family and medical reasons.

The FMLA applies to all public agencies and private sector employers who employ 50 or more employees in 20 or more workweeks in the current or preceding calendar year. To be eligible for FMLA benefits, an employee must work for a covered employer, have worked for the employer for a total of 12 months, have worked at least 1,250 hours over the previous 12 months, and work at a location in the United States where at least 50 employees are employed by the employer within 75 miles.

Granting leave

A covered employer must grant an eligible employee up to 12 work weeks of unpaid leave during any 12-month period for one or more of the following reasons: 1) for birth and care of a newborn child of the employee; 2) for placement with the employee of a son or daughter for adoption or foster care; 3) and to care for a spouse, son, daughter or parent with a serious health condition.

Of note is the fact that under certain circumstances, employees may take FMLA leave intermittently — taking leave in separate blocks of time for a single qualifying reason — or on a reduced leave schedule, reducing the employee's usual weekly or daily work schedule. However, if FMLA leave is for birth and care, or placement for adoption or foster care, use of intermittent leave is subject to the employer's approval.

In addition to holding both the salary and position of the employee, FMLA-covered employers must also maintain group health insurance coverage for an employee on FMLA leave whenever such insurance was provided before the leave was taken and on the same terms as if the employee had continued to work. If applicable, arrangements will need to be made for employees to pay their share of health insurance premiums while on leave; although in some instances the employer may later recover these paid premiums.

It would appear that under the FMLA act, Dr. Derm is, at day 64 post-delivery, required to give back his nursing coordinator both her previous job and previous salary. If he does not, she can file a complaint with the Department of Labor. If he is in violation, and the violation is not resolved, the Department of Labor may bring action in court to compel compliance.

Lastly, his employee may also be able to bring a private civil action against Dr. Derm. He would be wise to bring his employee back to her position and salary. **DT**

www.dermatologytimes/FMLA

EMPLOYMENT ISSUES: What staffing challenges have you encountered? Pass them along in confidence to: sthuerk@advanstar.com

This Little Piggy Had ONMEL™
(itraconazole) 200-mg tablets

Provide the efficacy of itraconazole in a single, once-daily tablet[1]

Indications and Usage

ONMEL is indicated for the treatment of onychomycosis of the toenail due to *Trichophyton rubrum* or *T. mentagrophytes* in non-immunocompromised patients. Prior to initiating treatment, appropriate nail specimens for laboratory testing (KOH preparation, fungal culture, or nail biopsy) should be obtained to confirm the diagnosis of onychomycosis.

Important Safety Information for ONMEL

WARNING: CONGESTIVE HEART FAILURE, CARDIAC EFFECTS, AND DRUG INTERACTIONS

Do not administer ONMEL for the treatment of onychomycosis in patients with evidence of ventricular dysfunction such as congestive heart failure (CHF) or a history of CHF. When itraconazole was administered intravenously to dogs and healthy human volunteers, negative inotropic effects were seen. If signs or symptoms of congestive heart failure occur during administration of ONMEL, discontinue administration.

Drug Interactions: Co-administration of cisapride, pimozide, quinidine, dofetilide, levacetylmethadol (levomethadyl), felodipine, oral midazolam, nisoldipine, triazolam, lovastatin, simvastatin, ergot alkaloids such as dihydroergotamine, ergometrine (ergonovine), ergotamine and methylergometrine (methylergonovine) or methadone with ONMEL is contraindicated. ONMEL, a potent cytochrome P450 3A4 isoenzyme system (CYP3A4) inhibitor, may increase plasma concentrations of drugs metabolized by this pathway. Serious cardiovascular events, including QT prolongation, torsades de pointes, ventricular tachycardia, cardiac arrest, and/or sudden death have occurred in patients using cisapride, pimozide, levacetylmethadol (levomethadyl), methadone or quinidine concomitantly with itraconazole and/or other CYP3A4 inhibitors.

Please see Important Safety Information included in accompanying full Prescribing Information for ONMEL, including BOXED WARNING.

For more information, please visit www.ONMEL.com

MERZ

ONMEL™
Itraconazole,
200 mg tablets

Reference: 1. ONMEL [package insert]. Greensboro, NC: Merz Pharmaceuticals, LLC; 2012.

ONMEL™ (itraconazole)

Initial U.S. Approval: 1992

Brief Summary: For complete details, please see full Prescribing Information.

WARNING: **CONGESTIVE HEART FAILURE, CARDIAC EFFECTS, AND DRUG INTERACTIONS**

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INDICATIONS AND USAGE

ONMEL is indicated for the treatment of onychomycosis of the toenail due to *Trichophyton rubrum* or *T. mentagrophytes* in non-immunocompromised patients. Prior to initiating treatment, appropriate nail specimens for laboratory testing (KOH preparation, fungal culture, or nail biopsy) should be obtained to confirm the diagnosis of onychomycosis.

CONTRAINDICATIONS

Congestive Heart Failure: Do not administer ONMEL for the treatment of onychomycosis in patients with evidence of ventricular dysfunction such as congestive heart failure (CHF) or a history of CHF.

Drug Interactions: Concomitant administration of ONMEL and certain drugs that are metabolized by the cytochrome P450 3A4 isoenzyme system (CYP3A4) or where gastrointestinal absorption is regulated by P-gp may result in increased plasma concentrations of those drugs, leading to potentially serious and/or life-threatening adverse events.

Co-administration of cisapride, dofetilide, ergot alkaloids such as dihydroergotamine, ergotamine, ergometrine (ergonovine), and methylergometrine (methylergonovine), felodipine, levacetylmethadol (levomethadyl), lovastatin, methadone, oral midazolam, nisoldipine, pimozide, quinidine, simvastatin, and triazolam with ONMEL is contraindicated.

Do not administer ONMEL for the treatment of onychomycosis to pregnant patients or to women contemplating pregnancy.

Anaphylaxis and hypersensitivity have been reported with use of itraconazole. ONMEL is contraindicated for patients who have shown hypersensitivity to itraconazole products.

WARNINGS AND PRECAUTIONS

Congestive Heart Failure, Peripheral Edema, and Pulmonary Edema

Cases of CHF, peripheral edema, and pulmonary edema have been reported with itraconazole administration among patients being treated for onychomycosis and/or systemic fungal infections.

Cardiac Dysrhythmias

Life-threatening cardiac dysrhythmias and/or sudden death have occurred in patients using cisapride, pimozide, levacetylmethadol (levomethadyl), methadone, or quinidine concomitantly with itraconazole and/or other CYP3A4 inhibitors. Concomitant administration of these drugs with ONMEL is contraindicated.

Cardiac Disease

ONMEL should not be administered in patients with evidence of ventricular dysfunction such as congestive heart failure (CHF) or a history of CHF.

Itraconazole has been shown to have a negative inotropic effect. When itraconazole was administered intravenously to anesthetized dogs, a dose-related negative inotropic effect was documented. In a healthy volunteer study of itraconazole injection, transient, asymptomatic decreases in left ventricular ejection fraction were observed using gated SPECT imaging; these resolved before the next infusion, 12 hours later.

For patients with risk factors for congestive heart failure, physicians should carefully review the risks and benefits of ONMEL therapy. These risk factors include cardiac disease such as ischemic and valvular disease; significant pulmonary disease such as chronic obstructive pulmonary disease; and renal failure and other edematous disorders. Such patients should be informed of the signs and symptoms of CHF, should be treated with caution, and should be monitored for signs and symptoms of CHF during treatment. If signs or symptoms of CHF appear during administration of ONMEL, discontinue administration.

Hepatic Effects

Itraconazole has been associated with rare cases of serious hepatotoxicity, including liver failure and death. Some of these cases had neither pre-existing liver disease nor a serious underlying medical condition, and some of these cases developed within the first week of treatment. If clinical signs or symptoms develop that are consistent with hepatotoxicity, treatment should be discontinued immediately and liver function testing performed.

In patients with elevated or abnormal liver enzymes or active liver disease, or who have experienced liver toxicity with other drugs, treatment with itraconazole is not recommended. Liver function monitoring should be done in patients with pre-existing hepatic function abnormalities or those who have experienced liver toxicity with other medications and should be considered in all patients receiving ONMEL.

Calcium Channel Blockers

Calcium channel blockers can have negative inotropic effects which may be additive to those of itraconazole. In addition, itraconazole can inhibit the metabolism of calcium channel blockers. Therefore, caution should be used when co-administering itraconazole and calcium channel blockers due to an increased risk of CHF. Concomitant administration of ONMEL and nisoldipine is contraindicated.

Neuropathy

If neuropathy occurs that may be attributable to ONMEL, the treatment should be discontinued.

Hearing Loss

Transient or permanent hearing loss has been reported in patients receiving treatment with itraconazole. Several of these reports included concurrent administration of quinidine which is contraindicated. The hearing loss usually resolves when treatment is stopped, but can persist in some patients.

ADVERSE REACTIONS

Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, the adverse reaction rate observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

Patients in the trial for toenail onychomycosis were treated with a dosing regimen of 200 mg once daily for 12 consecutive weeks.

The most commonly reported adverse reaction leading to discontinuation of ONMEL was increased hepatic enzyme (6 subjects, 1.0%), followed by dizziness (3 subjects, 0.5%). No other adverse reaction leading to discontinuation occurred in more than one subject.

The adverse reactions reported by at least 1% of ONMEL-treated patients (N=582) and placebo (N=191) during 12 weeks of treatment, respectively, were upper respiratory tract infection (6.0%, 7.3%), bacteriuria (1.4%, 1.6%), urinary tract infection (1.0%, 0.5%), hepatic enzymes increased (2.9%, 0.0%), electrocardiogram abnormal (1.4%, 1.6%), hypoacusis (3.3%, 3.1%), headache (2.2%, 1.6%), dizziness (1.2%, 0.0%), abdominal pain or discomfort (1.7%, 2.6%), diarrhea (1.7%, 3.1%), nausea (1.7%, 1.6%), fatigue (1.5%, 2.6%), sinus bradycardia (1.0%, 0.0%), cough (1.2%, 0.0%), pharyngolaryngeal pain (1.0%, 0.5%), and back pain (1.2%, 2.1%).

Post Marketing Experience

The following adverse reactions have been identified during post-approval use of itraconazole (all formulations). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establishing a causal relationship to drug exposure.

Blood and lymphatic system disorders: Leukopenia, neutropenia, thrombocytopenia

Immune system disorders: Anaphylaxis; anaphylactic, anaphylactoid and allergic reactions; serum sickness; angioneurotic edema

Metabolism and nutritional disorders: Hypertriglyceridemia, hypokalemia

Nervous system disorders: Peripheral neuropathy, paresthesia, hypoesthesia, headache, dizziness

Eye disorders: Visual disturbances, including vision blurred and diplopia

Ear and labyrinth disorders: Transient or permanent hearing loss, tinnitus

Cardiac disorders: Congestive heart failure

Respiratory, thoracic and mediastinal disorders: Pulmonary edema

Gastrointestinal disorders: Abdominal pain, vomiting, dyspepsia, nausea, diarrhea, constipation, dysgeusia

Hepato-biliary disorders: Serious hepatotoxicity (including some cases of fatal acute liver failure), hepatitis, reversible increases in hepatic enzymes

Skin and subcutaneous tissue disorders: Toxic epidermal necrolysis, Stevens-Johnson syndrome, exfoliative dermatitis, leukocytoclastic vasculitis, erythema multiforme, alopecia, photosensitivity, rash, urticaria, pruritus

Musculoskeletal and connective tissue disorders: Myalgia, arthralgia

Renal and urinary disorders: Urinary incontinence, pollakiuria

Reproductive system and breast disorders: Menstrual disorders, erectile dysfunction

General disorders and administration site conditions: Peripheral edema

DRUG INTERACTIONS

Effects of ONMEL on Other Drugs

Itraconazole and its major metabolite, hydroxy-itraconazole, are strong inhibitors of the cytochrome P450 3A4 isoenzyme system (CYP3A4). Therefore, concomitant administration of ONMEL and certain drugs metabolized by the cytochrome CYP3A4 may result in increased plasma concentrations of those drugs due to decreased elimination, leading to potentially serious and/or life-threatening adverse events. Itraconazole is also an inhibitor of P-glycoprotein (P-gp) transporter and may result in increased plasma concentrations of drugs whose gastrointestinal absorption is regulated by P-gp. Whenever possible, plasma concentrations of these drugs should be monitored, and dosage adjustments made after concomitant ONMEL therapy is initiated. When appropriate, clinical monitoring for signs or symptoms of increased or prolonged pharmacologic effects is advised. Upon discontinuation, itraconazole plasma concentrations decline gradually (especially in patients with hepatic cirrhosis or in those receiving CYP3A4 inhibitors). This is particularly important when initiating therapy with drugs whose metabolism is affected by itraconazole.

Effects of Other Drugs on ONMEL

Inducers of CYP3A4 may decrease the plasma concentrations of itraconazole. ONMEL may not be effective in patients concomitantly taking ONMEL and one of these drugs. Therefore, administration of these drugs with ONMEL is not recommended.

Inhibitors of CYP3A4 may increase the plasma concentrations of itraconazole. Patients who must take ONMEL concomitantly with one of these drugs should be monitored closely for signs or symptoms of increased or prolonged pharmacologic effects of ONMEL.

The following are selected drugs that altered or are predicted to alter the plasma concentration of itraconazole or have their plasma concentration altered by ONMEL.[1]

Drug plasma concentration increased by itraconazole

Antiarrhythmics: digoxin, dofetilide, quinidine, disopyramide

Anticonvulsants: carbamazepine

Anti-HIV Agents: indinavir, ritonavir, saquinavir, maraviroc

Antineoplastics: busulfan, docetaxel, vinca alkaloids

Antipsychotics: pimozide

Benzodiazepines: alprazolam, diazepam, midazolam,[2] triazolam

Calcium Channel Blockers: dihydropyridines (including nisoldipine and felodipine), verapamil

Gastrointestinal Motility Agents: cisapride

HMG CoA-Reductase Inhibitors: atorvastatin, cerivastatin, lovastatin, simvastatin

Immunosuppressants: Cyclosporine, tacrolimus, sirolimus

Oral Hypoglycemics: oral hypoglycemics (repaglinide)

Opiate Analgesics: fentanyl, levacetylmethadol (levomethadyl), methadone

Polyene Antifungals: amphotericin B

Other: ergot alkaloids, halofantrine, alfentanil, buspirone, methylprednisolone, budesonide, dexamethasone, fluticasone, warfarin, cilostazol, eletriptan, fexofenadine, loperamide

Decrease plasma concentration of itraconazole

Anticonvulsants: carbamazepine, phenobarbital, phenytoin

Anti-HIV Agents: nevirapine, efavirenz

Antimycobacterials: isoniazid, rifabutin, rifampin

Gastric Acid Suppressors/Neutralizers: antacids, H_2-receptor antagonists, proton pump inhibitors

Increase plasma concentration of itraconazole

Macrolide Antibiotics: clarithromycin, erythromycin

Anti-HIV Agents: indinavir, ritonavir

[1]This list is not all-inclusive.

[2]For information on parenterally administered midazolam, see the Benzodiazepine paragraph below.

Selected drugs that are contraindicated for use with itraconazole[1]

Antipsychotics: pimozide

Antiarrhythmics: dofetilide, quinidine

Benzodiazepines: oral midazolam[2], triazolam

Calcium Channel Blockers: Nisoldipine, felodipine

Ergot Alkaloids: dihydroergotamine, ergotamine, ergometrine (ergonovine), methylergometrine (methylergonovine)

Gastrointestinal Motility Agents: cisapride

HMG CoA-Reductase Inhibitors: lovastatin, simvastatin

Opiate Analgesics: levacetylmethadol (levomethadyl), methadone

[1]This list is not all-inclusive.

[2]For information on parenterally administered midazolam, see the Benzodiazepine paragraph below.

Antiarrhythmics

The Class IA antiarrhythmic, quinidine and

class III antiarrhythmic, dofetilide are known to prolong the QT interval. Co-administration of quinidine or dofetilide with itraconazole may increase plasma concentrations of quinidine or dofetilide, which could result in serious cardiovascular events. Therefore, concomitant administration of ONMEL and quinidine or dofetilide is contraindicated.

The Class IA antiarrhythmic, disopyramide has the potential to increase the QT interval at high plasma concentrations. Caution is advised when ONMEL and disopyramide are administered concomitantly.

Concomitant administration of digoxin and itraconazole has led to increased plasma concentrations of digoxin via inhibition of P-glycoprotein.

Anticonvulsants
Carbamazepine, phenobarbital, and phenytoin are all inducers of CYP3A4. Reduced plasma concentrations of itraconazole were reported when itraconazole was administered concomitantly with phenytoin. Although interactions with carbamazepine and phenobarbital have not been studied, concomitant administration of ONMEL and these drugs would be expected to result in decreased plasma concentrations of itraconazole. In addition, in vivo studies have demonstrated an increase in plasma carbamazepine concentrations in subjects concomitantly receiving ketoconazole. Although there are no data regarding the effect of itraconazole on carbamazepine metabolism, because of the similarities between ketoconazole and itraconazole, concomitant administration of ONMEL and carbamazepine may inhibit the metabolism of carbamazepine.

Anti-HIV Agents
Non-nucleoside Reverse Transcriptase Inhibitors (NNRTI) such as nevirapine and efavirenz are inducers of CYP3A4. Human pharmacokinetic studies have shown that efavirenz, when concomitantly administered with itraconazole, greatly decreased serum concentrations of itraconazole and hydroxyl-itraconazole. Concomitant use of ONMEL and efavirenz is not recommended.

In vivo studies have shown that nevirapine induces the metabolism of ketoconazole, significantly reducing the bioavailability of ketoconazole. Studies involving nevirapine and itraconazole have not been conducted. However, because of the similarities between ketoconazole and itraconazole, concomitant administration of ONMEL and nevirapine is not recommended.

Concomitant administration of ONMEL and protease inhibitors metabolized by CYP3A4, such as indinavir, ritonavir, and saquinavir, may increase plasma concentrations of these protease inhibitors. In addition, concomitant administration of ONMEL and indinavir and ritonavir (but not saquinavir) may increase plasma concentrations of itraconazole. Caution is advised when ONMEL and protease inhibitors must be given concomitantly.

Concomitant administration of ONMEL and maraviroc has been reported to increase plasma concentration of maraviroc. The dose of maraviroc should be decreased to 150 mg twice daily when given in combination with itraconazole.

Antimycobacterials
Drug interaction studies have demonstrated that plasma concentrations of azole antifungal agents and their metabolites, including itraconazole and hydroxyitraconazole, were significantly decreased when these agents were given concomitantly with rifabutin or rifampin. In vivo data suggest that rifabutin is metabolized in part by CYP3A4. ONMEL may inhibit the metabolism of rifabutin. Although no formal study data are available for isoniazid, similar effects should be anticipated. Therefore, the efficacy of ONMEL could be substantially reduced if given concomitantly with one of these agents and co-administration is not recommended.

Antineoplastics
ONMEL may inhibit the metabolism of busulfan, docetaxel, and vinca alkaloids.

Antipsychotics
Pimozide is known to prolong the QT interval and is partially metabolized by CYP3A4. Co-administration of pimozide with itraconazole could result in serious cardiovascular events. Therefore, concomitant administration of ONMEL and pimozide is contraindicated.

Increases in plasma aripiprazole concentrations have been demonstrated in subjects concomitantly receiving ketoconazole, requiring a reduction of the aripiprazole dose. Because of the similarities between ketoconazole and itraconazole, a similar dose reduction for aripiprazole is recommended when patients concomitantly receive itraconazole and aripiprazole.

Benzodiazepines
Concomitant administration of itraconazole and alprazolam, diazepam, oral midazolam, or triazolam could lead to increased plasma concentrations of these benzodiazepines. Increased plasma concentrations could potentiate and prolong hypnotic and sedative effects. Concomitant administration of ONMEL and oral midazolam or triazolam is contraindicated. If midazolam is administered parenterally, special precaution and patient monitoring is required since the sedative effect may be prolonged.

Calcium Channel Blockers
Calcium channel blockers can have a negative inotropic effect which may be additive to those of itraconazole; itraconazole can inhibit the metabolism of calcium channel blockers such as dihydropyridines (e.g., nifedipine, nisoldipine, and felodipine) and verapamil. Therefore, caution should be used when co-administering itraconazole and calcium channel blockers due to an increased risk of CHF.

Concomitant administration of ONMEL and nisoldipine results in clinically significant increases in nisoldipine plasma concentrations, which cannot be managed by dosage reduction, therefore the concomitant administration of ONMEL and nisoldipine is contraindicated. A clinical study showed that felodipine exposure was increased by co-administration of itraconazole, resulting in approximately 6-fold increase in the AUC and 8-fold increase in the C_{max}. The concomitant use of ONMEL and felodipine is contraindicated.

Edema has been reported in patients concomitantly receiving itraconazole and dihydropyridine calcium channel blockers. Appropriate dosage adjustment may be necessary.

Gastric Acid Suppressors/Neutralizers
Reduced plasma concentrations of itraconazole were reported when administered concomitantly with H_2-receptor antagonists. Studies have shown that absorption of itraconazole is impaired when gastric acid production is decreased. ONMEL should be administered with a cola beverage if the patient has achlorhydria or is taking H_2-receptor antagonists or other gastric acid suppressors. It is advised that antacids be administered at least 1 hour before or 2 hours after administration of ONMEL. In a clinical study, when itraconazole capsules were administered with omeprazole (a proton pump inhibitor), the bioavailability of itraconazole was significantly reduced.

Gastrointestinal Motility Agents
Co-administration of itraconazole with cisapride can elevate plasma cisapride concentrations, which could result in serious cardiovascular events. Therefore, concomitant administration of ONMEL with cisapride is contraindicated.

3-Hydroxy-3-Methyl-Glutaryl CoA-Reductase Inhibitors
Human pharmacokinetic data suggest that itraconazole inhibits the metabolism of atorvastatin, cerivastatin, lovastatin, and simvastatin, which may increase the risk of skeletal muscle toxicity, including rhabdomyolysis. Concomitant administration of ONMEL with 3-Hydroxy-3-Methyl-Glutaryl (HMG) CoA-Reductase inhibitors, such as lovastatin and simvastatin, is contraindicated.

Immunosuppressants
Concomitant administration of ONMEL and cyclosporine or tacrolimus has led to increased plasma concentrations of these immunosuppressants. Similarly, concomitant administration of ONMEL and sirolimus could increase plasma concentrations of sirolimus.

Monitoring of blood concentrations of cyclosporine, tacrolimus, or sirolimus are recommended when ONMEL are co-administered with these immunosuppressants and appropriate dosage adjustments should be made.

Macrolide Antibiotics
Erythromycin and clarithromycin are known inhibitors of CYP3A4 and may increase plasma concentrations of itraconazole.

Oral Hypoglycemic Agents
Severe hypoglycemia has been reported in patients concomitantly receiving azole antifungal agents and oral hypoglycemic agents. A human pharmacokinetic study showed that co-administration with itraconazole and a single dose of repaglinide (on the third day of a regimen of 200 mg initial dose, twice-daily 100 mg itraconazole) resulted in a 1.4-fold higher repaglinide AUC. Blood glucose concentrations should be carefully monitored when ONMEL and oral hypoglycemic agents are co-administered.

Polyenes Antifungal Agents
Prior treatment with itraconazole, like other azoles, may reduce or inhibit the activity of polyenes such as amphotericin B. However, the clinical significance of this drug effect has not been clearly defined.

Opiate Analgesics
Levacetylmethadol (levomethadyl) and methadone are known to prolong the QT interval and are metabolized by CYP3A4. Co-administration of methadone or levacetylmethadol with itraconazole could result in serious cardiovascular events. Therefore, concomitant administration of ONMEL and methadone or levacetylmethadol are contraindicated.

Fentanyl plasma concentrations could be increased or prolonged by concomitant use of itraconazole and may cause potentially fatal respiratory depression.

In vitro data suggest that alfentanil is metabolized by CYP3A4. Administration with itraconazole may increase plasma concentrations of alfentanil.

Other
- Elevated concentrations of ergot alkaloids can cause ergotism, i.e., a risk for vasospasm potentially leading to cerebral ischemia and/or ischemia of the extremities. Concomitant administration of ergot alkaloids such as dihydroergotamine, ergometrine (ergonovine), ergotamine and methylergometrine (methylergonovine) with ONMEL is contraindicated.
- Halofantrine has the potential to prolong the QT interval at high plasma concentrations. Caution is advised when ONMEL and halofantrine are administered concomitantly.
- Human pharmacokinetic data suggest that concomitant administration of itraconazole and buspirone results in significant increases in plasma concentrations of buspirone.
- Itraconazole may inhibit the metabolism of certain glucocorticosteroids such as budesonide, dexamethasone, fluticasone and methylprednisolone.
- Itraconazole enhances the anticoagulant effect of coumarin-like drugs, such as warfarin.
- Cilostazol and eletriptan are CYP3A4 metabolized drugs that should be used with caution when co-administered with ONMEL.
- Co-administration of itraconazole with meloxicam decreased peak plasma concentrations and the exposure of meloxicam by 64% and 37%, respectively. Monitor patients for responses to meloxicam when itraconazole is concomitantly administered and dose adjustment should be considered if warranted.
- Co-administration of itraconazole with fexofenadine increased the peak plasma concentration and the total exposure of fexofenadine by approximately 3-fold and augmented its anti-histamine effects.
- Co-administration of itraconazole with loperamide increased peak plasma concentrations of loperamide by 3-fold and the total exposure by 3.9-fold. In addition, itraconazole is an inhibitor of P-glycoprotein and may inhibit the transport of loperamide out of the brain, leading to elevated concentrations of loperamide in the brain. Patients should be monitored for signs and symptoms of loperamide overdose, such as CNS depression, including drowsiness, dizziness and respiratory depression, and a dose or dosing frequency should be adjusted as necessary.

USE IN SPECIFIC POPULATIONS
Pregnancy
Teratogenic effects.
Pregnancy Category C
There are no adequate and well-controlled clinical trials in the pregnant women with itraconazole. However, cases of congenital abnormalities have been reported with itraconazole drug products in post-marketing reports. Therefore, ONMEL should not be administered to pregnant women, women planning pregnancy, or women of child bearing potential unless these onychomycosis patients are using effective contraception measures to prevent pregnancy. Effective contraceptive measures should continue throughout the treatment period and for two months thereafter. ONMEL should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Itraconazole produced a significant dose-related increase in maternal toxicity, embryotoxicity, and teratogenicity in rats at dose levels of 40-160 mg/kg/day (2-10 times the maximum recommended human dose [MRHD], based on mg/m^2/day comparisons), and in mice at 80 mg/kg/day (2 times MRHD, based on mg/m^2/day comparisons). Teratogenic changes in rats included major skeletal defects; encephalocele and/or macroglossia developed in mice.

Nursing Mothers
Itraconazole is excreted in human milk; therefore, the expected benefits of ONMEL therapy for the mother should be weighed against the potential risk from exposure of itraconazole to the infant.

Pediatric Use
The safety and effectiveness of ONMEL in pediatric patients have not been established. No pharmacokinetic data on ONMEL are available in children.

Geriatric Use
ONMEL was evaluated in 42 of 593 subjects (7.1%) greater than 65 years of age.

Transient or permanent hearing loss has been reported in elderly patients receiving treatment with itraconazole. Several of these reports included concurrent administration of quinidine which is contraindicated. Itraconazole should be used with care in elderly patients.

Renal Impairment
Limited data are available on the use of oral itraconazole in patients with renal impairment. Caution should be exercised when ONMEL is administered to patients with renal impairment.

Hepatic Impairment
Limited data are available on the use of oral itraconazole in patients with hepatic impairment. Caution should be exercised when ONMEL is administered to patients with hepatic impairment.

OVERDOSAGE
Itraconazole is not removed by dialysis. In the event of accidental overdosage, supportive measures, including gastric lavage with sodium bicarbonate, should be employed.

Manufactured by:
Sanico N.V.
2300 Turnhout, Belgium

Manufactured for
Merz Pharmaceuticals, LLC
4215 Tudor Lane
Greensboro, NC 27410

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Many with psoriasis go untreated

Study findings were published online Aug. 14 in *JAMA Dermatology.*

http://archderm.jamanetwork.com/article.aspx?articleid=1729130

UP TO 30 PERCENT of patients with psoriasis do not seek medical care for their skin condition, patient surveys show.

As many as 50 percent of patients with mild psoriasis went untreated, while nearly 22 percent of patients with severe psoriasis were treated only with topical agents, according to the results.

Investigators with University of California, Davis, analyzed national survey data that had been gathered by the National Psoriasis Foundation from 2003 to 2011. Survey participants were 5,604 patients from the United States who had psoriasis and psoriatic arthritis.

Between 36.6 and 49.2 percent of patients who had mild psoriasis were not treated for their condition, survey results indicated. Among patients with moderate psoriasis, 23.6 to 35.5 percent weren't treated, and 9.4 to 29.7 percent of patients with severe psoriasis also were not treated. Nearly 30 percent of patients with moderate psoriasis were treated only with topical agents.

Survey respondents indicated an inability to get adequate insurance coverage was one of the main reasons for discontinuing treatment for psoriasis. Adverse effects and lack of effectiveness also led to patients discontinuing treatment.

"We want payers to understand the serious medical consequences of nontreatment and undertreatment of psoriasis and psoriatic arthritis," April W. Armstrong, M.D., M.P.H., lead author of the study and associate professor of dermatology at UC Davis, said in a news release. "There are also psychiatric consequences to these conditions. Patients often become depressed and some even suicidal because their quality of life is so poor."

More than 52 percent of patients with psoriasis and 45.5 percent with psoriatic arthritis reported dissatisfaction with the treatment they received for their condition.

"Efforts in advocacy and education are necessary to ensure that effective treatments are accessible to this patient population," study authors noted. **DT**

Antibodies' role in scleroderma variant uncertain

The study was published online Aug. 7 in *JAMA Dermatology.*

http://archderm.jamanetwork.com/article.aspx?articleid=1724033

A RECENT STUDY confirms the presence of certain antibodies in patients with morphea, but only in linear morphea is the presence associated with clinical indicators of severity.

Researchers with the University of Texas Southwestern Medical Center, Dallas, examined 187 patients from the Morphea in Adults and Children (MAC) cohort and Scleroderma Family Registry and DNA Repository along with 651 matched controls.

The most common subtype reported among the more than half (59 percent) of the patients who had adult-onset disease was generalized morphea. The most common subtype reported among the 41 percent of patients who had childhood-onset disease was linear morphea, MedPage Today reports.

Antinuclear antibodies (ANAs) and antihistone antibodies (AHAs) were detected in 34 percent and 12 percent, respectively, of patients with morphea, according to the *JAMA Dermatology* abstract. The prevalence of anti–single-stranded DNA antibodies (ssDNA abs) was detected in 8 percent of patients.

The presence of autoantibodies was not associated with clinical measures of morphea activity; however, in patients with linear morphea, it was associated with functional limitation (ssDNA ab, P=0.005; and AHA, P=0.006), extensive body surface area involvement (ssDNA ab, P= 0.01; and ANA, P=0 .005), and higher skin scores (ANA, P=0.004), researchers reported.

Investigators suggested the findings provide evidence for an underlying autoimmune component and underscore the need for future studies to identify biomarkers of disease. **DT**

Researchers find cause of sunburn pain

The study findings were published online Aug. 5 in the *Proceedings of the National Academy of Sciences.*

www.pnas.org/content/110/34/E3225.abstract?sid=53f21897

SCIENTISTS have found that blocking the molecule TRPV4 can help to prevent the pain caused by sunburns.

Researchers with Duke University School of Medicine, Durham, N.C., conducted experiments on mouse and human skin samples to identify what triggers pain caused by sunburn. They built a mouse model that was lacking the ion channel TRPV4 only in the cells of the epidermis.

Genetically engineered mice and controls had their hind paws exposed to UVB rays. The skin in normal mice became hypersensitive and blistered, while the genetically altered mice demonstrated little tissue injury and sensitization, according to a news release.

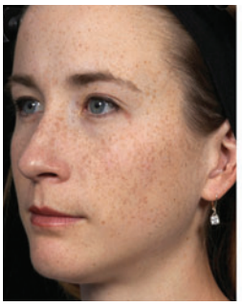
Using cultured mouse skin cells to dissect TRPV4's activities, researchers found that UVB causes calcium to flow into skin cells, but only when the TRPV4 ion channel is present. The researchers then dug deeper, learning that TRPV4 is activated by UVB, then causing an influx of calcium ions. This process brings in the molecule endothelin, triggering TRPV4 to send even more calcium to cells. The endothelin is responsible for the pain from sunburn.

Scientists then used the pharmaceutical compound GSK205 to inhibit TRPV4 in the hind paws of normal mice. These mice were mostly resistant to the effects of sunburn, study authors determined. They noted that further research into TRPV4 inhibition is necessary.

"I think we should be cautious because we want to see what inhibition of TRPV4 will do to other processes going on in the skin," Wolfgang Liedtke, M.D., Ph.D., a senior author of the study, said in the news release. "Once these concerns will be addressed, we will need to adapt TRPV4 blockers to make them more suitable for topical application. I imagine it being mixed with traditional sunblock to provide stronger protections against UVB exposure." **DT**

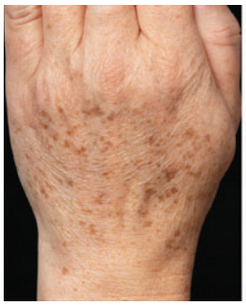
The Clearest Choice for Pigmentation Correction: Fraxel DUAL 1550/1927

by Elliot T Weiss M.D., Laser & Skin Surgery Center of New York, Southampton, and Manhattan

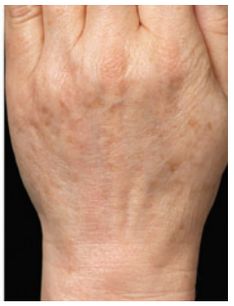


Before Fraxel DUAL (1927)

2 Weeks Post 2 Treatments



Before Fraxel DUAL (1927)



2 Weeks Post 3 Treatments

Photographs courtesy of Solta Medical Aesthetic Center

Treatment of photodamaged skin and hyperpigmentation is a significant concern for my sun-loving patients in the beach communities of eastern Long Island. Although many laser systems address skin quality, I have not found another device that can achieve the superior results in photodamaged skin as delivered by the Fraxel DUAL laser system. This device is a workhorse in our Hamptons and Manhattan practices with consistent, predictable results that routinely exceed patient expectations.

The Fraxel DUAL can be safely used to treat all body areas, enabling clinicians to address the most common sun-exposed areas of the face, chest, neck, hands and forearms in a single treatment. This system recently received FDA clearance for the treatment of pigmented lesions such as, but not limited to, lentigos, solar lentigos and ephelides.

The Fraxel DUAL 1550/1927 takes the original Fraxel technology one step further by including the novel 1927nm Thulium wavelength. This novel wavelength is ideally suited for superficial resurfacing of epidermal pigmentation and photodamage. With this addition, Fraxel DUAL enables both deep and superficial resurfacing for all types of sun-damaged skin, anywhere on the body, for patients of all ages. Fraxel DUAL 1927nm treatments reveal younger-looking skin with more uniform color and tone and noticeably smoother texture. The superficial nature of 1927nm fractional treatments minimizes patient downtime and recovery.

A nice advantage of the Fraxel DUAL treatment is that multiple aspects of skin quality can be addressed. Treatment improves the rough texture and uneven pigmentation associated with photodamage while also simultaneously targeting other undesired skin conditions. By combining the 1550/1927nm wavelengths in a single session, treatments can be tailored to also target acne- and surgical-scars, pore size, skin firmness and periorbital rhytids. Actinic keratoses are also effectively treated, giving patients healthier, younger-looking skin.

Fraxel DUAL system upgrades have helped shorten treatment times and enhance the user interface for a more efficient clinical experience. The rolling handpiece, which uses the Intelligent Optical Tracking System, glides easily over the skin's surface to distribute the energy evenly, maximizing patient outcomes by minimizing the risk of under-or overtreatment. Safety mechanisms closely monitor energy delivery to ensure appropriate dosing that adjusts to match the speed of handpiece movement. The Fraxel DUAL integrates forced-air cooling into the handpiece, which further improves safety and efficiency. This integrated cooling feature improves patient comfort and eliminates the need for an assistant to administer cooling, making this a single-operator treatment.

For patients undergoing a series of treatments, I frequently use both wavelengths during each treatment session. As skin pigmentation, tone, and texture improves, greater emphasis on fine lines and firmness can be accomplished by increasing the proportion of 1550nm treatment during the session. The end-result is a very natural looking improvement in skin quality, rather than an artificial, "done" appearance. Following a Fraxel DUAL treatment, patients are instructed to apply emollients and sunscreen several times daily. Make-up or tinted sunscreen can be applied immediately to cover any post-treatment erythema that can last up to several days, depending on treatment strength. My Fraxel DUAL patients are generally extremely satisfied with their clinical outcomes and are often quick to refer their friends and family to experience similarly satisfying results for themselves. Many patients schedule 1-2 treatments per year as a way to maintain healthy appearing skin. Fraxel DUAL is the clearest skin resurfacing choice for patients who want predictable, high-quality, natural-looking treatment of photodamaged skin with minimal downtime.

Elliot T. Weiss M.D. is Assistant Clinical Professor of Dermatology, Weil-Cornell Department of Dermatology, New York, NY

www.fraxel.com

Images spur skin self-examinations

This study was published in the July issue of the *Journal of the American Academy of Dermatology.*

www.jaad.org/article/S0190-9622(13)00098-4/abstract

PHOTOGRAPHS of skin cancers caused patients to be more likely to conduct skin self-examinations, according to results of a recent study.

Using seven databases, researchers with the School of Public Health and Health Systems, University of Waterloo, Ontario, found 25 studies to analyze the effectiveness of interventions or educational aids that utilize visual images to promote skin self-exams, according to the abstract.

Images of skin cancers motivated patients to perform skin self-exams and also increased the accuracy of these exams, as well as melanoma detection.

"Visual images capture our attention and are persuasive," Laurie Hoffman-Goetz, Ph.D., M.P.H., faculty of applied sciences and study co-author, said in a news release. "Incorporating images into clinical practice when educating patients can be a powerful tool."

One of the limitations of the study was a lack of image description in the studies. **DT**

Childhood ADHD may be linked to skin disorders

The study was published in the August issue of the *Annals of Allergy, Asthma & Immunology.*

www.annallergy.org/article/S1081-1206(13)00350-5/fulltext

CHILDREN with attention deficit hyperactivity disorder (ADHD) may be more likely to have skin infections, impetigo and atopic diseases, a recent study shows.

To examine a hypothesis examining the link between ADHD and allergies, researchers with University of Groningen, Netherlands, analyzed 884 boys who were diagnosed with ADHD, and 3,536 controls. After adjusting for age and presence of low birth weight or preterm delivery, independent odds ratios were 1.5 for impetigo, 1.5 for any antihistamine drug prescriptions, and 1.4 for medical history of asthma.

"Despite possible limitations inherent to observational studies, this study lends support to the emerging evidence that childhood ADHD is associated with atopic diseases and impetigo," study authors concluded, noting that further research is required to better understand underlying mechanisms and evaluate preventive and therapeutic interventions. **DT**

Dermatology Times

LASTING EFFECTS

Sustainability of ustekinumab established in patients with psoriatic arthritis

CHERYL GUTTMAN KRADER | SENIOR STAFF CORRESPONDENT

ROCHESTER, N.Y. — The human interleukin-12 and interleukin-23 (IL-12/IL-23) inhibitor ustekinumab (Stelara, Janssen) is effective and is well tolerated in patients who have active psoriatic arthritis.

Analyses of data collected through one year of follow-up in two phase 3 clinical trials demonstrated that ustekinumab was associated with significantly greater improvements in joint, tissue and skin manifestations after 24 weeks compared with placebo, had durable or increasing efficacy with ongoing quarterly injections, and provided benefit for individuals previously treated with a tumor necrosis factor-alpha (TNF-alpha) inhibitor.

"There is a major unmet need for alternative therapies in patients with psoriatic arthritis who cannot take or fail an anti-TNF-alpha agent. The phase 3 study results provide an evidence basis supporting use of ustekinumab in this patient population," says Christopher T. Ritchlin, M.D., M.P.H., study investigator and professor of medicine, allergy/immunology, and rheumatology, University of Rochester School of Medicine and Dentistry, Rochester, N.Y.

He adds, "We are looking forward to findings from radiologic data that are now being analyzed. In addition, while the safety of ustekinumab in patients with psoriatic arthritis has been favorable so far, data from longer follow-up are needed."

The phase 3 studies, known as PSUMMIT 1 (n=615) and PSUMMIT 2 (n=312), randomized patients to induction therapy with subcutaneous injections of ustekinumab 45 mg, ustekinumab 90 mg, or placebo at weeks zero and four; further injections were given every 12 weeks. Patients previously treated with an IL-12/23 inhibitor were excluded from both studies. Only patients who were naïve to TNF-alpha inhibitor treatment were enrolled in PSUMMIT 1; 180 patients in PSUMMIT 2 had prior treatment with one or more TNF-alpha inhibitors.

QUICK READ

The efficacy of ustekinumab in patients with active psoriatic arthritis has been demonstrated in two phase 3 clinical trials.

GOOD RESPONSE AT BOTH DOSES

The proportion of patients achieving a ≥ 20 percent improvement in joint signs and symptoms according to the American College of Rheumatology criteria (ACR 20 responder rate) at week 24 was analyzed as the primary efficacy endpoint. The results showed statistically significant differences favoring both ustekinumab 45 mg and 90 mg compared with placebo in both PSUMMIT 1 (42.4 percent

USTEKINUMAB see page 24

Quotable

"Finding the 'right' therapy may take time and will often require patience on the part of the patient and physician."

Sarina Elmariah, M.D., Ph.D.
Harvard Medical School, Boston

On treating chronic pruritus
See story, page 22

DTExtra

A recent study confirms the **presence of certain antibodies in patients with morphea**, but only in linear morphea is the presence associated with clinical indicators of severity. Researchers from the University of Texas Southwestern Medical Center, Dallas, examined 187 patients along with 651 matched controls. **In patients with linear morphea, the presence of autoantibodies was associated with functional limitation** (ssDNA ab, P=0.005; and AHA, P=0.006), extensive body surface area involvement (ssDNA ab, P=0.01; and ANA, P=0.005), and higher skin scores (ANA, P=0.004).

SOURCE: *JAMA DERMATOLOGY*

PLAQUE PSORIASIS IS NOT A FOUR-WEEK DISEASE[1]

CHOOSE A TREATMENT THAT CAN GO THE DISTANCE

Right from the start, Calcitrene® (Calcipotriene) Ointment, 0.005% may provide a lasting foundation for the long-term treatment of plaque psoriasis.

- **Improvements beginning as early as two weeks[2]**
- **Can be used for long-term efficacy – up to one year[2]**
- **Available in convenient 120 g size**
- **Both brand and generic available from TaroPharma®**

Important Safety Information: Calcipotriene ointment, 0.005% is indicated for the treatment of plaque psoriasis in adults. The safety and effectiveness of topical calcipotriene in dermatoses other than psoriasis have not been established. Calcipotriene is contraindicated in those patients with a history of hypersensitivity to any of the components of the preparation. It should not be used by patients with demonstrated hypercalcemia or evidence of vitamin D toxicity. Calcipotriene should not be used on the face. Use of calcipotriene may cause irritation of lesions and surrounding uninvolved skin. If skin irritation develops, calcipotriene should be discontinued. Transient, rapidly reversible elevation of serum calcium has occurred with use of calcipotriene. If elevation in serum calcium outside the normal range should occur, discontinue treatment until normal calcium levels are restored. In controlled clinical trials, the most frequent adverse reactions reported for calcipotriene were burning, itching and skin irritation, which occurred in approximately 10-15% of patients. Erythema, dry skin, peeling, rash, dermatitis, worsening of psoriasis including development of facial/scalp psoriasis were reported in 1 to 10% of patients. Other experiences reported in less than 1% of patients included skin atrophy, hyperpigmentation, hypercalcemia, and folliculitis. Once daily dosing has not been shown to be superior in safety to twice daily dosing.

References: 1. American Academy of Dermatology. "Psoriasis." Available at: www.aad.org/dermatology-a-to-z/diseases-and-treatments/m---p/psoriasis.
2. Calcitrene® (calcipotriene) Ointment, 0.005% Package Insert. Taro Pharmaceuticals U.S.A., Inc. October 2012.

START WITH IT. **STAY WITH IT.**™

TaroPharma®

See Prescribing Information on reverse side.

AD930-0023 July 2013

Calcitrene® (Calcipotriene) Ointment 0.005%

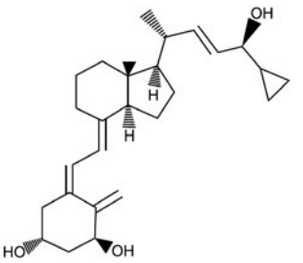
FOR TOPICAL DERMATOLOGIC USE ONLY.
Not for Ophthalmic, Oral or Intravaginal Use.

RX Only

DESCRIPTION

Calcitrene® (calcipotriene) ointment, 0.005% contains the compound calcipotriene, a synthetic vitamin D_3 derivative for topical dermatological use.

Chemically, calcipotriene is (5Z,7E,22E,24S)-24-cyclopropyl-9,10-secochola-5,7,10(19),22-tetraene-1α,3β,24-triol-, with the empirical formula $C_{27}H_{40}O_3$, a molecular weight of 412.6, and the following structural formula:



Calcipotriene is a white or off-white crystalline substance. Calcitrene® (calcipotriene) ointment, 0.005% contains calcipotriene 50 µg/g in an ointment base of disodium phosphate dihydrate, edetate disodium, mineral oil, petrolatum, propylene glycol, α-tocopherol, steareth-2 and purified water.

CLINICAL PHARMACOLOGY

In humans, the natural supply of vitamin D depends mainly on exposure to the ultraviolet rays of the sun for conversion of 7-dehydrocholesterol to vitamin D_3 (cholecalciferol) in the skin. Calcipotriene is a synthetic analog of vitamin D_3. Clinical studies with radiolabelled ointment indicate that approximately 6% (± 3%, SD) of the applied dose of calcipotriene is absorbed systemically when the ointment is applied topically to psoriasis plaques or 5% (± 2.6%, SD) when applied to normal skin, and much of the absorbed active is converted to inactive metabolites within 24 hours of application.

Vitamin D and its metabolites are transported in the blood, bound to specific plasma proteins. The active form of the vitamin, 1,25-dihydroxy vitamin D_3 (calcitriol), is known to be recycled via the liver and excreted in the bile. Calcipotriene metabolism following systemic uptake is rapid, and occurs via a similar pathway to the natural hormone. The primary metabolites are much less potent than the parent compound.

There is evidence that maternal 1,25-dihydroxy vitamin D_3 (calcitriol) may enter the fetal circulation, but it is not known whether it is excreted in human milk. The systemic disposition of calcipotriene is expected to be similar to that of the naturally occurring vitamin.

CLINICAL STUDIES

Adequate and well-controlled trials of patients treated with Calcitrene® (calcipotriene) ointment, 0.005% have demonstrated improvement usually beginning after two weeks of therapy. This improvement continued in patients using calcipotriene once daily and twice daily. After 8 weeks of once daily calcipotriene, 56.7% of patients showed at least marked improvements (6.4% showed complete clearing). After 8 weeks of twice daily calcipotriene, 70.0% of patients showed at least marked improvement (11.3% showed complete clearing).

Subtracting percentages of patients using placebo (vehicle only) from percentages of patients using calcipotriene who had at least marked improvements after 8 weeks yields 39.9% for once daily and 49.6% for twice daily. This adjustment for placebo effect indicated that what might appear to be differences between once and twice daily use may reflect differences in the studies independent from the frequency of dosing. Although there was a numerical difference in comparison across studies, twice daily dosing has not been shown to be superior in efficacy to once daily dosing.

Over 400 patients have been treated in open label clinical studies of calcipotriene for periods of up to one year. In half of these studies, patients who previously had not responded well to calcipotriene were excluded. The adverse events in these extended studies included skin irritation in approximately 25% and worsening of psoriasis in approximately 10% of patients. In one of these open label studies, half of the patients no longer required calcipotriene by 16 weeks of treatment, because of satisfactory therapeutic results.

INDICATIONS AND USAGE

Calcitrene® (calcipotriene) ointment, 0.005%, is indicated for the treatment of plaque psoriasis in adults. The safety and effectiveness of topical calcipotriene in dermatoses other than psoriasis have not been established.

CONTRAINDICATIONS

Calcitrene® (calcipotriene) ointment, 0.005%, is contraindicated in those patients with a history of hypersensitivity to any of the components of the preparation. It should not be used by patients with demonstrated hypercalcemia or evidence of vitamin D toxicity. Calcipotriene should not be used on the face.

PRECAUTIONS

General

Use of calcipotriene may cause irritation of lesions and surrounding uninvolved skin. If irritation develops, calcipotriene should be discontinued.

For external use only. Keep out of the reach of children. Always wash hands thoroughly after use.

Transient, rapidly reversible elevation of serum calcium has occurred with use of calcipotriene. If elevation in serum calcium outside the normal range should occur, discontinue treatment until normal calcium levels are restored.

Information for Patients

Patients using calcipotriene should receive the following information and instructions:

1. This medication is to be used as directed by the physician. It is for external use only. Avoid contact with the face or eyes. As with any topical medication, patients should wash hands after application.
2. This medication should not be used for any disorder other than that for which it was prescribed.
3. Patients should report to their physician any signs of local adverse reactions.
4. Patients that apply calcipotriene to exposed portions of the body should avoid excessive exposure to either natural or artificial sunlight (including tanning booths, sun lamps, etc.)

Carcinogenesis, Mutagenesis, Impairment of Fertility

When calcipotriene was applied topically to mice for up to 24 months at dosages of 3, 10 and 30 µg/kg/day (corresponding to 9, 30, and 90 µg/m^2/day), no significant changes in tumor incidence were observed when compared to control. In a study in which albino hairless mice were exposed to both UVR and topically applied calcipotriene, a reduction in the time required for UVR to indicate the formation of skin tumors was observed (statistically significant in males only), suggesting that calcipotriene may enhance the effect of UVR to induce skin tumors. Patients that apply calcipotriene to exposed portions of the body should avoid excessive exposure to either natural or artificial sunlight (including tanning booths, sun lamps, etc.). Physicians may wish to limit or avoid use of phototherapy in patients that use calcipotriene.

Calcipotriene did not elicit any mutagenic effects in an Ames mutagenicity assay, a mouse lymphoma TK locus assay, a human lymphocyte chromosome aberration assay, or in a micronucleus assay conducted in mice.

Studies in rats at doses up to 54 µg/kg/day (324 µg/m^2/day) of calcipotriene indicated no impairment of fertility or general reproductive performance.

Pregnancy

Teratogenic Effects: Pregnancy Category C

Studies of teratogenicity were done by the oral route where bioavailability is expected to be approximately 40-60% of the administered dose. In rabbits, increased maternal and fetal toxicity were noted at a dosage of 12 µg/kg/day (132 µg/m^2/day); a dosage of 36 µg/kg/day (396 µg/m^2/day) resulted in a significant increase in the incidence of incomplete ossification of the pubic bones and forelimb phalanges of fetuses. In a rat study, a dosage of 54 µg/kg/day (318 µg/m^2/day) resulted in a significantly increased incidence of skeletal abnormalities (enlarged fontanelles and extra ribs). The enlarged fontanelles are most likely due to calcipotriene's effect upon calcium metabolism. The estimated maternal and fetal no-effect exposure levels in the rat (43.2 µg/m^2/day) and rabbit (17.6 µg/m^2/day) studies are approximately equal to the expected human systemic exposure level (18.5 µg/m^2/day) from dermal application. There are no adequate and well-controlled studies in pregnant women. Therefore, Calcitrene® (calcipotriene) ointment, 0.005% should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers

It is not known whether calcipotriene is excreted in human milk. Because many drugs are excreted in human milk, caution should be excercised when Calcitrene® (calcipotriene) ointment, 0.005% is administered to a nursing woman.

Pediatric Use

Safety and effectiveness of calcipotriene in pediatric patients have not been established. Because of a higher ratio of skin surface area to body mass, pediatric patients are at greater risk than adults of systemic adverse effects when they are treated with topical medication.

Geriatric Use

Of the total number of patients in clinical studies of Calcitrene® (calcipotriene) ointment, 0.005%, approximately 12% were 65 or older, while approximately 4% were 75 and over. The results of an analysis of severity of skin-related adverse events showed a statistically significant difference for subjects over 65 years (more severe) compared to those under 65 years (less severe).

ADVERSE REACTIONS

In controlled clinical trials, the most frequent adverse reactions reported for calcipotriene were burning, itching and skin irritation, which occurred in approximately 10-15% of patients. Erythema, dry skin, peeling, rash, dermatitis, worsening of psoriasis including development of facial/scalp psoriasis were reported in 1 to 10% of patients. Other experiences reported in less than 1% of patients included skin atrophy, hyperpigmentation, hypercalcemia, and folliculitis. Once daily dosing has not been shown to be superior in safety to twice daily dosing.

OVERDOSAGE

Topically applied calcipotriene can be absorbed in sufficient amounts to produce systemic effects. Elevated serum calcium has been observed with excessive use of Calcitrene® (calcipotriene) ointment, 0.005%.

DOSAGE AND ADMINISTRATION

Apply a thin layer of Calcitrene® (calcipotriene) ointment, 0.005% once or twice daily and rub in gently and completely.

HOW SUPPLIED

Calcitrene® (calcipotriene) ointment, 0.005% is available in:
60 gram aluminum tube **NDC (51672-5278-3)**
120 gram aluminum tube **NDC (51672-5278-4)**

STORAGE

Store at controlled room temperature 15°C-25°C (59°F-77°F). Do not freeze.

Manufactured by:
Glenmark Generics Ltd.
Colvale-Bardez, Goa 403 513, India

Distributed by:
TaroPharma a division of Taro Pharmaceuticals U.S.A., Inc.
Hawthorne, NY 10532

October 2012

ACNE CONTROVERSIES

Risks associated with isotretinoin, contraceptive pills marginal

BY JOHN JESITUS
SENIOR STAFF CORRESPONDENT

Miami Beach, Fla. — Popular media coverage of purported links between isotretinoin and inflammatory bowel disease (IBD) are largely overblown, as are patients' concerns regarding the risks of oral contraceptive pills (OCPs) for acne, according to an expert.

Regarding the highly publicized link between OCPs and venous thromboembolism (VTE), says Julie C. Harper, M.D., "We have traditionally thought that pills with a higher estrogen dose were associated with the risk of venous clotting. We still believe that, but over the last decade or so, we've been paying more attention to the progestin." Dr. Harper, who spoke at the annual meeting of the American Academy of Dermatology, is clinical associate professor of dermatology, University of Alabama, Birmingham.

Early studies in this regard showed no association, she says. "But more recently, studies have shown that those pills that contain third-generation progestins (especially drospirenone) may be associated with a higher risk of venous clotting."

One such study involving 3.3 million woman-years of oral contraceptive use showed that the risk of VTEs among those who did not use oral contraceptives was 3.01 per 10,000 woman-years, versus 7.9 per 10,000 woman-years for drospirenone users (Lidegaard Ø, Løkkegaard E, Svendsen AL, Agger C. *BMJ*. 2009;339:b2890). Likewise, a retrospective, case-controlled U.S. study showed that the incidence of nonfatal VTEs among drospirenone users was 30.8 per 100,000 woman-years, versus 12.5 per 100,000 woman-years for levonorgestrel (Jick SS, Hernandez RK. *BMJ*. 2011;342:d2151).

QUICK READ

For patients with acne, thromboembolic risks of oral contraceptives are marginal, and the association between isotretinoin and IBD is tenuous.

LOW RISK OF AES

Accordingly, "Our patients may hear that drospirenone-containing OCPs are associated with a doubled risk of venous clotting versus other pills. That sounds alarming. But to put it in perspective, when you look at the total numbers of women in these studies, the absolute risk is a marginal change, from probably six VTEs per 10,000 woman-years to 10 per 10,000 woman-years (*http://www.fda.gov/drugs/drugsafety/ucm273021.htm*)."

As for other adverse events, Dr. Harper says, risk of ischemic stroke rises around 2.5-fold for women ages 20 to 24 who use OCPs. However, she says, "The numbers of women in their 20s who have strokes and myocardial infarctions are very low at baseline." Moreover, recent research highlights other factors that help predict which OCP users may face the highest risks. For example, "Eighty percent of heart attacks in OCP users can be attributed to cigarette smoking. We are also considering other risk factors like diabetes and hypertension." By the same token, "There's not a strong association between OCPs and breast cancer. But in women on birth control pills, breast cancer is diagnosed earlier than in women who are not on birth control pills (Bjelic-Radisic V, Petru E. *Wien Med Wochenschr*. 2010;160(19-20):483-486). This can serve as a reminder to dermatologists — traditionally, women who have received prescriptions for birth control pills have also had well-woman examinations, because they'd been getting these pills from an OB/GYN."

> "**Eighty percent** of **heart attacks** in OCP users can be attributed to **cigarette smoking**. We are also considering other risk factors like diabetes and hypertension."
>
> **Julie C. Harper, M.D.**
> Birmingham, Ala.

ACNE CONTROVERSIES see page 27

ACCURATE ASSESSMENT

Finding cause of chronic pruritus helps to narrow down treatment strategies

BY ILYA PETROU, M.D. | SENIOR STAFF CORRESPONDENT

MIAMI BEACH, FLA. — An accurate assessment of the potential cause of chronic pruritus, coupled by a careful selection of current standard treatments as well as new and emerging therapies, can be instrumental in helping to quell the symptoms of this sometimes severely debilitating condition.

Identifying the cause of pruritus is essential and, according to Sarina Elmariah, M.D., Ph.D., it is crucial that the clinician distinguish between pruritus that reflects inflammation in the skin and that which reflects inflammation or damage within the nervous system, as conclusions from this critical assessment will help direct appropriate therapy.

"As the pathophysiology of pruritus in most cutaneous or systemic disorders remains unclear, antipruritic therapy is often directed against a variety of targets including the epidermal barrier, immune system or the nervous system," says Dr. Elmariah, of the department of dermatology, Massachusetts General Hospital, Harvard Medical School, Boston. Dr. Elmariah spoke at the annual meeting of the American Academy of Dermatology.

"While topical therapies are the cornerstone of anti-pruritic treatment, combining such therapies with systemic anti-itch agents may prove beneficial for more challenging cases involving generalized pruritus or pruritus due to systemic disease," she says.

ESTABLISHING TREATMENT STRATEGIES

After taking a thorough history to elicit timing, duration, location, severity and potential triggers for a patient's itch, Dr. Elmariah will assess the integrity of the skin for signs of inflammation, dryness and barrier disruption, helping to further establish the etiology of the pruritus and potential treatment strategies.

Particularly in elderly patients although not exclusively, one of the most common causes of chronic pruritus is xerosis Dr. Elmariah says, followed by other chronic inflammatory skin diseases such as atopic dermatitis, psoriasis, seborrheic dermatitis, lichen planus and urticaria.

While xerosis can be best treated by avoiding bathing in hot water, not using harsh soaps, and moisturizing with heavy creams or ointments, Dr. Elmariah says inflammatory skin diseases can be treated with several approaches including emollients, topical corticosteroids, phototherapy, oral antihistamines, as well as systemic immunosuppressive agents for more extreme cases.

> "Many medications can cause pruritus even after years of being taken, particularly in elderly patients where polypharmacy is an issue."
>
> **Sarina Elmariah, M.D., Ph.D.**
> Boston

Though idiopathic pruritus is relatively uncommon, it is one of the most difficult types of pruritus to treat because the therapeutic target remains unknown, she says. In many cases, however, underlying systemic diseases are identified as causing pruritus, whether due to renal or hepatic disease, endocrine abnormalities or underlying hematologic malignancies.

In those cases that remain "idiopathic," Dr. Elmariah says she will often proceed with phototherapy or oral neuromodulatory agents, such as anticonvulsants, selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs) and other antidepressants, or drugs that alter opioid signaling to help with potential neuropathic components and/or when underlying systemic disease is contributing to the patient's itch.

"Pouring on topical steroids or giving antihistamines doesn't help when the patient's itch isn't due to inflammation or excess histamine in the skin," she says. "Finding the 'right' therapy may take time and will often require patience on the part of the patient and physician."

DRUG REACTIONS

A cutaneous reaction to medications is another common cause that is often overlooked in patients with chronic pruritus, Dr. Elmariah says. This possibility must always be considered in the clinical evaluation and diagnostic follow-up of the patient.

"It is important not to overlook potential drug reactions as the cause of 'idiopathic itch.' Many medications can cause pruritus even after years of being taken, particularly in elderly patients where polypharmacy is an issue. To adequately assess if a drug is the culprit, I find that patients must discontinue the drug for at least three to six months," Dr. Elmariah says.

The gold standard of topical therapy for chronic pruritus is corticosteroids in cream or

CHRONIC PRURITUS see page 27

QUICK READ

Pruritus, particularly when chronic and of an unknown etiology, can be difficult to treat. Individualizing treatment protocols in each patient using standard and emerging therapies can help to better manage symptoms.

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USTEKINUMAB:

Sustainability established in patients with psoriatic arthritis

from page 18

and 49.5 percent vs. 22.8 percent) and PSUMMIT 2 (43.7 percent and 43.8 percent vs. 20.2 percent).

ACR 20 responder rates for PSUMMIT 2 patients naïve to anti-TNF-alpha treatment were similar to those observed in the PSUMMIT 1 population, but higher than for PSUMMIT 2 patients with a history of anti-TNF-alpha treatment who had more active disease at baseline. Among anti-TNF-alpha-experienced patients, the ACR 20 response rate was higher among those who had received a single anti-TNF-alpha agent versus more than one, although the population with the latter history was small.

Psoriasis Area Severity Index 75 (PASI 75) responder rates at week 24 (assessed in patients with ≥ 3 percent body surface area involvement with psoriasis at entry) were significantly higher for the ustekinumab 45 and 90 mg versus placebo in both PSUMMIT 1 (57.2 percent and 62.4 percent vs. 11 percent) and PSUMMIT 2 (51.3 percent and 55.6 percent vs. 5.0 percent).

> The benefits of ustekinumab in the PSUMMIT and psoriasis trials … provide some insights on pathophysiology.

Analyses of secondary efficacy endpoints related to joint symptoms (ACR 50 and ACR 70 response rates, 28-joint disease activity score based on CRP, improvements and enthesitis and dactylitis scores), also consistently showed significant differences favoring ustekinumab versus placebo, as did changes in the Health Assessment Questionnaire-Disability Index (HAQ-DI).

ASSESSING AES

In the two studies, patients with a < 5 percent improvement in tender and swollen joint counts at week 16 were considered nonresponders in the primary efficacy analysis and switched to ustekinumab 45 mg if they were receiving placebo or to ustekinumab 90 mg if they were receiving the lower dose. All patients still on placebo at week 24 were crossed over to ustekinumab. Analyses of data collected through week 52 showed ustekinumab treatment benefits were generally sustained or improved.

Adverse event rates were similar in the ustekinumab and control groups at the end of the 16-week placebo-controlled period. Rates of serious adverse events were low and also similar for ustekinumab and placebo. There were no deaths or opportunistic infections in the studies, and during follow-up from week 24 to 52, there were five myocardial infarctions and 1 cerebrovascular accident.

"It is difficult to know the impact of ustekinumab on cardiovascular risk based on these events since they did not occur during the placebo-controlled period and do not appear to be dose-related," Dr. Ritchlin says.

Dr. Ritchlin also observed that the benefits of ustekinumab in the PSUMMIT and psoriasis trials taken together with the fact that neither it nor anti-IL-17 antibodies or anti-IL-17R antibody demonstrated efficacy for rheumatoid arthritis provide some insights on pathophysiology.

"These findings support a disease pathogenesis model for psoriasis and psoriatic arthritis that includes both a Th1 and Th17 immune response where IL-23, IL-17, and possibly other cytokines released by Th17 cells, such as IL-22, are of central importance," he says.

> "There is a major unmet need for alternative therapies in patients with psoriatic arthritis who cannot take or fail an anti-TNF-alpha agent."
>
> **Christopher Ritchlin, M.D., M.P.H.**
> Rochester, N.Y.

The one-year results were recently published for PSUMMIT 1 (McInnes IB, Kavanaugh A, Gottlieb AB, et al. *Lancet.* 2013 Jun 12. Epub ahead of print) and reported for PSUMMIT 2 at the 2013 Annual European Congress of Rheumatology. Janssen submitted a biologic license application seeking approval for ustekinumab for the treatment of active psoriatic arthritis in December 2012. **DT**

Disclosures: Dr. Ritchlin is a consultant to and receives grant/research support from Janssen and other companies marketing or developing products for the treatment of psoriatic arthritis.

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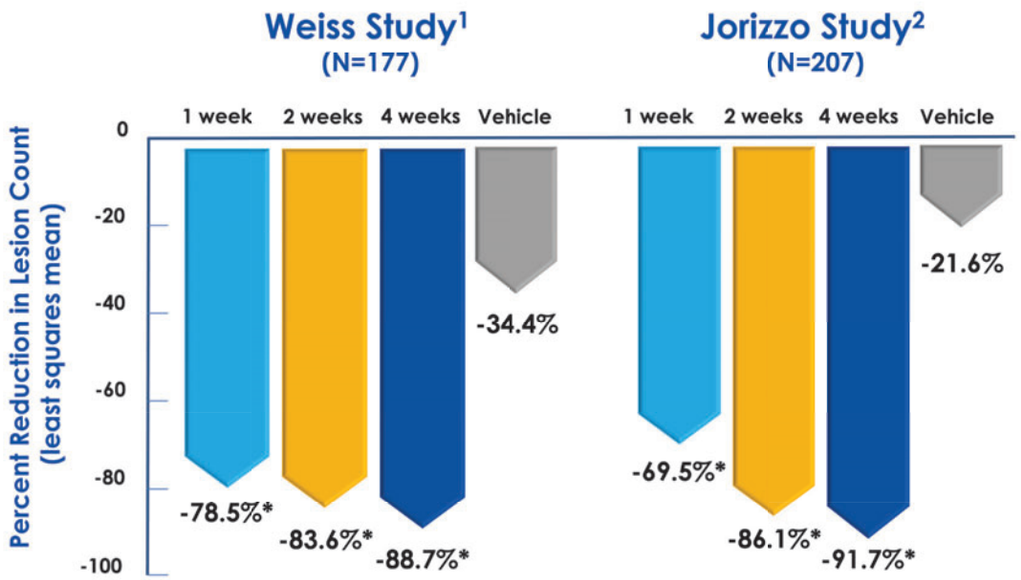

*P<.001 vs vehicle.

Results from two Phase 3 vehicle-controlled, randomized, double-blind, multicenter studies of patients (N=384) with actinic keratoses. Secondary endpoint of percent reduction (least squares mean) in AK lesions at 1, 2 and 4 weeks compared active to vehicle.

Significant mean reduction in the number of AK lesions with 1 week of treatment compared to vehicle[1,2]

- Flexibility to prescribe for as little as 1 week or as long as 4 weeks, depending on tolerability and treatment goals.

Carac is indicated for the topical treatment of multiple actinic or solar keratoses of the face and anterior scalp.

Important Safety Information

Carac is contraindicated in women who are nursing, pregnant or may become pregnant as fluorouracil may cause fetal harm.

Carac should not be used in patients with dihydropyrimidine dehydrogenase (DPD) enzyme deficiency.

Rarely, unexpected, systemic toxicity (e.g., stomatitis, diarrhea, neutropenia, and neurotoxicity) associated with parenteral administration of fluorouracil has been attributed to deficiency of dihydropyrimidine dehydrogenase "DPD" activity. Symptoms included severe abdominal pain, bloody diarrhea, vomiting, fever, and chills.

Carac should be discontinued if severe abdominal pain, bloody diarrhea, vomiting, fever, or chills develop when using the product.

Application of Carac to mucous membranes should be avoided due to the possibility of local inflammation and ulceration.

In clinical trials, the most common drug-related adverse events were application site reactions (94.6%), which included: erythema, dryness, burning, erosion, pain, and edema, and eye irritation (5.4%).

Patients using Carac should avoid prolonged exposure to sunlight or other forms of ultraviolet irradiation during treatment, as the intensity of the reaction maybe increased.

Please see brief summary of full Prescribing Information on adjacent page.

References: 1. Weiss J, Menter A, Hevia O, et al. Effective treatment of actinic keratosis with 0.5% fluorouracil cream for 1, 2, or 4 weeks. *Cutis.* 2002;70(suppl 2):2229. **2.** Jorizzo J, Stewart D, Bucko A, et al. Randomized trial evaluating a new 0.5% fluorouracil formulation demonstrates efficacy after 1-, 2-, or 4-week treatment in patients with actinic keratosis. *Cutis.* 2002;70:335-339.

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BRIEF SUMMARY

IMPORTANT NOTE: This information is a BRIEF SUMMARY of the complete prescribing information provided with the product and therefore should not be used as the basis for prescribing the product. This summary has been prepared by deleting information from the complete prescribing information such as certain text, tables, and references. The physician should be thoroughly familiar with the complete prescribing information before prescribing the product.

FOR TOPICAL DERMATOLOGICAL USE ONLY (NOT FOR OPHTHALMIC, ORAL, OR INTRAVAGINAL USE)

INDICATIONS AND USAGE

Carac is indicated for the topical treatment of multiple actinic or solar keratoses of the face and anterior scalp.

CONTRAINDICATIONS

Fluorouracil may cause fetal harm when administered to a pregnant woman. Fluorouracil is contraindicated in women who are or may become pregnant. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus.

No adequate and well-controlled studies have been conducted in pregnant women with either topical or parenteral forms of fluorouracil. One birth defect (ventricular septal defect) and cases of miscarriage have been reported when fluorouracil was applied to mucous membrane areas. Multiple birth defects have been reported in the fetus of a patient treated with intravenous fluorouracil.

Animal reproduction studies have not been conducted with Carac. Fluorouracil, the active ingredient, has been shown to be teratogenic in mice, rats, and hamsters when administered parenterally at doses greater than or equal to 10, 15 and 33 mg/kg/day, respectively, [4X, 11X and 20X, respectively, the Maximum Recommended Human Dose (MRHD) based on body surface area (BSA)]. Fluorouracil was administered during the period of organogenesis for each species. Embryolethal effects occurred in monkeys at parenteral doses greater than 40 mg/kg/day (65X the MRHD based on BSA) administered during the period of organogenesis.

Carac should not be used in patients with dihydropyrimidine dehydrogenase (DPD) enzyme deficiency. A large percentage of fluorouracil is catabolized by the enzyme dihydropyrimidine dehydrogenase (DPD). DPD enzyme deficiency can result in shunting of fluorouracil to the anabolic pathway, leading to cytotoxic activity and potential toxicities.

Carac is contraindicated in patients with known hypersensitivity to any of its components.

WARNINGS

The potential for a delayed hypersensitivity reaction to fluorouracil exists. Patch testing to prove hypersensitivity may be inconclusive.

Patients should discontinue therapy with Carac if symptoms of DPD enzyme deficiency develop.

Rarely, unexpected, systemic toxicity (e.g. stomatitis, diarrhea, neutropenia, and neurotoxicity) associated with parenteral administration of fluorouracil has been attributed to deficiency of dihydropyrimidine dehydrogenase "DPD" activity. One case of life threatening systemic toxicity has been reported with the topical use of 5% fluorouracil in a patient with a complete absence of DPD enzyme activity. Symptoms included severe abdominal pain, bloody diarrhea, vomiting, fever, and chills. Physical examination revealed stomatitis, erythematous skin rash, neutropenia, thrombocytopenia, inflammation of the esophagus, stomach, and small bowel. Although this case was observed with 5% fluorouracil cream, it is unknown whether patients with profound DPD enzyme deficiency would develop systemic toxicity with lower concentrations of topically applied fluorouracil.

Applications to mucous membranes should be avoided due to the possibility of local inflammation and ulceration.

PRECAUTIONS

General

There is a possibility of increased absorption through ulcerated or inflamed skin.

Information for the Patient

Patients using Carac should receive the following information and instructions:

1. This medication is to be used as directed.
2. This medication should not be used for any disorder other than that for which it was prescribed.
3. It is for external use only.
4. Avoid contact with the eyes, eyelids, nostrils, and mouth.
5. Cleanse affected area and wait 10 minutes before applying Carac.
6. Wash hands immediately after applying Carac.
7. Avoid prolonged exposure to sunlight or other forms of ultraviolet irradiation during treatment, as the intensity of the reaction may be increased.
8. Most patients using Carac get skin reactions where the medicine is used. These reactions include redness, dryness, burning, pain, erosion (loss of the upper layer of skin), and swelling. Irritation at the application site may persist for two or more weeks after therapy is discontinued. Treated areas may be unsightly during and after therapy.
9. If you develop abdominal pain, bloody diarrhea, vomiting, fever, or chills while on Carac therapy, stop the medication and contact your physician and/or pharmacist.
10. Report any side effects to the physician and/or pharmacist.

Laboratory Tests

To rule out the presence of a frank neoplasm, a biopsy may be considered for those areas failing to respond to treatment or recurring after treatment.

Carcinogenesis, Mutagenesis and Impairment of Fertility

Adequate long-term studies in animals to evaluate carcinogenic potential have not been conducted with fluorouracil. Studies with the active ingredient of Carac, fluorouracil, have shown positive effects in *in vitro* and *in vivo* tests for mutagenicity and on impairment of fertility in *in vivo* animal studies. *Fluorouracil* produced morphological transformation of cells in *in vitro* cell transformation assays. Morphological transformation was also produced in an *in vitro* assay by a metabolite of fluorouracil, and the transformed cells produced malignant tumors when injected into immunosuppressed syngeneic mice.

Fluorouracil has been shown to exert mutagenic activity in yeast cells, *Bacillus subtilis*, and *Drosophila* assays. In addition, fluorouracil has produced chromosome damage at concentrations of 1.0 and 2.0 mcg/mL in an *in vitro* hamster fibroblast assay, was positive in a microwell mouse lymphoma assay, and was positive in *in vivo* micronucleus assays in rats and mice following intraperitoneal administration. Some patients receiving cumulative doses of 0.24 to 1.0 g of fluorouracil parenterally have shown an increase in numerical and structural chromosome aberrations in peripheral blood lymphocytes.

Fluorouracil has been shown to impair fertility after parenteral administration in rats. Fluorouracil administered at intraperitoneal doses of 125 and 250 mg/kg has been shown to induce chromosomal aberrations and changes in chromosome organization of spermatogonia in rats. In mice, single-dose intravenous and intraperitoneal injections of fluorouracil have been reported to kill differentiated spermatogonia and spermatocytes at a dose of 500 mg/kg and produce abnormalities in spermatids at 50 mg/kg.

Pediatric Use

Actinic keratosis is not a condition seen within the pediatric population, except in association with rare genetic diseases. Carac should not be used in children. The safety and effectiveness of Carac have not been established in patients less than 18 years old.

Geriatric Use

No significant differences in safety and efficacy measures were demonstrated in patients age 65 and older compared to all other patients.

Pregnancy

Teratogenic Effects: Pregnancy Category X

See CONTRAINDICATIONS

Nursing Women

It is not known whether fluorouracil is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from fluorouracil, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

ADVERSE REACTIONS

The following were adverse events considered to be drug-related and occurring with a frequency of ≥1% with Carac: application site reaction (94.6%), and eye irritation (5.4%). The signs and symptoms of facial irritation (application site reaction) are presented below.

Summary of Facial Irritation Signs and Symptoms - Pooled Phase 3 Studies

Clinical Sign or Symptom	Active One Week N=85	Active Two Week N=87	Active Four Week N=85	ALL Active Treatments N=257	Vehicle Treatments N=127
	n (%)	n (%)	n (%)	n (%)	n (%)
Erythema	76 (89.4)	82 (94.3)	82 (96.5)	240 (93.4)	76 (59.8)
Dryness	59 (69.4)	76 (87.4)	79 (92.9)	214 (83.3)	60 (47.2)
Burning	51 (60.0)	70 (80.5)	71 (83.5)	192 (74.7)	28 (22.0)
Erosion	21 (24.7)	38 (43.7)	54 (63.5)	113 (44.0)	17 (13.4)
Pain	26 (30.6)	34 (39.1)	52 (61.2)	112 (43.6)	7 (5.5)
Edema	12 (14.1)	28 (32.2)	51 (60.0)	91 (35.4)	6 (4.7)

During clinical trials, irritation generally began on day 4 and persisted for the remainder of treatment. Severity of facial irritation at the last treatment visit was slightly below baseline for the vehicle group, mild to moderate for the 1 week active treatment group, and moderate for the 2 and 4 week active treatment groups. Mean severity declined rapidly for each active group after completion of treatment and was below baseline for each group at the week 2 post-treatment follow-up visit.

Thirty-one patients (12% of those treated with Carac in the Phase 3 clinical studies) discontinued study treatment early due to facial irritation. Except for three patients, discontinuation of treatment occurred on or after day 11 of treatment.

Eye irritation adverse events, described as mild to moderate in intensity, were characterized as burning, watering, sensitivity, stinging and itching. These adverse events occurred across all treatment arms in one of the two Phase 3 studies.

Summary of All Adverse Events Reported in ≥ 1% of Patients in the Combined Active Treatment and Vehicle Groups - Pooled Phase 3 Studies

	9721 and 9722 Combined				
Adverse Event	Active One Week N=85	Active Two Week N=87	Active Four Week N=85	ALL Active Treatments N=257	Vehicle Treatments N=127
	n (%)	n (%)	n (%)	n (%)	n (%)
BODY AS A WHOLE	7 (8.2)	6 (6.9)	12 (14.1)	25 (9.7)	15 (11.8)
Headache	3 (3.5)	2 (2.3)	3 (3.5)	8 (3.1)	3 (2.4)
Common Cold	4 (4.7)	0	2 (2.4)	6 (2.3)	3 (2.4)
Allergy	0	2 (2.3)	1 (1.2)	3 (1.2)	2 (1.6)
Infection Upper Respiratory	0	0	0	0	2 (1.6)
MUSCULOSKELETAL	1 (1.2)	1 (1.1)	1 (1.2)	3 (1.2)	5 (3.9)
Muscle Soreness	0	0	0	0	2 (1.6)
RESPIRATORY	5 (5.9)	0	1 (1.2)	6 (2.3)	6 (4.7)
Sinusitis	4 (4.7)	0	0	4 (1.6)	2 (1.6)
SKIN & APPENDAGES	78 (91.8)	83 (95.4)	82 (96.5)	243 (94.6)	85 (66.9)
Application Site Reaction	78 (91.8)	83 (95.4)	82 (96.5)	243 (94.6)	83 (65.4)
Irritation Skin	1 (1.2)	0	2 (2.4)	3 (1.2)	0
SPECIAL SENSES	6 (7.1)	4 (4.6)	6 (7.1)	16 (6.2)	6 (4.7)
Eye Irritation	5 (5.9)	3 (3.4)	6 (7.1)	14 (5.4)	3 (2.4)

Adverse Experiences Reported by Body System

In the Phase 3 studies, no serious adverse event was considered related to study drug. A total of five patients, three in the active treatment groups and two in the vehicle group, experienced at least one serious adverse event. Three patients died as a result of adverse event(s) considered unrelated to study drug (stomach cancer, myocardial infarction and cardiac failure).

Post-treatment clinical laboratory tests other than pregnancy tests were not performed during the Phase 3 clinical studies. Clinical laboratory tests were performed during conduct of a Phase 2 study of 104 patients and 21 patients in a Phase 1 study. No abnormal serum chemistry, hematology, or urinalysis results in these studies were considered clinically significant.

DOSAGE AND ADMINISTRATION

Carac cream should be applied once a day to the skin where actinic keratosis lesions appear, using enough to cover the entire area with a thin film. Carac cream should not be applied near the eyes, nostrils or mouth. Carac cream should be applied ten minutes after thoroughly washing, rinsing, and drying the entire area. Carac cream may be applied using the fingertips. Immediately after application, the hands should be thoroughly washed. Carac should be applied up to 4 weeks as tolerated. Continued treatment up to 4 weeks results in greater lesion reduction. Local irritation is not markedly increased by extending treatment from 2 to 4 weeks, and is generally resolved within 2 weeks of cessation of treatment.

OVERDOSE

Ordinarily, topical overdosage will not cause acute problems. If Carac is accidentally ingested, induce emesis and gastric lavage. Administer symptomatic and supportive care as needed. If contact is made with the eye, flush with copious amounts of water.

HOW SUPPLIED

Cream - 30 gram tube NDC 0187-5200-30

Store at Controlled Room Temperature 20° to 25° C (68° to 77° F) [see USP].

Prescribing Information as of November 2012

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CRC-006

CHRONIC PRURITUS:

Identifying cause of condition can narrow treatment strategies from page 22

ointment bases. In those cases where pruritus is due to primary inflammatory skin disease and where topical regimens prove inadequate, effective in gaining control of inflammation and associated pruritus.

For idiopathic or noninflammatory pruritic skin recalcitrant to topical therapy, Dr. Elmariah says she may try phototherapy as well as a host of oral neuromodulatory agents — including her first choice, gabapentin, due to its high tolerability and good efficacy, followed by SSRIs, SNRIs, mu-opioid antagonists or kappa-opioid agonists. Finding the most effective drug in a given patient can be very challenging and therapy needs to be individualized, as there is no magic bullet across the cases, she says.

> "Pouring on **topical steroids** or giving antihistamines **doesn't help** when the patient's itch isn't due to inflammation or excess histamine in the skin."
>
> **Sarina Elmariah, M.D., Ph.D.**
> Boston

"There are many medications already available that can help to effectively treat pruritus of any cause. As our understanding about the mechanisms of itch sensation and cutaneous inflammation grows, our therapeutic armamentarium is also expanding and here, new and innovative therapies to target itch pathways are just on the horizon," Dr. Elmariah says. **DT**

Disclosures: Dr. Elmariah reports no relevant financial interests.

ACNE CONTROVERSIES:

Risks associated with isotretinoin, contraceptive pills marginal from page 21

The fact that dermatologists don't perform breast exams or Pap smears doesn't mean they can't prescribe OCPs, she says. "But when we do, we need to remind our patients to have an annual well-woman examination."

Additionally, "We spend a lot of time talking about risks with our patients. But there are also some benefits of OCPs that patients don't usually know about. These include protection against ovarian and endometrial cancers. OCPs also help with control of bleeding in the monthly cycle."

EXPLAINING IBD ASSOCIATION

As for isotretinoin, she says that when patients hear about large awards won by patients who claim the drug gave them IBD, "They assume this is a known, strong association. But when you look through the literature, you can't find it. A few studies show a statistically significant association between isotretinoin and IBD. But two very large, well-done studies showed absolutely no association (Alhusayen RO, Juurlink DN, Mamdani MM, et al. *J Invest Dermatol*. 2013;133(4):907-912; Etminan M, Bird ST, Delaney JA, et al. *JAMA Dermatol*. 2013;149(2):216-220).

Conversely, Dr. Harper says that until six or seven years ago, "The verdict was that diet is not associated with acne. We can't say that anymore," because newer evidence suggests the contrary. The bulk of these studies tend to show that hyperglycemic foods, which promote insulin response, may make acne tougher to treat, she says. However, "I don't routinely adjust the diets of people who have acne yet. We need more evidence. But I'm glad we're talking about it again."

> "I don't routinely adjust the diets of people who have acne yet. We need more evidence."
>
> **Julie C. Harper, M.D.**
> Birmingham, Ala.

Somewhat similarly, Dr. Harper says that many studies show that a particular laser or light source appears effective for acne. "But most of these studies are too small, too short or lack a good control group. We need more information." Some devices indeed deliver benefits, Dr. Harper says. "But right now, these are adjunctive treatments at best. They don't replace the treatments we already have — they complement them." **DT**

Disclosures: Dr. Harper has been a speaker, adviser and investigator for Bayer/Intendis.

ALTERNATIVES:

Don't be too quick to discard alternative treatments, clinician says

from page 1

possibly in part fueled by the great interest some of their patients have in this field.

"While conventional medicine still holds most of the answers, it may not have them all. Our patients are aware of this and many are searching in the 'alternative' realm for treatment solutions," says Dr. Lio, assistant professor of clinical dermatology and pediatrics, Northwestern University Feinberg School of Medicine, Chicago. "I find that if I do not mention or discuss alternative approaches with my patients, particularly those with a chronic and debilitating disease such as atopic dermatitis, they will often be quickly discouraged and seek help elsewhere."

UNCONVENTIONAL THINKING

Evidence-based conventional medicine is practiced by mainstream dermatologists largely because of the traditional education they receive in medical school and specialist training. This may discourage outside-the-box thinking, according to Dr. Lio.

"Dermatologists may not be aware of the positive data that is out there regarding the treatment successes achieved with alternative therapies and, therefore, they should not be too quick to discard the whole of alternative treatments as humbug," Dr. Lio says.

In controlled settings, many treatments have been tested and found not to work as claimed or hoped, Dr. Lio says; however, a much larger number of therapies do not yet have sufficient evidence upon which to pass judgment. Therefore, he encourages physicians to keep an open mind.

In one study, researchers found that 51 percent of patients with eczema reported use of one or more forms of alternative medicine, with homeopathy, health foods and herbal remedies being the most common (Jensen P. *Acta Derm Venereol.* 1990;70(5):421-424). A similar questionnaire-based study of 70 patients with atopic dermatitis gave almost identical results, with 50 percent reporting use of one or more forms of alternative medicine for their skin disease (Simpson EL, Basco M, Hanifin J. *Am J Contact Dermat.* 2003;14(3):144-147).

Many parents or guardians of pediatric patients will often prefer and request more natural treatment approaches based in alternative medicine, Dr. Lio says, because they are apprehensive of pharmacological-based treatments such as topical and oral corticosteroids, in part due to the associated potential adverse events.

"Even if you are pessimistic regarding the positive data available on alternative therapies, I think it is still important to embrace it and talk about it with your patients, leaving no stone unturned in the planning of the patient's comprehensive treatment strategy," he says.

ATOPIC DERMATITIS REMEDIES

Some alternative therapies that have been shown to ameliorate the symptoms of atopic dermatitis include the supplementation of essential fatty acids, traditionally thought to be deficient in patients with atopic dermatitis.

According to Dr. Lio, the topical application of sunflower seed oil, coconut oil, borage oil and primrose oil, as well as vitamin B12 have all been shown to be effective in improving the symptoms of atopic dermatitis in some studies, possibly due to the anti-inflammatory and/or antibacterial effects that these agents have. Oral vitamin D supplementation and probiotics have also shown effectiveness in improving symptoms of atopic dermatitis. This could result in the patient requiring fewer topical pharmacological-based medicines and a tapering off of systemic medicines.

"Though efficacy with these alternative therapies has been shown in varying degrees, more research is required before they can be considered as potentially viable treatment options. A better understanding of their mechanisms is needed in order to ensure more robust effects and safety before their roles can be more clearly defined," Dr. Lio says.

The more severe the disease or condition, however, the more the potential risk one may have to take in its treatment, he says. The "riskiness" of a given medicine is usually very closely associated with its potency and therapeutic effect, and, according to Dr. Lio, finding the delicate balance in the risk-benefit ratio of a proposed therapy is key in choosing optimal treatment in patients, whether conventional or alternative treatment approaches.

"I think there are a lot of situations in dermatology where conventional medicines do not work well enough and here, alternative treatments could help fill that void," he says. "In those patients who are interested in other less-conventional approaches and when their disease is not life or health-threatening, alternative medicine could be tried, particularly where traditional medicine has failed." **DT**

Disclosures: Dr. Lio reports no relevant financial interests.

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- Local adverse reactions may be more likely to occur with occlusive use, prolonged use or use of higher potency corticosteroids. Reactions may include atrophy, striae, telangiectasias, burning, itching, irritation, dryness, folliculitis, acneiform eruptions, hypopigmentation, perioral dermatitis, allergic contact dermatitis, secondary infection, and miliaria. Some local reactions may be irreversible.
- Safety and effectiveness of Topicort® Topical Spray in patients younger than 18 years of age have not been studied; therefore use in pediatric patients is not recommended.

TaroPharma®

See brief summary of Prescribing Information on reverse side.

AD100-0033 July 2013

TOPICORT® (desoximetasone) Topical Spray, 0.25%
Rx Only

BRIEF SUMMARY

1 INDICATIONS AND USAGE
Topicort® Topical Spray is a corticosteroid indicated for the treatment of plaque psoriasis in patients 18 years of age or older.

4 CONTRAINDICATIONS
None

5 WARNINGS AND PRECAUTIONS

5.1 Effect on Endocrine System
Topicort® Topical Spray is a topical corticosteroid that has been shown to suppress the hypothalamic-pituitary-adrenal (HPA) axis.

Systemic absorption of topical corticosteroids can produce reversible HPA axis suppression with the potential for glucocorticosteroid insufficiency. This may occur during treatment or upon withdrawal of the topical corticosteroid.

In a study including 21 evaluable subjects 18 years of age or older with moderate to severe plaque psoriasis, adrenal suppression was identified in 1 out of 12 subjects having involvement of 10-15% of body surface area (BSA) and 2 out of 9 subjects having involvement of >15% of BSA after treatment with Topicort® Topical Spray twice a day for 28 days. [*see Clinical Pharmacology (12.2)*]

Because of the potential for systemic absorption, use of topical corticosteroids may require that patients be periodically evaluated for HPA axis suppression. Factors that predispose a patient using a topical corticosteroid to HPA axis suppression include the use of high potency steroids, larger treatment surface areas, prolonged use, use of occlusive dressings, altered skin barrier, liver failure and young age.

An ACTH stimulation test may be helpful in evaluating patients for HPA axis suppression.

If HPA axis suppression is documented, an attempt should be made to gradually withdraw the drug, to reduce the frequency of application, or to substitute a less potent steroid. Manifestations of adrenal insufficiency may require supplemental systemic corticosteroids. Recovery of HPA axis function is generally prompt and complete upon discontinuation of topical corticosteroids.

Cushing's syndrome, hyperglycemia, and unmasking of latent diabetes mellitus can also result from systemic absorption of topical corticosteroids.
Use of more than one corticosteroid-containing product at the same time may increase the total systemic corticosteroid exposure.
Pediatric patients may be more susceptible to systemic toxicity from use of topical corticosteroids. [*see Use in Specific Populations (8.4)*]

5.2 Local Adverse Reactions with Topical Corticosteroids
Local adverse reactions may be more likely to occur with occlusive use, prolonged use or use of higher potency corticosteroids. Reactions may include atrophy, striae, telangiectasias, burning, itching, irritation, dryness, folliculitis, acneiform eruptions, hypopigmentation, perioral dermatitis, allergic contact dermatitis, secondary infection, and miliaria. Some local adverse reactions may be irreversible.

5.3 Allergic Contact Dermatitis with Topical Corticosteroids
Allergic contact dermatitis to any component of topical corticosteroids is usually diagnosed by a failure to heal rather than a clinical exacerbation. Clinical diagnosis of allergic contact dermatitis can be confirmed by patch testing.

5.4 Concomitant Skin Infections
Concomitant skin infections should be treated with an appropriate antimicrobial agent.
If the infection persists, Topicort® Topical Spray should be discontinued until the infection has been adequately treated.

5.5 Flammable Contents
Topicort® Topical Spray is flammable; keep away from heat or flame.

ADVERSE REACTIONS

6.1 Clinical Trials Experience
Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

In randomized, multicenter, prospective vehicle-controlled clinical trials, subjects with moderate to severe plaque psoriasis of the body applied Topicort® Topical Spray or vehicle spray twice daily for 4 weeks. A total of 149 subjects applied Topicort® Topical Spray.

Adverse reactions that occurred in ≥ 1% of subjects treated with Topicort® Topical Spray were application site dryness (2.7%), application site irritation (2.7%) and application site pruritus (2.0%).

Another less common adverse reaction (<1% but >0.1%) was folliculitis.

Table 1. Number (%) of Subjects with Adverse Reactions Occurring in ≥ 1%

	Topicort® Topical Spray, 0.25% b.i.d. (N = 149)	Vehicle spray b.i.d. (N = 135)
Number of Subjects with Adverse Reactions	13 (8.7%)	18 (13.3%)
Application site dryness	4 (2.7%)	7 (5.2%)
Application site irritation	4 (2.7%)	5 (3.7%)
Application site pruritus	3 (2.0%)	5 (3.7%)

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy
Teratogenic Effects: Pregnancy Category C
There are no adequate and well-controlled studies in pregnant women. Topicort® Topical Spray should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Corticosteroids have been shown to be teratogenic in laboratory animals when administered systemically at relatively low dosage levels.

Desoximetasone has been shown to be teratogenic and embryotoxic in mice, rats, and rabbits when given by subcutaneous or dermal routes of administration at doses 3 to 30 times the human dose of Topicort® Topical Spray based on a body surface area comparison.

8.3 Nursing Mothers
Systemically administered corticosteroids appear in human milk and could suppress growth, interfere with endogenous corticosteroid production, or cause other untoward effects. It is not known whether topical administration of corticosteroids could result in sufficient systemic absorption to produce detectable quantities in breast milk. Because many drugs are excreted in human milk, caution should be exercised when Topicort® Topical Spray is administered to a nursing woman.

If used during lactation, Topicort® Topical Spray should not be applied on the chest to avoid accidental ingestion by the infant.

8.4 Pediatric Use
Safety and effectiveness of Topicort® Topical Spray in patients younger than 18 years of age have not been studied; therefore use in pediatric patients is not recommended. Because of a higher ratio of skin surface area to body mass, pediatric patients are at a greater risk than adults of HPA axis suppression and Cushing's syndrome when they are treated with topical corticosteroids. They are therefore at greater risk of adrenal insufficiency during and/or after withdrawal of treatment. Adverse effects including striae have been reported with inappropriate use of topical corticosteroids in infants and children. [*see Warnings and Precautions (5.1)*]
HPA axis suppression, Cushing's syndrome, linear growth retardation, delayed weight gain, and intracranial hypertension have been reported in children receiving topical corticosteroids. Manifestations of adrenal suppression in children include low plasma cortisol levels and absence of response to ACTH stimulation. Manifestations of intracranial hypertension include bulging fontanelles, headaches, and bilateral papilledema. [*see Warnings and Precautions (5.1)*]

8.5 Geriatric Use
Clinical studies of Topicort® Topical Spray did not include sufficient numbers of subjects aged 65 years and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

10 OVERDOSAGE
Topicort® Topical Spray can be absorbed in sufficient amounts to produce systemic effects. [*see Warnings and Precautions (5.1)*]

17 PATIENT COUNSELING INFORMATION
See FDA-approved patient labeling (Patient Information and Instructions for Use)

Inform patients of the following:
- Use this medication as directed by the physician.
- Topicort® Topical Spray is for external use only. Avoid use on the face, axilla or groin.
- Do not use this medication for any disorder other than that for which it was prescribed.
- Do not bandage or otherwise cover or wrap the treated skin so as to be occlusive.
- Report any signs of local or systemic adverse reactions to the physician.
- Do not use other corticosteroid-containing products with Topicort® Topical Spray without first consulting with the physician.
- Discontinue therapy when control is achieved. If no improvement is seen within 4 weeks, contact the physician.
- This medication is flammable; avoid heat, flame, or smoking when applying this product.
- Discard this product 30 days after dispensed by pharmacist.

Mfd. by: Taro Pharmaceuticals Inc., Brampton, Ontario, Canada L6T 1C1
Dist. by: TaroPharma® a division of Taro Pharmaceuticals U.S.A., Inc., Hawthorne, NY 10532
Revised: April 2013

AD100-0030

RESEARCH AGENDA:

AAD targets three gaps for continuing specialty research from page 1

facilitating research in those areas.

The group narrowed down eight identified gaps in research to these three key areas that the AAD can facilitate movement on, according to Henry W. Lim, M.D., chairman and C.S. Livingood Chair, department of dermatology, Henry Ford Hospital, in Detroit.

The initiative's objective is to develop a collaborative research agenda in dermatology, which will help dermatologists prepare for significant changes facing the healthcare system.

"We started discussing that we need to evaluate as a specialty what we considered to be the gaps in the research arena from the vantage point of what the academy can promote, facilitate and advocate for the research agenda," says Dr. Lim, who notes the initiative will translate, integrate and disseminate findings to all stakeholders.

Over the past year and a half, the research work group has created a process for developing the first specialty-wide collaborative research agenda for dermatology, which will serve as the foundation for the academy's efforts around clinical guidelines, maintenance of certification (MOC), continuing medical education (CME), performance measurement, outcomes and delivery of evidence-based care. The group broadly defined research and then established a steering committee to plan out the initiative.

RESEARCH AGENDA

In June 2012, the research agenda committee met with the key opinion leaders and they agreed upon the final three areas of research. An article regarding the consensus conference was published in the August issue of *Journal American Academy Dermatology.*

"The group selected pruritus because this is the area that we as dermatologist all deal with it. However, treatment of pruritus is less than satisfactory, and in terms of how do we grade the degree of the pruritus, there is no consensus," Dr. Lim says.

Clearly creating guidelines for an agreed-upon scale will aid in the diagnosis of the condition and also help when the Food and Drug Administration is regulating new drugs in the category. The broad area of cutaneous oncology is one that all dermatologists handle, Dr. Lim says. "It is an area that has a lot of morbidity and mortality of patients, and it is an area where significant prevention, patient education, and research can be conducted," he says.

The final area is performance measurement and outcomes, which Dr. Lim says is very important to the future of healthcare.

"The time has come that dermatology can have a significant input on how we can measure our own performance, how we measure outcomes, and the quality of care," Dr. Lim says. It is imperative to determine how it is best to measure the medications that come up in terms of affecting the clinical results. Data collection must be conducted to get to that level, he says, noting the performance measurement and outcomes category will also serve as a foundation for the pruritus and cutaneous oncology agendas.

MOVING FORWARD

Dr. Lim notes the group has made significant progress since last June's meeting. A work group was established for each category. The pruritus work group has proposed an annual multidisciplinary session at the annual AAD meeting to increase the awareness among dermatologists about the latest developments in research, etiology, and treatment of the condition.

The first proposed session will be at the 2014 annual AAD meeting in Denver in March. The session will host pruritus experts in the fields of dermatology, and have outside speakers from other specialties.

> "Treatment of pruritus is less than satisfactory, and in terms of **how do we grade** the degree of the pruritus, there is **no consensus**."
>
> **Henry Lim, M.D.**
> Detroit

The cutaneous oncology work group will examine the mortality rates from squamous cell carcinoma (SCC) in transplant patients and coordinate a skin cancer registry. "We know that patients who have received organ transplant are immunosuppressed and because of this there is a higher risk of developing skin cancers and SCC," he explains. The group will work to coordinate eight to 10 transplant academic centers in the U.S., and develop a database to evaluate the mortality caused by SCC among these patients.

The proposal was approved by AAD's board of directors at their August meeting, Dr. Lim says.

Finally, performance measurement and outcomes is a key element of future research. Multiple areas within the academy are performing work on data collection for various data points, mortality, patient registries, and outcomes.

"The data collection work group will help coordinate the entire effort within the different structures within the academy," he says. "It is very helpful for the Academy to be able to do this. So we can step back, think of what are steps we can do as an Academy to help facilitate the research, with the eventual aim of improving the quality of care that we can deliver to our patients," he says. **DT**

RARE ADVERSE EVENTS

Parkinson's disease treatment can cause nail dyschromia

QUICK READ

Rare side effects that are dermatological in nature can occur as a result of treatments for conditions that are not dermatological, such as Parkinson's disease.

BY LOUISE GAGNON | STAFF CORRESPONDENT

TORONTO — Dermatological side effects can occur with treatments for non-dermatological conditions, and consultation with a dermatologist may be a wise step in such cases.

For example, a case report on a treatment for Parkinson's disease produced the side effect of nail dyschromia, necessitating cessation of treatment for the discoloration to resolve.

Published this year in *Neurology*, the case report, which was originally presented at the 15th International Congress of Parkinson's Disease and Movement Disorders in Toronto, highlights the impact that patch therapy with rotigotine, a nonergot dopamine agonist, produced, according to an expert.

"The drug brought significant motor improvement," says Helio Teive, M.D., Ph.D., a neurologist and assistant professor of neurology, Federal University of Parana, coordinator of the movement disorders in Parana, Brazil, who treated the patient. "Unfortunately, this side effect is produced. I had never seen such a problem in any of my patients (with Parkinson's disease)."

The 80-year-old patient, who had a 15-year history of Parkinson's disease, had been taking levodopa therapy for his condition, but he began to experience complications such as the wearing-off phenomenon and peak-dose dyskinesias, Dr. Teive says.

The patient had no other medical conditions and was switched to transdermal rotigotine therapy, known by the brand name Neupro (rotigotine transdermal system, UCB). One of the perceived advantages of the therapy is that it provides continuous delivery of medication over a 24-hour period. The patch therapy is also indicated for the treatment of moderate-to-severe restless legs syndrome.

The patient was switched to a 2 mg patch rotigotine, which was titrated to 6 mg daily. Nail dyschromia in fingernails on both hands, which featured green discoloration, appeared within days of the treatment regimen. There was no accompanying pain or discomfort associated with the dyschromia. Rotigotine therapy was halted, and the nail dyschromia disappeared after two months, according to Dr. Teive.

The product monograph notes that Neupro can cause skin reactions at the site where the therapy is applied. The most common side effects reported in patients taking the therapy for Parkinson's disease include application site reactions, nausea, vomiting, sleepiness, dizziness, loss of appetite, increased sweating, difficulty sleeping, and leg swelling.

Dr. Teive recommends that a patient's **skin and nails be checked regularly** if the patient is **exposed to rotigotine.**

The treatment regimen was switched again, and the patient is currently being managed with high doses of levodopa, associated to entacapone, a drug that inhibits the enzyme catechol-O-methyl transferase (COMT). This particular COMT inhibitor is recognized as not posing liver toxicity and acting peripherally but not centrally in the nervous system, Dr. Teive notes.

"We don't know the mechanism by which rotigotine produced this side effect," Dr. Teive says. "In this case, the patient was examined by a dermatologist and had no other problems. The patient is now doing well."

Dr. Teive recommends that a patient's skin and nails be checked regularly if the patient is exposed to rotigotine. There is a concern that such a side effect would negatively affect compliance to Parkinson's disease therapy, Dr. Teive adds.

Nail disorders can be induced with the use of other drugs, including chemotherapies to treat cancers, psoralens, retinoids, tetracyclines, and anti-malarial therapies. Nail disorders can be strictly cosmetic, but they can also be painful and impair patients in performing manual activities.

Other dermatological toxicities have been detected in patients with Parkinson's disease. There has been growing epidemiologic and clinical evidence of the link between melanoma and Parkinson's disease with findings from *Neurology* showing men with Parkinson's disease were twice as likely to develop melanoma while women with Parkinson's disease were 1.5 times as likely to develop it. (Liu R, Gao X, Lu Y, Chen H. *Neurology*. 2011;76(23):2002-2009).

This link has created heightened awareness amongst some neurologists to send their patients with Parkinson's disease to dermatologists for annual skin examinations.

But a more recent investigation, in which researchers were looking for shared genetic risk factors between the two diseases, showed no association between Parkinson disease genome-wide association studies single-nucleotide polymorphisms and melanoma risk (Meng S, Song F, Chen H, et al. *Cancer Epidemiol Biomarkers Prev*. 2012;21(1):243-245). **DT**

Disclosures: Dr. Teive reports no relevant financial interests.

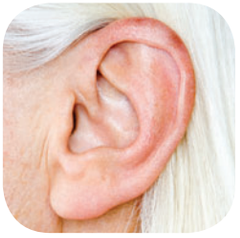
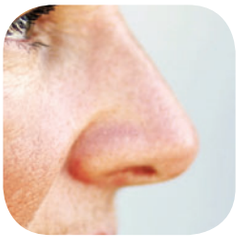
High Clearance[1*]

Low Down Time[†]

Monitored Completion[**]

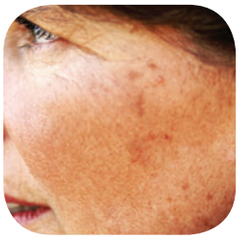
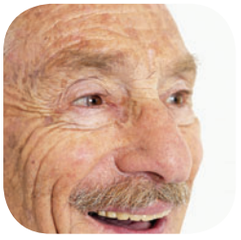
Few AKs

Localized area | Sensitive area | Larger area


Multiple AKs

Localized area | Larger area

The Levulan® Kerastick® for Topical Solution plus blue light illumination using the BLU-U® Blue Light Photodynamic Therapy Illuminator is indicated for the treatment of minimally to moderately thick actinic keratoses of the face or scalp.

*At 8 weeks, 77% of patients treated with Levulan PDT experienced 75% clearance of AK lesions vs 23% of the control group. 83% of the patients treated with Levulan PDT had 75% clearance of face lesions and 60% of the patients had 75% clearance of scalp lesions. 66% of patients treated with Levulan PDT experienced 100% clearance of AK lesions vs 13% of the control group. 70% of the patients treated with Levulan PDT had 100% clearance of face lesions and 55% of the patients had 100% clearance of scalp lesions.

*Results from two identical, randomized, multi-center, two-arm Phase 3 studies with a total of 243 patients. Patients who were not complete responders at week 8 had a retreatment of the persistent target lesions. All patients returned at week 12 after initial treatment.

†Patients treated with Levulan PDT should avoid exposure of the photosensitized lesions to sunlight or prolonged or intense light for at least 40 hours.

**Levulan PDT is a 2-part treatment procedure that can be completed within a 24 hour period.

Important Risk Information

Application of Levulan Kerastick should involve either scalp or face lesions, but not both simultaneously. Levulan Kerastick should not be applied to the periorbital area or allowed to contact ocular or mucosal surfaces. Excessive irritation may be experienced if this product is applied under occlusion.

Contraindicated in patients with cutaneous photosensitivity at wavelengths of 400-450 nm, porphyria, or known allergies to porphyrins, and in patients with known sensitivity to any of the components of the Levulan Kerastick for Topical Solution. Levulan Kerastick has not been tested on patients with inherited or acquired coagulation defects.

Transient local symptoms of stinging and/or burning, itching, erythema, and edema were observed in all clinical studies. Severe stinging and/or burning at one or more lesions being treated was reported by at least 50% of patients at some time during treatment. However, less than 3% of patients discontinued light treatment due to stinging and/or burning. The most common adverse events include scaling/crusting, hypo/hyperpigmentation, itching, stinging and/or burning, erythema and edema. In 99% of active treatment patients, some or all lesions were erythematous shortly after treatment, while in 79% of vehicle-treated patients, some or all lesions were erythematous. In 35% of active treatment patients, some or all lesions were edematous, while no vehicle-treated patients had edematous lesions.

Please see safety information on adjacent page.

1. Levulan® Kerastick® Prescribing Information. DUSA Pharmaceuticals, Inc.®

Levulan® Kerastick®
(aminolevulinic acid HCl)
for Topical Solution, 20%

Levulan® Kerastick® (aminolevulinic acid HCl) for Topical Solution, 20%
Initial U.S. approval: 1999

INDICATIONS AND USAGE

The LEVULAN KERASTICK for Topical Solution, a porphyrin precursor, plus blue light illumination using the BLU-U® Blue Light Photodynamic Therapy Illuminator is indicated for the treatment of minimally to moderately thick actinic keratoses of the face or scalp.

CONTRAINDICATIONS

The LEVULAN KERASTICK for Topical Solution plus blue light illumination using the BLU-U Blue Light Photodynamic Therapy Illuminator is contraindicated in patients with cutaneous photosensitivity at wavelengths of 400-450 nm, porphyria or known allergies to porphyrins, and in patients with known sensitivity to any of the components of the LEVULAN KERASTICK for Topical Solution.

WARNINGS AND PRECAUTIONS

Photosensitivity

During the time period between the application of LEVULAN KERASTICK Topical Solution and exposure to activating light from the BLU-U Blue Light Photodynamic Therapy Illuminator, the treatment site will become photosensitive. After LEVULAN KERASTICK Topical Solution application, patients should avoid exposure of the photosensitive treatment sites to sunlight or bright indoor light (e.g., examination lamps, operating room lamps, tanning beds, or lights at close proximity) during the period prior to blue light treatment. Exposure may result in a stinging and/or burning sensation and may cause erythema and/or edema of the lesions. Before exposure to sunlight, patients should, therefore, protect treated lesions from the sun by wearing a wide-brimmed hat or similar head covering of light-opaque material. Sunscreens will not protect against photosensitivity reactions caused by visible light. It has not been determined if perspiration can spread the LEVULAN KERASTICK Topical Solution outside the treatment site to eye or surrounding skin.

Application of LEVULAN KERASTICK Topical Solution to perilesional areas of photodamaged skin of the face or scalp may result in photosensitization. Upon exposure to activating light from the BLU-U Blue Light Photodynamic Therapy Illuminator, such photosensitized skin may produce a stinging and/or burning sensation and may become erythematous and/or edematous in a manner similar to that of actinic keratoses treated with LEVULAN KERASTICK Photodynamic Therapy. Because of the potential for skin to become photosensitized, the LEVULAN KERASTICK should be used by a qualified health professional to apply drug only to actinic keratoses and not perilesional skin. If for any reason the patient cannot return for blue light treatment during the prescribed period after application of LEVULAN KERASTICK Topical Solution (14 to 18 hours), the patient should call the doctor. The patient should also continue to avoid exposure of the photosensitized lesions to sunlight or prolonged or intense light for at least 40 hours. If stinging and/or burning is noted, exposure to light should be reduced.

Irritation

The LEVULAN KERASTICK Topical Solution contains alcohol and is intended for topical use only. Do not apply to the eyes or to mucous membranes. Excessive irritation may be experienced if this product is applied under occlusion.

Coagulation Defects

The LEVULAN KERASTICK for Topical Solution has not been tested on patients with inherited or acquired coagulation defects.

ADVERSE REACTIONS

In Phase 3 studies, no non-cutaneous adverse events were found to be consistently associated with LEVULAN KERASTICK Topical Solution application followed by blue light exposure.

Photodynamic Therapy Response: The constellation of transient local symptoms of stinging and/or burning, itching, erythema and edema as a result of LEVULAN KERASTICK Topical Solution plus BLU-U treatment was observed in all clinical studies of LEVULAN KERASTICK for Topical Solution Photodynamic Therapy for actinic keratoses treatment. Stinging and/or burning subsided between 1 minute and 24 hours after the BLU-U Blue Light Photodynamic Therapy Illuminator was turned off, and appeared qualitatively similar to that perceived by patients with erythropoietic protoporphyria upon exposure to sunlight. There was no clear drug dose or light dose dependent change in the incidence or severity of stinging and/or burning.

In two Phase 3 trials, the sensation of stinging and/or burning appeared to reach a plateau at 6 minutes into the treatment. Severe stinging and/or burning at one or more lesions being treated was reported by at least 50% of the patients at some time during treatment. The majority of patients reported that all lesions treated exhibited at least slight stinging and/or burning. Less than 3% of patients discontinued light treatment due to stinging and/or burning.

In the Phase 3 trials, the most common changes in lesion appearance after LEVULAN KERASTICK for Topical Solution Photodynamic Therapy were erythema and edema. In 99% of active treatment patients, some or all lesions were erythematous shortly after treatment, while in 79% of vehicle treatment patients, some or all lesions were erythematous. In 35% of active treatment patients, some or all lesions were edematous, while no vehicle-treated patients had edematous lesions. Both erythema and edema resolved to baseline or improved by 4 weeks after therapy. LEVULAN KERASTICK Topical Solution application to photodamaged perilesional skin resulted in photosensitization of photodamaged skin and in a photodynamic response (see Warnings and Precautions).

Other Localized Cutaneous Adverse Experiences: Table 1 depicts the incidence and severity of cutaneous adverse events in Phase 3 studies, stratified by anatomic site treated.

TABLE 1 Post-PDT Cutaneous Adverse Events - ALA-018/ALA-019

	FACE				SCALP			
	LEVULAN (n=139)		Vehicle (n=41)		LEVULAN (n=42)		Vehicle (n=21)	
Degree of Severity	Mild/ Moderate	Severe	Mild/ Moderate	Severe	Mild/ Moderate	Severe	Mild/ Moderate	Severe
Scaling/Crusting	71%	1%	12%	0%	64%	2%	10%	0%
Pain	1%	0%	0%	0%	0%	0%	0%	0%
Tenderness	1%	0%	0%	0%	2%	0%	0%	0%
Itching	35%	1%	7%	0%	14%	7%	10%	0%
Edema	1%	0%	0%	0%	0%	0%	0%	0%
Ulceration	4%	0%	0%	0%	2%	0%	0%	0%
Bleeding/Hemorrhage	4%	0%	0%	0%	2%	0%	0%	0%
Hypo/hyper-pigmentation	22%		20%		36%		33%	
Vesiculation	4%	0%	0%	0%	5%	0%	0%	0%
Pustules	4%	0%	0%	0%	0%	0%	0%	0%
Oozing	1%	0%	0%	0%	0%	0%	0%	0%
Dysesthesia	2%	0%	0%	0%	0%	0%	0%	0%
Scabbing	2%	1%	0%	0%	0%	0%	0%	0%
Erosion	14%	1%	0%	0%	2%	0%	0%	0%
Excoriation	1%	0%	0%	0%	0%	0%	0%	0%
Wheal/Flare	2%	1%	0%	0%	2%	0%	0%	0%
Skin disorder NOS	5%	0%	0%	0%	12%	0%	5%	0%

Adverse Experiences Reported by Body System: In the Phase 3 studies, 7 patients experienced a serious adverse event. All were deemed remotely or not related to treatment. No clinically significant patterns of clinical laboratory changes were observed for standard serum chemical or hematologic parameters in any of the controlled clinical trials.

OVERDOSAGE

LEVULAN KERASTICK Topical Solution Overdose

LEVULAN KERASTICK Topical Solution overdose has not been reported. In the unlikely event that the drug is ingested, monitoring and supportive care are recommended. The patient should be advised to avoid incidental exposure to intense light sources for at least 40 hours after ingestion. The consequences of exceeding the recommended topical dosage are unknown.

BLU-U Light Overdose

There is no information on overdose of blue light from the BLU-U Blue Light Photodynamic Therapy Illuminator following LEVULAN KERASTICK Topical Solution application.

Information for Patients:
LEVULAN KERASTICK Photodynamic Therapy for Actinic Keratoses.

- The first step in LEVULAN KERASTICK Photodynamic Therapy (PDT) for actinic keratoses is application of the LEVULAN KERASTICK Topical Solution to actinic keratoses located on the patient's face or scalp.
- After LEVULAN KERASTICK Topical Solution is applied to the actinic keratoses in the doctor's office, the patient will be told to return the next day. During this time the actinic keratoses will become sensitive to light (photosensitive). Care should be taken to keep the treated actinic keratoses dry and out of bright light. After LEVULAN KERASTICK Topical Solution is applied, it is important for the patient to wear light-protective clothing, such as a wide-brimmed hat, when exposed to sunlight or sources of light.
- Fourteen to eighteen hours after application of LEVULAN KERASTICK Topical Solution the patient will return to the doctor's office to receive blue light treatment, which is the second and final step in the treatment. Prior to blue light treatment, the actinic keratoses will be rinsed with tap water. The patient will be given goggles to wear as eye protection during the blue light treatment.
- The blue light is of low intensity and will not heat the skin. However, during the light treatment, which lasts for approximately 17 minutes, the patient will experience sensations of tingling, stinging, prickling or burning of the treated lesions. These feelings of discomfort should improve at the end of the light treatment.
- Following treatment, the actinic keratoses and, to some degree, the surrounding skin, will redden, and swelling and scaling may also occur. However, these lesion changes are temporary and should completely resolve by 4 weeks after treatment.

US Patents: 5,079,262 5,211,938 5,954,703,
Manufactured for: DUSA Pharmaceuticals, Inc.®
25 Upton Drive, Wilmington, MA 01887

For more information please contact: 1-877-533-3872 or 1-978-657-7500
www.dusapharma.com

LAB-1442AW Rev A

DUSA®

NOVO SOLUTIONS

Scar cream contains purified human umbilical cord serum

NovoScarMD is a scar cream containing patent-pending NovoSerum, a cell free concentration of multiple growth factors taken from purified human umbilical cord serum.

The product is designed to eliminate scars by disrupting the formation process at all levels, the company claims. NovoSerum helps to promote wound healing by releasing platelet-derived growth factors. The serum is provided by a cryobank in the United States that has been certified by the Food and Drug Administration.

NovoScarMD Physicians Formula, which the company states can produce visible results in days, is available at clinicians' offices and in medical spas.

FOR MORE INFORMATION:
855-480-6686
www.novoscarmd.com

VISION USA

Glasses reduce distortions for wider field of view

Task Vision High Power +4.00, +5.00 and +6.00 glasses have aspheric lenses, which are designed to eliminate distortions and allow for a wider field of view and better peripheral vision by focusing incoming light.

The glasses come in unisex acrylic frames, alloy frames, contemporary frames and half-eye frame designs in several colors. Frame designs also feature long temples with sturdy spring hinges, the company states.

FOR MORE INFORMATION:
800-257-5782
www.visionusasupplies.com

IAGNOSIS

App lets patients submit skin photos to derms

An online dermatologic care site now has a mobile application that will allow patients to upload diagnostic images and send them to board-certified dermatologists.

DermatologistOnCall features a platform in which patients can create private and secure accounts to submit to dermatologists photos and descriptions of their skin conditions. They can get a response on the condition within three business days, according to the company.

The online "visit" includes a treatment plan based on the patient's history, condition and diagnosis by the dermatologist. This may include a recommendation for an in-office visit. Any necessary prescriptions are sent to the patient's pharmacy electronically.

FOR MORE INFORMATION:
www.iagnosis.com
www.dermatologistoncall.com

EXSURCO MEDICAL

Tissue excision technology improves overall yield

Amalgatome MD Skin Recovery Device utilizes a more maneuverable device to access hard-to-reach areas, increasing the potential for better overall yield, such as for more transplantable skin grafts, according to the company.

The device is designed for cadaveric tissue bank use only, and requires minimal maintenance and a single-use blade that may be used during an entire skin recovery.

Features of the device also include controlled depth adjustments, a specially designed depth plate that allows technicians to maintain consistent excision depth, and a minimal maintenance design so that technicians do not have to calibrate between each donor recovery. Single-use disposable blades help to prevent the risk of cross-contamination.

FOR MORE INFORMATION:
www.exsurco.com

IMPORTANT SAFETY INFORMATION, INCLUDING BOXED WARNING

WARNING: DISTANT SPREAD OF TOXIN EFFECT

Postmarketing reports indicate that the effects of BOTOX® Cosmetic (onabotulinumtoxinA) and all botulinum toxin products may spread from the area of injection to produce symptoms consistent with botulinum toxin effects. These may include asthenia, generalized muscle weakness, diplopia, ptosis, dysphagia, dysphonia, dysarthria, urinary incontinence and breathing difficulties. These symptoms have been reported hours to weeks after injection. Swallowing and breathing difficulties can be life threatening and there have been reports of death. The risk of symptoms is probably greatest in children treated for spasticity but symptoms can also occur in adults treated for spasticity and other conditions, particularly in those patients who have an underlying condition that would predispose them to these symptoms. In unapproved uses, including spasticity in children, and in approved indications, cases of spread of effect have been reported at doses comparable to those used to treat cervical dystonia and at lower doses.

CONTRAINDICATIONS

BOTOX® Cosmetic (onabotulinumtoxinA) is contraindicated in the presence of infection at the proposed injection site(s) and in individuals with known hypersensitivity to any botulinum toxin preparation or to any of the components in the formulation.

WARNINGS AND PRECAUTIONS

Lack of Interchangeability between Botulinum Toxin Products

The potency Units of BOTOX® Cosmetic are specific to the preparation and assay method utilized. They are not interchangeable with other preparations of botulinum toxin products and, therefore, units of biological activity of BOTOX® Cosmetic cannot be compared to nor converted into units of any other botulinum toxin products assessed with any other specific assay method.

Spread of Toxin Effect

Please refer to Boxed Warning for Distant Spread of Toxin Effect.

No definitive, serious adverse event reports of distant spread of toxin effect associated with dermatologic use of BOTOX® Cosmetic at the labeled dose of 20 Units (for glabellar lines) have been reported.

Injections In or Near Vulnerable Anatomic Structures

Care should be taken when injecting in or near vulnerable anatomic structures. Serious adverse events including fatal outcomes have been reported in patients who had received BOTOX® injected directly into salivary glands, the oro-lingual-pharyngeal region, esophagus and stomach. Safety and effectiveness have not been established for indications pertaining to these injection sites. Some patients had preexisting dysphagia or significant debility. Pneumothorax associated with injection procedure has been reported following the administration of BOTOX® near the thorax. Caution is warranted when injecting in proximity to the lung, particularly the apices.

Hypersensitivity Reactions

Serious and/or immediate hypersensitivity reactions have been reported. These reactions include anaphylaxis, serum sickness, urticaria, soft-tissue edema, and dyspnea. If such reactions occur, further injection of BOTOX® Cosmetic should be discontinued and appropriate medical therapy immediately instituted. One fatal case of anaphylaxis has been reported in which lidocaine was used as the diluent and, consequently, the causal agent cannot be reliably determined.

Cardiovascular System

There have been reports following administration of BOTOX® of adverse events involving the cardiovascular system, including arrhythmia and myocardial infarction, some with fatal outcomes. Some of these patients had risk factors including pre-existing cardiovascular disease. Use caution when administering to patients with pre-existing cardiovascular disease.

Pre-existing Neuromuscular Disorders

Individuals with peripheral motor neuropathic diseases, amyotrophic lateral sclerosis, or neuromuscular junctional disorders (eg, myasthenia gravis or Lambert-Eaton syndrome) should be monitored particularly closely when given botulinum toxin. Patients with neuromuscular disorders may be at increased risk of clinically significant effects including severe dysphagia and respiratory compromise from typical doses of BOTOX® Cosmetic (onabotulinumtoxinA).

Human Albumin

This product contains albumin, a derivative of human blood. Based on effective donor screening and product manufacturing processes, it carries an extremely remote risk for transmission of viral diseases. A theoretical risk for transmission of Creutzfeldt-Jakob disease (CJD) also is considered extremely remote. No cases of transmission of viral diseases or CJD have ever been identified for albumin.

Pre-existing Conditions at the Injection Site

Caution should be used when BOTOX® Cosmetic treatment is used in the presence of inflammation at the proposed injection site(s) or when excessive weakness or atrophy is present in the target muscle(s); and when used in patients who have marked facial asymmetry, ptosis, excessive dermatochalasis, deep dermal scarring, thick sebaceous skin or the inability to substantially lessen glabellar lines by physically spreading them apart.

ADVERSE REACTIONS

The most frequently reported adverse events following injection of BOTOX® Cosmetic include blepharoptosis and nausea.

DRUG INTERACTIONS

Co-administration of BOTOX® Cosmetic and aminoglycosides or other agents interfering with neuromuscular transmission (eg, curare-like nondepolarizing blockers, lincosamides, polymyxins, quinidine, magnesium sulfate, anticholinesterases, succinylcholine chloride) should only be performed with caution as the effect of the toxin may be potentiated. Use of anticholinergic drugs after administration of BOTOX® Cosmetic may potentiate systemic anticholinergic effects.

The effect of administering different botulinum neurotoxin serotypes at the same time or within several months of each other is unknown. Excessive neuromuscular weakness may be exacerbated by administration of another botulinum toxin prior to the resolution of the effects of a previously administered botulinum toxin.

Excessive weakness may also be exaggerated by administration of a muscle relaxant before or after administration of BOTOX® Cosmetic.

USE IN SPECIFIC POPULATIONS

BOTOX® Cosmetic is not recommended for use in children or pregnant women.

Please see brief summary of full Prescribing Information on the following pages.

1. BOTOX® Cosmetic Prescribing Information, November 2012. **2.** Data on file, Allergan, Inc.

Confidence comes from experience

Proven to last up to 4 months in 25% of patients (102/403) vs 2% (2/128) for placebo per physician assessment[1]

- **Dosing and injection techniques you know well**
- **#1 prescribed product of its kind in the world**[2,*]

*Data collected through March 2013.

Indication

BOTOX® Cosmetic (onabotulinumtoxinA) for injection is indicated for the temporary improvement in the appearance of moderate to severe glabellar lines associated with corrugator and/or procerus muscle activity in adult patients ≤ 65 years of age.

Please see Important Safety Information, including Boxed Warning, on adjacent page.

BOTOX® Cosmetic
onabotulinumtoxinA injection

There's only one BOTOX® Cosmetic

BOTOX® Cosmetic (onabotulinumtoxinA)
for injection
(Brief summary of full prescribing information)

Manufactured by: Allergan Pharmaceuticals Ireland
a subsidiary of: Allergan, Inc. 2525 Dupont Dr., Irvine, CA 92612

Warning: Distant Spread of Toxin Effect

Postmarketing reports indicate that the effects of **BOTOX® Cosmetic** and all botulinum toxin products may spread from the area of injection to produce symptoms consistent with botulinum toxin effects. These may include asthenia, generalized muscle weakness, diplopia, ptosis, dysphagia, dysphonia, dysarthria, urinary incontinence, and breathing difficulties. These symptoms have been reported hours to weeks after injection. Swallowing and breathing difficulties can be life threatening and there have been reports of death. The risk of symptoms is probably greatest in children treated for spasticity but symptoms can also occur in adults treated for spasticity and other conditions, particularly in those patients who have an underlying condition that would predispose them to these symptoms. In unapproved uses, including spasticity in children, and in approved indications, cases of spread of effect have been reported at doses comparable to those used to treat cervical dystonia and at lower doses.

INDICATIONS AND USAGE

BOTOX® Cosmetic is indicated for the temporary improvement in the appearance of moderate to severe glabellar lines associated with corrugator and/or procerus muscle activity in adult patients ≤ 65 years of age.

CONTRAINDICATIONS

BOTOX® Cosmetic is contraindicated in the presence of infection at the proposed injection site(s) and in individuals with known hypersensitivity to any botulinum toxin preparation or to any of the components in the formulation.

WARNINGS AND PRECAUTIONS

Lack of Interchangeability between Botulinum Toxin Products

The potency Units of BOTOX® Cosmetic are specific to the preparation and assay method utilized. They are not interchangeable with other preparations of botulinum toxin products and, therefore, units of biological activity of BOTOX® Cosmetic cannot be compared to or converted into units of any other botulinum toxin products assessed with any other specific assay method.

Spread of Toxin Effect

Postmarketing safety data from **BOTOX® Cosmetic** and other approved botulinum toxins suggest that botulinum toxin effects may, in some cases, be observed beyond the site of local injection. The symptoms are consistent with the mechanism of action of botulinum toxin and may include asthenia, generalized muscle weakness, diplopia, ptosis, dysphagia, dysphonia, dysarthria, urinary incontinence, and breathing difficulties. These symptoms have been reported hours to weeks after injection. Swallowing and breathing difficulties can be life threatening and there have been reports of death related to spread of toxin effects. The risk of symptoms is probably greatest in children treated for spasticity but symptoms can also occur in adults treated for spasticity and other conditions, and particularly in those patients who have an underlying condition that would predispose them to these symptoms. In unapproved uses, including spasticity in children, and in approved indications, symptoms consistent with spread of toxin effect have been reported at doses comparable to or lower than doses used to treat cervical dystonia. Patients or caregivers should be advised to seek immediate medical care if swallowing, speech or respiratory difficulties occur.

No definitive serious adverse event reports of distant spread of toxin effect associated with dermatologic use of **BOTOX®/BOTOX® Cosmetic** at the labeled dose of 20 Units (for glabellar lines) or 100 Units (for severe primary axillary hyperhidrosis) have been reported.

No definitive serious adverse event reports of distant spread of toxin effect associated with **BOTOX®** for blepharospasm at the recommended dose (30 Units and below) or for strabismus at the labeled doses have been reported.

Injections In or Near Vulnerable Anatomic Structures

Care should be taken when injecting in or near vulnerable anatomic structures. Serious adverse events including fatal outcomes have been reported in patients who had received **BOTOX®** injected directly into salivary glands, the oro-lingual-pharyngeal region, esophagus and stomach. Safety and effectiveness have not been established for indications pertaining to these injection sites. Some patients had pre-existing dysphagia or significant debility. Pneumothorax associated with injection procedure has been reported following the administration of **BOTOX®** near the thorax. Caution is warranted when injecting in proximity to the lung, particularly the apices.

Hypersensitivity Reactions

Serious and/or immediate hypersensitivity reactions have been reported. These reactions include anaphylaxis, serum sickness, urticaria, soft tissue edema, and dyspnea. If such a reaction occurs, further injection of **BOTOX® Cosmetic** should be discontinued and appropriate medical therapy immediately instituted. One fatal case of anaphylaxis has been reported in which lidocaine was used as the diluent, and consequently the causal agent cannot be reliably determined.

Cardiovascular System

There have been reports following administration of **BOTOX®** of adverse events involving the cardiovascular system, including arrhythmia and myocardial infarction, some with fatal outcomes. Some of these patients had risk factors including pre-existing cardiovascular disease. Use caution when administering to patients with pre-existing cardiovascular disease.

Pre-Existing Neuromuscular Disorders

Individuals with peripheral motor neuropathic diseases, amyotrophic lateral sclerosis, or neuromuscular junctional disorders (e.g., myasthenia gravis or Lambert-Eaton syndrome) should be monitored particularly closely when given botulinum toxin. Patients with neuromuscular disorders may be at increased risk of clinically significant effects including severe dysphagia and respiratory compromise from typical doses of **BOTOX® Cosmetic** (*see Warnings and Precautions*).

Dysphagia and Breathing Difficulties in Treatment of Cervical Dystonia

Treatment with **BOTOX®** and other botulinum toxin products can result in swallowing or breathing difficulties. Patients with pre-existing swallowing or breathing difficulties may be more susceptible to these complications. In most cases, this is a consequence of weakening of muscles in the area of injection that are involved in breathing or swallowing. When distant effects occur, additional respiratory muscles may be involved (*see Warnings and Precautions*).

Deaths as a complication of severe dysphagia have been reported after treatment with botulinum toxin. Dysphagia may persist for several months, and require use of a feeding tube to maintain adequate nutrition and hydration. Aspiration may result from severe dysphagia and is a particular risk when treating patients in whom swallowing or respiratory function is already compromised.

Treatment of cervical dystonia with botulinum toxins may weaken neck muscles that serve as accessory muscles of ventilation. This may result in a critical loss of breathing capacity in patients with respiratory disorders who may have become dependent upon these accessory muscles. There have been postmarketing reports of serious breathing difficulties, including respiratory failure, in cervical dystonia patients.

Patients with smaller neck muscle mass and patients who require bilateral injections into the sternocleidomastoid muscle have been reported to be at greater risk for dysphagia. Limiting the dose injected into the sternocleidomastoid muscle may reduce the occurrence of dysphagia. Injections into the levator scapulae may be associated with an increased risk of upper respiratory infection and dysphagia.

Patients treated with botulinum toxin may require immediate medical attention should they develop problems with swallowing, speech, or respiratory disorders. These reactions can occur within hours to weeks after injection with botulinum toxin (*see Warnings and Precautions*).

Pre-existing Conditions at the Injection Site

Caution should be used when **BOTOX® Cosmetic** treatment is used in the presence of inflammation at the proposed injection site(s) or when excessive weakness or atrophy is present in the target muscle(s).

Caution should be used when **BOTOX® Cosmetic** treatment is used in patients who have marked facial asymmetry, ptosis, excessive dermatochalasis, deep dermal scarring, thick sebaceous skin or the inability to substantially lessen glabellar lines by physically spreading them apart as these patients were excluded from the Phase 3 safety and efficacy trials.

Corneal Exposure and Ulceration in Patients Treated with BOTOX® for Blepharospasm

Reduced blinking from **BOTOX® Cosmetic** injection of the orbicularis muscle can lead to corneal exposure, persistent epithelial defect, and corneal ulceration, especially in patients with VII nerve disorders. Vigorous treatment of any epithelial defect should be employed. This may require protective drops, ointment, therapeutic soft contact lenses, or closure of the eye by patching or other means.

Spatial Disorientation, Double Vision or Past-pointing in Patients Treated for Strabismus

Inducing paralysis in one or more extraocular muscles may produce spatial disorientation, double vision or past pointing. Covering the affected eye may alleviate these symptoms.

Human Albumin and Transmission of Viral Disease

This product contains albumin, a derivative of human blood. Based on effective donor screening and product manufacturing processes, it carries an extremely remote risk for transmission of viral diseases. A theoretical risk for transmission of Creutzfeldt-Jakob disease (CJD) also is considered extremely remote. No cases of transmission of viral diseases or CJD have ever been identified for albumin.

ADVERSE REACTIONS

The following adverse reactions to **BOTOX® Cosmetic** (onabotulinumtoxinA) for injection are discussed in greater detail in other sections of the labeling:

- Spread of Toxin Effects *[see Warnings and Precautions]*
- Hypersensitivity *[see Contraindications and Warnings and Precautions]*
- Dysphagia and Breathing Difficulties in Treatment of Cervical Dystonia *[see Warnings and Precautions]*

Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, the adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

BOTOX® and **BOTOX® Cosmetic** contain the same active ingredient in the same formulation, but have different labeled Indications and Usage. Therefore, adverse events observed with the use of **BOTOX®** also have the potential to be observed with the use of **BOTOX® Cosmetic**.

In general, adverse reactions occur within the first week following injection of **BOTOX® Cosmetic** and while generally transient, may have a duration of several months or longer. Localized pain, infection, inflammation, tenderness, swelling, erythema, and/or bleeding/bruising may be associated with the injection. Needle-related pain and/or anxiety may result in vasovagal responses (including e.g., syncope, hypotension), which may require appropriate medical therapy.

Local weakness of the injected muscle(s) represents the expected pharmacological action of botulinum toxin. However, weakness of nearby muscles may also occur due to spread of toxin *[see Warnings and Precautions]*.

Glabellar Lines

In clinical trials of **BOTOX® Cosmetic** the most frequently reported adverse events following injection of **BOTOX® Cosmetic** were headache*, respiratory infection*, flu syndrome*, blepharoptosis and nausea.

Less frequently occurring (<3%) adverse reactions included pain in the face, erythema at the injection site*, paresthesia* and muscle weakness. While local weakness of the injected muscle(s) is representative of the expected pharmacological action of botulinum toxin, weakness of adjacent muscles may occur as a result of the spread of toxin. These events are thought to be associated with the injection and occurred within the first week. The events were generally transient but may last several months or longer.

(* incidence not different from Placebo)

The data described in Table 2 reflect exposure to **BOTOX® Cosmetic** in 405 subjects aged 18 to 75 who were evaluated in the randomized, placebo-controlled clinical studies to assess the use of **BOTOX® Cosmetic** in the improvement of the appearance of glabellar lines *[see Clinical Studies (14)]*. Adverse events of any cause were reported for 44% of the **BOTOX® Cosmetic** treated subjects and 42% of the placebo treated subjects. The incidence of blepharoptosis was higher in the **BOTOX® Cosmetic** treated arm than in placebo (3% vs. 0).

In the open-label, repeat injection study, blepharoptosis was reported for 2% (8/373) of subjects in the first treatment cycle and 1% (4/343) of subjects in the second treatment cycle. Adverse events of any type were reported for 49% (183/373) of subjects overall. The most frequently reported of these adverse events in the open-label study included respiratory infection, headache, flu syndrome, blepharoptosis, pain and nausea.

Table 2: Adverse Events Reported at Higher Frequency (>1%) in the BOTOX® Cosmetic Group Compared to the Placebo Group

	Percent of Patients Reporting Adverse Events	
Adverse Events by Body System	**BOTOX® Cosmetic (N=405) %**	**Placebo (N=130) %**
Overall	44	42
Body as a Whole Pain in Face	2	1
Skin and Appendages Skin Tightness	1	0
Digestive System Nausea Dyspepsia Tooth Disorder	3 1 1	2 0 0
Special Senses Blepharoptosis	3	0
Musculoskeletal System Muscle Weakness	2	0
Cardiovascular Hypertension	1	0

Immunogenicity
Treatment with botulinum toxins may result in the formation of neutralizing antibodies that may reduce the effectiveness of subsequent treatments by inactivating biological activity of the toxin.

The rate of formation of neutralizing antibodies in patients receiving **BOTOX® Cosmetic** has not been well studied. The results from some studies suggest that botulinum toxin injections at more frequent intervals or at higher doses may lead to greater incidence of antibody formation. The potential for antibody formation may be minimized by injecting with the lowest effective dose given at the longest feasible intervals between injections. The critical factors for neutralizing antibody formation have not been well characterized.

The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to **BOTOX® Cosmetic** with the incidence of antibodies to other products may be misleading.

Post-marketing Experience
Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

There have been spontaneous reports of death, sometimes associated with dysphagia, pneumonia, and/or other significant debility or anaphylaxis, after treatment with botulinum toxin *[see Warnings and Precautions]*.

There have also been reports of adverse events involving the cardiovascular system, including arrhythmia and myocardial infarction, some with fatal outcomes. Some of these patients had risk factors including cardiovascular disease.

New onset or recurrent seizures have also been reported, typically in patients who are predisposed to experiencing these events.

The following adverse reactions by System Organ Class have been identified during post-approval use of **BOTOX®/BOTOX® Cosmetic**:

Ear and labyrinth disorders
Hypoacusis; tinnitus; vertigo

Eye disorders
Diplopia; strabismus; visual disturbances; vision blurred

Gastrointestinal disorders
Abdominal pain; diarrhea; dry mouth; nausea; vomiting

General disorders and administration site conditions
Denervation; malaise; pyrexia

Metabolism and nutrition disorders
Anorexia

Musculoskeletal and connective tissue disorders
Muscle atrophy; myalgia

Nervous system disorders
Brachial plexopathy; dysarthria; facial palsy; hypoaesthesia; localized numbness; myasthenia gravis; paresthesia; peripheral neuropathy; radiculopathy; syncope

Respiratory, thoracic and mediastinal disorders
Aspiration pneumonia; dyspnea; respiratory depression and/or respiratory failure

Skin and subcutaneous tissue disorders
Alopecia, including madarosis; hyperhidrosis; pruritus; skin rash (including erythema multiforme, dermatitis psoriasiform, and psoriasiform eruption)

DRUG INTERACTIONS
No formal drug interaction studies have been conducted with **BOTOX® Cosmetic** (onabotulinumtoxinA) for injection.

Aminoglycosides and Other Agents Interfering with Neuromuscular Transmission
Co-administration of **BOTOX® Cosmetic** and aminoglycosides or other agents interfering with neuromuscular transmission (e.g., curare-like compounds) should only be performed with caution as the effect of the toxin may be potentiated.

Anticholinergic Drugs
Use of anticholinergic drugs after administration of **BOTOX® Cosmetic** may potentiate systemic anticholinergic effects.

Other Botulinum Neurotoxin Products
The effect of administering different botulinum neurotoxin products at the same time or within several months of each other is unknown. Excessive neuromuscular weakness may be exacerbated by administration of another botulinum toxin prior to the resolution of the effects of a previously administered botulinum toxin.

Muscle Relaxants
Excessive weakness may also be exaggerated by administration of a muscle relaxant before or after administration of **BOTOX® Cosmetic**.

USE IN SPECIFIC POPULATIONS
Pregnancy
Teratogenic Effects: Pregnancy Category C.

There are no adequate and well-controlled studies in pregnant women. **BOTOX® Cosmetic** should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers
It is not known whether **BOTOX® Cosmetic** is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when **BOTOX® Cosmetic** is administered to a nursing woman.

Pediatric Use
Safety and effectiveness in patients below the age of 18 years have not been established.

Geriatric Use
The two clinical studies of **BOTOX® Cosmetic** did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. However, the responder rates appeared to be higher for patients younger than age 65 than for patients 65 years or older.

OVERDOSAGE
Excessive doses of **BOTOX® Cosmetic** (onabotulinumtoxinA) for injection may be expected to produce neuromuscular weakness with a variety of symptoms.

Symptoms of overdose are likely not to be present immediately following injection. Should accidental injection or oral ingestion occur or overdose be suspected, these patients should be considered for further medical evaluation and appropriate medical therapy immediately instituted, which may include hospitalization. The person should be medically supervised for several weeks for signs and symptoms of systemic muscular weakness which could be local, or distant from the site of injection *[see Boxed Warning and Warnings and Precautions]*.

If the musculature of the oropharynx and esophagus are affected, aspiration may occur which may lead to development of aspiration pneumonia. If the respiratory muscles become paralyzed or sufficiently weakened, intubation and assisted respiration may be necessary until recovery takes place. Supportive care could involve the need for a tracheostomy and/or prolonged mechanical ventilation, in addition to other general supportive care.

In the event of overdose, antitoxin raised against botulinum toxin is available from the Centers for Disease Control and Prevention (CDC) in Atlanta, GA. However, the antitoxin will not reverse any botulinum toxin-induced effects already apparent by the time of antitoxin administration. In the event of suspected or actual cases of botulinum toxin poisoning, please contact your local or state Health Department to process a request for antitoxin through the CDC. If you do not receive a response within 30 minutes, please contact the CDC directly at 1-770-488-7100. More information can be obtained at http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5232a8.htm.

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2525 Dupont Dr.
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BUILDING BONDS

Scar revision treatment can facilitate lasting relationships with aesthetic patients

BY JOHN JESITUS | SENIOR STAFF CORRESPONDENT

ASPEN, COLO. — Treating existing scars can help dermatologists and other core aesthetic specialists build lasting relationships with patients, says an expert who spoke at Cosmetic Boot Camp, held here.

Scars rank among the most common aesthetic concerns worldwide, says Daniel L. Kapp, M.D., a plastic surgeon based in West Palm Beach, Fla. Furthermore, he says that according to a survey performed by St. Louis plastic surgeon Leroy Young, M.D., more than 90 percent of people with scars would gladly do something about them if effective treatment is available (Young VL, Hutchison J. *Plast Reconstr Surg.* 2009;124(1):256-265).

In this regard, Dr. Kapp says, scar revision treatments are usually fairly straightforward. "Scars can always be made better — whether through surgery, nonsurgical methods or just giving someone a steroid injection or silicone sheeting."

AESTHETIC IMPACT

Scar revision also yields high patient satisfaction and frequently boosts patients' self-confidence.

QUICK READ

Scar revision procedures can provide a low-risk entry point for new patients, an expert says, who adds that minimizing surgical scars requires sharp tools and careful technique.

Accordingly, he says that when consulting with patients, "We need to ask them how they feel about their scars, because in general, people with scars live less happy lives than those who don't (have scars). And this isn't body dysmorphism," because scars are visible. Besides, he notes, "Nearly everybody likes to talk about how they got their scars. So you get them talking about themselves, and they will talk themselves into allowing you to treat their scars."

It's also important to be upfront with patients about any scars that aesthetic surgeries will create. "After plastic surgery, patients will always have scars. I tell my patients that when they get their pants altered, their tailor uses the seams to hide the repair. Because the human body doesn't have seams, I have to make one" after a tummy tuck, breast augmentation or other surgery.

The key to successful scar revision is choosing appropriate candidate scars, Dr. Kapp says. Regarding size, he notes that it's usually very difficult to offer substantial improvement on scars that cover an entire arm or leg, for example.

"The ideal scars are flat and narrow, with good color match to surrounding skin," he says. In the latter area, he usually waits one year — or 18 months in children — for any postsurgical redness to subside before treating scars.

STRATEGIC SCAR LOCATION

To minimize surgical scars, Dr.

BUILDING BONDS see page 44

Quotable

"The safest are the long-pulsed 1,064 nm Nd:YAG lasers, and when using conservative settings ... we can perform this treatment safely."

Andrew Alexis, M.D., M.P.H.
New York

On pseudofolliculitis barbae, page 47

DTExtra

Nearly half (47 percent) of lip products tested in a recent study were found to have **lead concentrations higher than the maximum level approved by the Food and Drug Administration**. Researchers analyzed 32 lipstick and lipgloss products. They found that **75 percent contained average lead concentrations of 0.36 ± 0.39 ppm**. In addition, most of the lip products contained high concentrations of titanium and aluminum, and all had detectable manganese.

SOURCE: *ENVIRONMENTAL HEALTH PERSPECTIVES*, EHP.NIEHS.NIH.GOV/1205518/

“THANKS, DOC.”

When you tell your patients about **Mederma**®, they’ll get the #1 doctor recommended brand for scars.[1] Plus, they’ll get confidence from products that are clinically shown to improve the appearance of scars and stretch marks. Because the only thing more powerful than making people feel better is making people feel better about themselves.

Call 1-888-925-8989 to request samples and literature.

AV146

[1]IMS Health, NDTI, December 2011

Joely Kaufman, M.D., and **Jeremy Green, M.D.,** are in private practice at Dr. Brandt Dermatology Assoc., and voluntary assistant professors, University of Miami Department of Dermatology & Cutaneous Surgery.

Sabrina G. Fabi, M.D., is in private practice with Goldman, Butterwick, Fitzpatrick, Groff and Fabi Cosmetic Laser Dermatology, San Diego.

Up to the challenge

1,927 nm thulium laser shows promise for melasma treatment

Melasma is one of the most challenging aesthetic conditions we face in our dermatology practices. Driven by both internal (hormonal) and external (sun exposure) factors, melasma can be improved with sunscreen, topical bleaching agents, chemical peels, and laser and light sources, but long-term remission has proven elusive.

When a new laser or light-based device addressing pigment is introduced there is much enthusiasm regarding its potential for this stubborn condition. For instance, the 1,550 nm erbium:glass nonablative fractional laser (NAFL; Fraxel re:store; Solta Medical) was suggested as a potential melasma treatment modality and showed success in initial studies (Rokhsar CK, Fitzpatrick RE. *Dermatol Surg.* 2005;31(12):1645-1650. Katz TM, Glaich AS, Goldberg LH, et al. *Dermatol Surg.* 2010;36(8):1273-1280). Subsequent investigations, however, found the laser to be less efficacious.

In 2010, Wind et al studied 29 melasma patients in a split-face fashion and found that four to five sessions of 1,550 nm laser worsened hyperpigmentation and patients preferred the side with triple topical therapy (tretinoin/hydroquinone/triamcinolone; Wind BS, Kroon MW, Meesters AA, et al. *Lasers Surg Med.* 2010;42(7):607-612).

Investigators from a group in Germany treated 26 melasma patients with four sessions of 1,550 nm fractional laser plus sunscreen versus the 25 melasma patient controls who received sunscreen alone. Both groups improved, but there was no statistically significant difference between subjective or objective measurements of improvement (Karsai S, Fischer T, Pohl L, et al. *Eur Acad Dermatol Venereol.* 2012;26(4):470-476).

> Melasma **can be improved** with sunscreen, topical bleaching agents, chemical peels, and laser and light sources, but **long-term remission has proven elusive.**

BENEFITS OF 1,927 NM LASER

The most recently evaluated nonablative fractional laser for melasma is the 1,927 nm thulium fiber laser (Fraxel re:store DUAL, Solta Medical) first described in the literature in 2011 (Polder KD, Harrison A, Eubanks LE, Bruce S. *Dermatol Surg.* 2011;37(3):342-348). This wavelength is potentially attractive due to its higher water absorption coefficient than 1,550 nm and subsequent shallow depth of penetration of approximately 200 µm. The investigators treated 14 patients with melasma who had Fitzpatrick skin types II through IV with three to four sessions of the 1,927 nm laser at varied parameters (10 mJ to 20 mJ, 20 to 45 percent density, six to eight passes). A statistically significant reduction in Melasma Area and Severity Index (MASI) score of 51 percent was seen one month after treatment, however at three (33 percent reduction vs. baseline) and six (34 percent) months there was a partial rebound.

Another recent publication of the 1,927 nm laser for melasma comes from a group in San Diego, which includes one of the authors of this column (Massaki ABM, Eimpunth S, Fabi S, et al. *Lasers Surg Med.* 2013;45(2):95-101). In this study, 20 female patients with Fitzpatrick types II through IV who had recalcitrant melasma underwent a single treatment at the following parameters: 10 mJ to 20 mJ, 60 to 70 percent surface area coverage (treatment level nine through 11). A high potency corticosteroid cream (clobetasol propionate 0.05 percent) was used over the melasma for three days following the procedure. Four independent investigators determined MASI score before, at four weeks, at three to six months, and at six to 12 months after the laser session.

One month after the treatment patients were advised to begin treatment with 4 percent hydroquinone cream to prolong remission. Twelve of 20 subjects (60 percent) had more than 50 percent clear-

Questions? Comments?
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ance of their melasma at four-week follow-up. Recurrence was reported in seven of 15 patients who were followed up a mean of 10.2 months, which subsided within three months with topical bleaching creams. Eleven patients completed the three to six month follow-up and eight (40 percent) completed the final visit.

Mean MASI scores continued to decrease for the duration of the study, 13.4 before, to 8.5 (37 percent reduction from baseline) at four weeks, to 6.1 (54 percent reduction from baseline) at the final follow-up. Two of the subjects felt they experienced poor (<25 percent) clearance and two of the nine (22.2 percent) of skin type IV patients, 10 percent of the whole cohort, had worsening of their melasma.

The most recently published data comes from South Korea, where investigators sought to evaluate the effects of the 1,927 nm fractional laser on melasma and photoaging in Asian skin (Lee HM, Haw S, Kim JK, et al. *Dermatol Surg*. 2013;39(6):879-888). The authors evaluated 25 Asian women with photoaging, eight of whom had melasma in a split-face fashion, treated with the 1,927 nm thulium laser three times at three-week intervals with the following parameters: 10 mJ 30 percent density (treatment level 3, no mention of number of passes) compared to the untreated control side. No topical bleaching agents were permitted two months prior to initial treatment or during the study.

Patients were evaluated at two (8/8) and six months (6/8) following the final treatment. Two subjects had 2 mm punch biopsies taken prior to treatment and at the two-month follow-up. The mean MASI score at baseline was 6.06, at two months, 4.04 (33 percent decrease from baseline), and at six months, 4.34 (28 percent decrease), a slight rebound in contrast to the aforementioned high density single treatment protocol.

REBOUND EFFECT

This slight rebound may be attributed to the lack of bleaching agents allowed to be used during the study, compared to the high-density single treatment study. All subjects (photoaging and melasma) were satisfied at two and six months, with 80 percent and 57.1 percent stating they were more than moderately satisfied respectively. In the two subjects who underwent biopsy, at two months a marked increase in procollagen 3 and a decrease in basal melanin was observed with immunostaining.

Despite the relative paucity of published data on the 1,927 nm NAFL for melasma treatment, the available results appear encouraging. Whether the most effective approach with this laser is with low density and multiple treatments versus the high density single treatment technique remains to be seen. Furthermore, the impact of topical treatment before and after the laser has not as of yet been delineated.

One of the authors (SGF) and her colleagues recommend high potency topical corticosteroid two days before and three days after the laser session. They theorize that this can be beneficial in the immediate post-treatment period to ameliorate the inflammatory cascade that eventuates in postinflammatory hyperpigmentation. Since their report using a single high density treatment, one of the authors (SGF) and her colleagues now initiate topical bleaching creams as early as one week after the procedure, as tolerated, to maximize the longevity of their results and minimize any rebound.

They also treat type IV skin with a lower density than they initially reported, 50 percent. The authors await additional well-executed studies and long-term follow-up to refine and enhance this potentially beneficially laser intervention for melasma. In the meantime, other modalities that may show promise in ameliorating this condition include the 1,927 nm diode (Perméa handpiece, Clear + Brilliant System, Solta Medical) combined with topical lightening agents, as well as the picosecond 755 nm alexandrite laser (Picosure, Cynosure) with defractive lens, for which clinical trials are currently under way. **DT**

BUILDING BONDS:

Scar revision can facilitate lasting relationships with aesthetic patients from page 40

Kapp says, "We try to hide our scars in strategic locations. When we perform a scar revision, we change the scar's location" to one that offers natural camouflage, such as a junction between facial subunits.

With surgical technique, "It's all about the tools, the sutures, careful tissue handling and precise approximation of the tissues." Regarding tools of the trade, he says, "When I perform a facelift in a hospital, I use my own surgical tray from my office. I know exactly how many times that pair of scissors has been used to perform a facelift. I replace my scissors around every three to five years, depending on the scissors and what I use them for, because they don't last."

> "It's all about the tools, the sutures, careful tissue handling and precise approximation of the tissues."
>
> **Daniel L. Kapp, M.D.**
> West Palm Beach, Fla.

With scalpels, he says, good technique requires using perpendicular incisions to minimize tissue trauma. To retract tissues, "I always use skin hooks. No matter how strongly you believe you're just grabbing the dermis when you're using an Adson forceps, you're grabbing the full thickness of the skin," Dr. Kapp says. "Skin hooks are the least traumatic way of lifting and elevating the tissue."

SUTURING CONSIDERATIONS

Similarly, he says, "Suture matters. Suturing is not just about using a string to close a wound. The suture material and needle you use play very important roles." For primary closures, he prefers Vicryl (polyglactin 910, Ethicon) sutures because he finds them easy to use, and their braided construction helps hold fast.

"I usually use either Monocryl (poliglecaprone 25, Ethicon) or Prolene (polypropylene, Ethicon), and sometimes nylon. I like Prolene best because it's easiest to remove." For scar revisions, Dr. Kapp says he prefers sutures that dissolve by hydrolysis because they are unlikely to cause inflammation.

Simulated image based on patient with locally advanced BCC at Week 24.

Regarding needles, "The best ones are laser-honed and sharp. A sharp needle may be used three times, or up to an hour and a half, depending on what you're suturing," before losing its edge.

Among newer techniques, Dr. Kapp says he does a fair amount of fat grafting for depressed scars. "I incorporate it with a little liposuction, so patients feel they're getting value added: an improvement of their scar, and a little liposuction. I also use a fair amount of acellular dermal matrix — I tend to prefer the bovine neonatal ones because they have high amounts of type 3 collagen. In my experience they seem to revascularize better, and I can place one underneath a depressed scar to elevate it." In his opinion, he suggests that dermatologists could make more use of acellular dermal matrices for similar purposes. **DT**

Disclosures: Dr. Kapp reports no relevant financial interests.

Erivedge® (vismodegib) capsule

ERIVEDGE (vismodegib) capsule
Initial U.S. Approval: 2012

This is a brief summary of information about ERIVEDGE. Before prescribing, please see full prescribing information.

WARNING: EMBRYO-FETAL DEATH AND SEVERE BIRTH DEFECTS

ERIVEDGE (vismodegib) capsule can result in embryo-fetal death or severe birth defects. ERIVEDGE is embryotoxic and teratogenic in animals. Teratogenic effects included severe midline defects, missing digits, and other irreversible malformations.

Verify pregnancy status prior to the initiation of ERIVEDGE. Advise male and female patients of these risks. Advise female patients of the need for contraception and advise male patients of the potential risk of ERIVEDGE exposure through semen [see *Warnings and Precautions (5.1), Use in Specific Populations (8.1, 8.6)*].

1 INDICATIONS AND USAGE

ERIVEDGE capsule is indicated for the treatment of adults with metastatic basal cell carcinoma, or with locally advanced basal cell carcinoma that has recurred following surgery or who are not candidates for surgery, and who are not candidates for radiation.

2 DOSAGE AND ADMINISTRATION

The recommended dose of ERIVEDGE is 150 mg taken orally once daily until disease progression or until unacceptable toxicity [see *Clinical Studies (14)*].

ERIVEDGE may be taken with or without food. Swallow capsules whole. **Do not open or crush capsules.**

If a dose of ERIVEDGE is missed, do not make up that dose; resume dosing with the next scheduled dose.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Embryo-Fetal Death and Severe Birth Defects

ERIVEDGE capsules can cause fetal harm when administered to a pregnant woman based on its mechanism of action. Vismodegib is teratogenic, embryotoxic, and fetotoxic in rats at maternal exposures lower than the human exposures at the recommended dose of 150 mg/day. In rats, malformations included craniofacial anomalies, open perineum, and absent or fused digits. Fetal retardations and variations were also observed.

Verify pregnancy status prior to the initiation of ERIVEDGE. Advise male and female patients of the risks of embryo-fetal death and severe birth defects and the need for contraception during and after treatment. Advise patients to contact their healthcare provider immediately if they suspect they (or, for males, their female partner) may be pregnant. Female and male patients of reproductive potential should be counseled regarding pregnancy prevention and planning. If ERIVEDGE is used during pregnancy or if a patient becomes pregnant while taking (or for a male patient, if his female partner is exposed to) ERIVEDGE, the patient should be apprised of the potential hazard to the fetus. Report immediately exposure to ERIVEDGE during pregnancy to the Genentech Adverse Event Line at 1-888-835-2555. Encourage women who may have been exposed to ERIVEDGE during pregnancy, either directly or through seminal fluid, to participate in the ERIVEDGE pregnancy pharmacovigilance program by contacting the Genentech Adverse Event Line at 1-888-835-2555 [see *Boxed Warning, Use in Specific Populations (8.1, 8.6)*].

5.2 Blood Donation

Advise patients not to donate blood or blood products while receiving ERIVEDGE and for at least 7 months after the last dose of ERIVEDGE.

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

ERIVEDGE capsule was administered as monotherapy at doses ≥ 150 mg orally daily in four open-label, uncontrolled, dose-ranging or fixed single dose clinical trials enrolling a total of 138 patients with advanced basal cell carcinoma (BCC). The median age of these patients was 61 years (range 21 to 101), 100% were White (including Hispanics), and 64% were male. The median duration of treatment was approximately 10 months (305 days; range 0.7 to 36 months); 111 patients received ERIVEDGE for 6 months or longer.

The most common adverse reactions (≥ 10%) were muscle spasms, alopecia, dysgeusia, weight loss, fatigue, nausea, diarrhea, decreased appetite, constipation, arthralgias, vomiting, and ageusia (Table 1).

Table 1: Adverse Reactions Occurring in ≥ 10% of Advanced BCC Patients

	All aBCC[1] Patients (N = 138)		
MedDRA Preferred Term[2]	All Grades[3] (%)	Grade 3 (%)	Grade 4 (%)
Gastrointestinal disorders			
Nausea	42 (30.4%)	1 (0.7%)	-
Diarrhea	40 (29.0%)	1 (0.7%)	-
Constipation	29 (21.0%)	-	-
Vomiting	19 (13.8%)	-	-
General disorders and administration site conditions			
Fatigue	55 (39.9%)	7 (5.1%)	1 (0.7%)
Investigations			
Weight loss	62 (44.9%)	10 (7.2%)	-

Table 1: Adverse Reactions Occurring in ≥ 10% of Advanced BCC Patients (cont)

	All aBCC[1] Patients (N = 138)		
MedDRA Preferred Term[2]	All Grades[3] (%)	Grade 3 (%)	Grade 4 (%)
Metabolism and nutrition disorders			
Decreased appetite	35 (25.4%)	3 (2.2%)	-
Musculoskeletal and connective tissue disorders			
Muscle spasms	99 (71.7%)	5 (3.6%)	-
Arthralgias	22 (15.9%)	1 (0.7%)	
Nervous system disorders			
Dysgeusia	76 (55.1%)	-	-
Ageusia	15 (10.9%)	-	-
Skin and subcutaneous tissue disorders			
Alopecia	88 (63.8%)	-	-

[1]aBCC = Advanced Basal Cell Carcinoma.

[2]MedDRA = Medical Dictionary for Regulatory Activities.

[3]Grading according to NCI-CTCAE v3.0.

Amenorrhea:

In clinical trials, a total of 3 of 10 pre-menopausal women developed amenorrhea while receiving ERIVEDGE [see *Non-Clinical Toxicology (13.1)*].

Laboratory Abnormalities:

Treatment-emergent Grade 3 laboratory abnormalities observed in clinical trials were hyponatremia in 6 patients (4%), hypokalemia in 2 patients (1%), and azotemia in 3 patients (2%).

7 DRUG INTERACTIONS

7.1 Effects of Other Drugs on Vismodegib

Drugs that Inhibit or Induce Drug Metabolizing Enzymes

Vismodegib elimination involves multiple pathways. Vismodegib is predominantly excreted as an unchanged drug. Several minor metabolites are produced by multiple CYP enzymes. Although vismodegib is a substrate of CYP2C9 and CYP3A4 *in vitro*, CYP inhibition is not predicted to alter vismodegib systemic exposure since similar steady-state plasma vismodegib concentrations were observed in patients in clinical trials concomitantly treated with CYP3A4 inducers (i.e., carbamazepine, modafinil, phenobarbital) and those concomitantly treated with CYP3A4 inhibitors (i.e., erythromycin, fluconazole).

Drugs that Inhibit Drug Transport Systems

In vitro studies indicate that vismodegib is a substrate of the efflux transporter P-glycoprotein (P-gp). When ERIVEDGE is coadministered with drugs that inhibit P-gp (e.g. clarithromycin, erythromycin, azithromycin), systemic exposure of vismodegib and incidence of adverse events of ERIVEDGE may be increased.

Drugs that Affect Gastric pH

Drugs that alter the pH of the upper GI tract (e.g. proton pump inhibitors, H_2-receptor antagonists, and antacids) may alter the solubility of vismodegib and reduce its bioavailability. However, no formal clinical study has been conducted to evaluate the effect of gastric pH altering agents on the systemic exposure of vismodegib. Increasing the dose of ERIVEDGE when coadministered with such agents is not likely to compensate for the loss of exposure. When ERIVEDGE is coadministered with a proton pump inhibitor, H_2-receptor antagonist or antacid, systemic exposure of vismodegib may be decreased and the effect on efficacy of ERIVEDGE is unknown.

7.2 Effects of Vismodegib on Other Drugs

Results of a drug-drug interaction study conducted in cancer patients demonstrated that the systemic exposure of rosiglitazone (a CYP2C8 substrate) or oral contraceptives (ethinyl estradiol and norethindrone) is not altered when either drug is co-administered with vismodegib.

In vitro studies indicate that vismodegib is an inhibitor of CYP2C8, CYP2C9, CYP2C19 and the transporter BCRP. Vismodegib does not induce CYP1A2, CYP2B6, or CYP3A4/5 in human hepatocytes.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category D

ERIVEDGE capsule can cause fetal harm when administered to a pregnant female based on its mechanism of action. Vismodegib is teratogenic in rats at doses corresponding to an exposure of 20% of the exposure at the recommended human dose (estimated $AUC_{0\text{-}24hr}$ steady-state exposure). In rats, malformations included craniofacial anomalies, open perineum, and absent or fused digits. Fetal retardations and variations were also observed. Vismodegib is embryolethal in rats at exposures within the range achieved at the recommended human dose. If ERIVEDGE is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the embryo or fetus. Report immediately exposure to ERIVEDGE during pregnancy to the Genentech Adverse Event Line at 1-888-835-2555. Encourage women who may have been exposed to ERIVEDGE during pregnancy, either directly or through seminal fluid, to participate in the ERIVEDGE pregnancy pharmacovigilance program by contacting the Genentech Adverse Event Line at 1-888-835-2555 [see *Boxed Warning, Warnings* and *Precautions (5.1)*].

In an embryo-fetal developmental toxicity study, pregnant rats were administered oral vismodegib at doses of 10, 60, or 300 mg/kg/day during the period of organogenesis. Pre- and post-implantation loss were increased at doses of ≥ 60 mg/kg/day (approximately ≥ 2 times the systemic exposure (AUC) in patients at the recommended human dose), which included early resorption of 100% of the fetuses. A dose of 10 mg/kg/day (approximately 0.2 times the AUC in patients at the recommended dose) resulted in malformations (including missing and/or fused digits, open perineum and craniofacial anomalies) and retardations or variations (including dilated renal pelvis, dilated ureter, and incompletely or unossified sternal elements, centra of vertebrae, or proximal phalanges and claws).

8.3 Nursing Mothers

It is not known whether vismodegib is excreted in human breast milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from ERIVEDGE, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

8.4 Pediatric Use

The safety and effectiveness of ERIVEDGE capsule have not been established in pediatric patients.

In repeat-dose toxicology studies in rats, administration of oral vismodegib resulted in toxicities in bone and teeth. Effects on bone consisted of closure of the epiphyseal growth plate when oral vismodegib was administered for 26 weeks at ≥ 50 mg/kg/day (approximately ≥ 0.4 times the systemic exposure (AUC) in patients at the recommended human dose). Abnormalities in growing incisor teeth (including degeneration/necrosis of odontoblasts, formation of fluid-filled cysts in the dental pulp, ossification of the root canal, and hemorrhage resulting in breakage or loss of teeth) were observed after administration of oral vismodegib at ≥ 15 mg/kg/day (approximately ≥ 0.2 times the AUC in patients at the recommended human dose).

8.5 Geriatric Use

Clinical studies of ERIVEDGE capsule did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently from younger patients.

8.6 Females of Reproductive Potential and Males

ERIVEDGE capsule can cause harm to the embryo or fetus when administered during pregnancy. Counsel female and male patients regarding pregnancy prevention and planning. Advise patients to contact their healthcare provider immediately if they suspect they (or, for males, their female partner) may be pregnant [see *Boxed Warning, Warnings and Precautions (5.1), Use in Specific Populations (8.1)*]

Female patients

Determine pregnancy status within 7 days prior to initiation of treatment in females of reproductive potential. For females with a negative pregnancy test, initiate a highly effective form of contraception (failure rate of less than 1%) prior to the first dose. Continue highly effective contraception during therapy and for 7 months after the last dose of ERIVEDGE. If a patient becomes pregnant while taking ERIVEDGE, or during the 7 months after the last dose of treatment, report the pregnancy to the Genentech Adverse Event Line at 1-888-835-2555. Encourage pregnant females to participate in the ERIVEDGE pregnancy pharmacovigilance program by calling the Genentech Adverse Event Line at 1-888-835-2555. Counsel pregnant females about the teratogenic risk to the fetus.

Amenorrhea has been observed in clinical trials in females of reproductive potential. Reversibility of amenorrhea is unknown [see *Adverse Reactions (6), Nonclinical Toxicology (13.1)*].

Male patients

Male patients should use condoms with spermicide, even after a vasectomy, during sexual intercourse with female partners while being treated with ERIVEDGE capsule and for 2 months after the last dose to avoid exposing an embryo or fetus to vismodegib.

8.7 Hepatic Impairment

The safety and effectiveness of ERIVEDGE capsule have not been established in patients with hepatic impairment [see *Clinical Pharmacology (12.3)*].

8.8 Renal Impairment

The safety and effectiveness of ERIVEDGE capsule have not been established in patients with renal impairment [see *Clinical Pharmacology (12.3)*].

10 OVERDOSAGE

There is no information on overdosage in humans. In clinical trials, ERIVEDGE capsule was administered at 540 mg orally once daily; exposure did not increase between 150 mg and 540 mg daily.

17 PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (Medication Guide).

- Advise patients that ERIVEDGE exposure during pregnancy can cause embryo-fetal death or severe birth defects.
- Instruct female patients of reproductive potential to use a highly effective form of contraception (failure rate of less than 1%) while taking ERIVEDGE and for at least 7 months after the last dose of ERIVEDGE.
- Instruct all male patients, even those with prior vasectomy, to use condoms with spermicide, during sexual intercourse with female partners while taking ERIVEDGE and for at least 2 months after the last dose of ERIVEDGE.
- Instruct patients to immediately contact their healthcare provider if they (or, for males, their female partner) become pregnant or if pregnancy is suspected following exposure to ERIVEDGE.
- Instruct patients to immediately report any pregnancy exposure to ERIVEDGE and encourage participation in the ERIVEDGE pregnancy pharmacovigilance program by calling the Genentech Adverse Event Line at 1-888-835-2555.
- Inform female patients of the potential for serious adverse reactions in nursing infants from ERIVEDGE, taking into account the importance of the drug to the mother.
- Advise patients not to donate blood or blood products while taking ERIVEDGE and for at least 7 months after the last dose of ERIVEDGE.
- Advise patients to swallow ERIVEDGE capsules whole and not to crush or open the capsules.

Genentech
A Member of the Roche Group

ERIVEDGE® [vismodegib] capsule

Manufactured by:
Patheon, Inc.
Mississauga, Canada

Distributed by:
Genentech USA, Inc.
A Member of the Roche Group
1 DNA Way
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Q & A

IDENTIFYING DISTINCTIONS

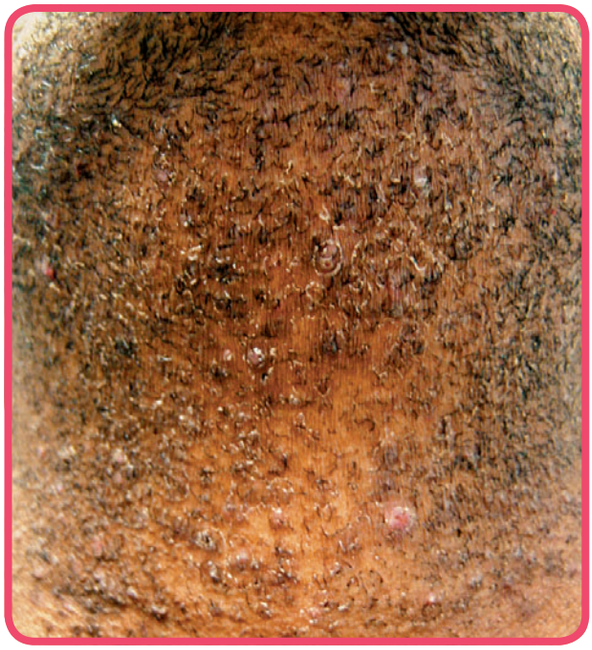
Men with skin of color require subtle differences in care

quick read

Three experts discuss the nuances, challenges and considerations in men of skin of color.

BY LISETTE HILTON | STAFF CORRESPONDENT

WHILE THE MOST OBVIOUS difference among ethnic skin types is color, there are underlying structural and functional differences that result in conditions unique to some skin types and may make certain skin conditions more challenging to treat. Gender adds another layer of consideration. In this simulated roundtable, *Dermatology Times* spoke with three experts to find out what are the unique differences that may affect presentation of disease and treatment considerations in men of skin of color.



Pseudofolliculitis barbae is estimated to affect between 45 and 83 percent of black men.
Photo: Andrew Alexis, M.D., M.P.H.

Q. Talk in general about African-American male skin.

A. Andrew Alexis, M.D., M.P.H., *associate professor of clinical dermatology, Columbia University College of Physicians and Surgeons, practices in New York*

I'm going to … call it … men of African ancestry, so it's not limited to African-Americans per se in the United States but Africans globally.

Men of African ancestry represent a geographically and culturally diverse group, but they share some basic hair structure and grooming characteristics. (They have the tendency) to … groom the hair and the beard in certain ways and have the structure of the hair in common. … The follicle tends to be curved; giving rise to a hair shaft that is curly or coiled shape. This has implications on skin and hair disorders.

So there are a number of hair and skin disorders that disproportionately affect men of African ancestry. These include pseudofolliculitis barbae, acne keloidalis nuchae and dissecting cellulitis of the scalp.

Q. How about on the cosmetic side? What are major cosmetic concerns in this population?

A. Dr. Alexis: Similar to other groups with darker pigmented skin: disorders of pigmentation, including postinflammatory hyperpigmentation, and to a lesser extent melasma, which is less common in men but still affects men of color.

Q. Are there nuances to how you treat these patients?

A. Dr. Alexis: Yes. Starting with pseudofolliculitis barbae, one of the treatment options for pseudofolliculitis barbae is laser hair removal. That has really been the greatest advantages in the management of this often difficult to treat disorder. The greatest advance that we've seen in the past 10 to 15 years is the development of lasers that can be safely used in this population. There are certainly nuances to which lasers to use and the types of settings that one uses in darker skin types. Specifically, the safest lasers are the long-pulsed 1,064 nm Nd:YAG lasers, and, when using conservative settings, including lower fluences and longer pulse durations, we can perform this treatment safely. Now, for lighter skin types, different lasers would be frequently used.

Acne keloidalis nuchae presents with keloid-like or fibrotic papules on the posterior part of the scalp. Haircare practices — namely, the use of electric clippers to groom the hair short — might play a role. Mechanical factors, such as the friction from electric clippers, can at least exacerbate the condition, although they have not been shown to be causative. Since that haircare practice is so common in men of African

DISTINCTIONS see page 48

"The safest lasers are the long-pulsed 1,064 nm Nd:YAG lasers, and, when using conservative settings, including lower fluences and longer pulse durations."

Andrew Alexis, M.D., M.P.H.
New York

DISTINCTIONS:

Subtle differences necessitate considerations in care

from page 47

ancestry, it's very relevant to treating this condition in this group.

We're often advised to decrease the use of anything that would create friction on the back of the scalp. (This means) growing the hair a little bit longer and trying to minimize the degree of friction from clippers at the barber shop that might aggravate the papules on the back of the scalp.

There aren't any specific nuances to treating (dissecting cellulitis of the scalp) in this group; it's just that it's seen more frequently and more prevalent in men of African ancestry. It … can cause a lot of psychological and quality-of-life impairment because, in severe cases, it can be quite disfiguring.

Q: What about treating the pigmentary issues in men of African descent?

A. Dr. Alexis: There aren't that many major differences in treating men versus women with hyperpigmentation on the face. The treatments include superficial chemical peels, the use of topical bleaching agents and sun protection. There can be some additional barriers in terms of getting men to use sunscreen daily. It's a bit more difficult for them to get into that routine than female patients … just generally speaking.

Q: What about cultural considerations or psychosocial concerns specific to this population?

A. Dr. Alexis: There is some literature that suggests that there are barriers to access to healthcare, in general … in the United States among African-American men.

When it comes to grooming practices and how they relate to the scalp and hair conditions, like acne keloidalis nuchae, just understanding the tendency to wear the hair very short and go to get haircuts at the barber shop on a weekly or every two week basis. (This) is quite a common practice among African-American men.

Q: Is there anything I haven't asked you that dermatologists need to know?

A. Dr. Alexis: Talking about pseudofolliculitis barbae, that's the most common of the three disorders that we mentioned and it's estimated to affect between 45 and 83 percent of black men. In the past, it has been the source of racial tensions in the military and in other places where a clean, shaven face is required. It can be quite problematic when shaving is associated with a tremendous amount of irritation and exacerbation of razor bumps.

In some instances where men who have the condition are in workplaces where a clean shaven face is typically required, the option of growing a beard exists. The option of discontinuation of shaving results in improvement or resolution of the problem within four to six weeks, on average.

So, I do give patients the option of growing a beard, and those that wish to do so, I'm happy to give letters to their employers to allow them to grow a beard — usually a well-groomed beard. … A typical example in my office would be police officers who do have a code where their faces need to be shaved. I do write letters for them, and they are able to keep a well-groomed, short-cropped beard.

However, in many cases, with alterations in shaving technique (including pre- and post-shaving routine), men with pseudofolliculitis barbae can continue to shave safely. Patient education about proper shaving technique is a must. A helpful resource is on the American Academy of Dermatology website — *www.aad.org/dermatology-a-to-z/health-and-beauty/general-skin-care/how-to-shave.*

Q: Speak about Asian-American skin in men.

A. Ronald Moy, M.D., ***Beverly Hills, Calif., is past-president of the American Academy of Dermatology and dermatology professor at UCLA's David Geffen School of Medicine.***

There are a couple of differences in Asians versus Caucasians. One of the differences in ethnic skin, overall, is people who are of darker color usually (have thicker, more pigmented skin). It wrinkles, but not as much. Because the skin is thicker, when we're doing surgery, the healing is a little different. There can be more keloids … if not keloids, hypertrophic scars.

Generally, the other way to look at it is the differences aren't that great. There are light-skinned Chinese. My wife would say that I'm really dark-skinned compared to what she is. She is really fair

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"If we're doing a facelift in an Asian … we have to be very careful about not getting any type of hypertrophic scars. So, we might … do things under less tension."

Ronald Moy, M.D.
Beverly Hills, Calif.

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Please see Brief Summary of Prescribing Information.

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Onset DERMATOLOGICS

 *IMS, Sept. 2012 LOC AD DT Rev.2 01/13

DISTINCTIONS:

Subtle differences necessitate considerations in care from page 48

— closer to Caucasian skin. You could argue that the differences are really small, depending on the pigment of the person. Because in America, everybody is so mixed, it's hard to know what percentage (a person is).

But, if we talk about generalities, we'd say (the population) has thicker skin, more pigment, and often with aging people get the darker pigmented lesions. There can be sun damage, even with more pigment. You get blotchiness. You get the brown spots and things.

Q: What skin concerns are prevalent in this population?

A: Dr. Moy: In Asians, bags around the eyes is a little more common than in Caucasians. There is generally more fat around the eyes with aging. With Caucasians, there can be fat accumulation, but often it's the loss of fat around the orbital rim.

And … when we're doing surgery (on Asians), we end up being a little more careful about trying to prevent scars. If we're doing a facelift in an Asian, for example, we have to be very careful about not getting any type of hypertrophic scars. So, we might … do things under less tension. And (we should realize) that getting a hypertrophic scar would require treatment with steroids, which is easier with someone who has thinner skin.

Those are the major differences. The majority of the time, we see the same skin diseases; the same skin problems.

Q: What about skin cancer among Asian-Americans?

A: Dr. Moy: It's less common. In our practice, we maybe remove 2,000 skin cancers a year and maybe five or six among Asians. … We do see basal cell carcinomas and melanomas in Chinese and Asians and Japanese. I personally have an actinic keratosis on my left ear. So, it happens.

voice of the dermatologist

"The greatest advance that we've seen in the past 10 to 15 years is **the development of lasers that can be safely used** (for pseudofolliculitis barbae)."

Andrew Alexis, M.D., M.P.H., New York **page 47**

Q: What cultural considerations or psychosocial concerns should dermatologists be aware of when treating these patients?

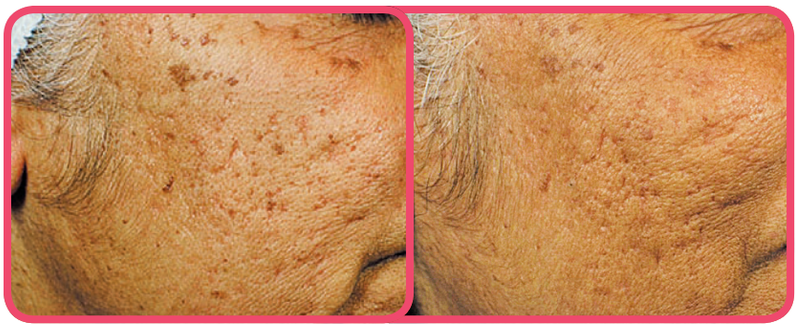
A. Dr. Moy: Among darker skinned people, it's actually more attractive to be lighter skinned. It's sort of a Western influence. People like my mother would always say put sunscreen on (not to prevent skin cancer but because you're getting dark).

Q: Please talk about South Asian skin types among men. What do dermatologists need to know?

A. Vic Narurkar, M.D., ***San Francisco, is associate clinical professor of dermatology at University of California, Davis, Medical School.***

There are several issues that are very prominent on South Asian skin. The first one is the under-eye hyperpigmentation, which patients often refer to as dark circles. That is one of the things that a lot of the men come in for because of the appearance of eyes always being tired, the skin underneath the eyes looking darker.

The second issue that is quite significant is the presence of postinflammatory hyperpigmentation, especially occurring after inflammatory conditions, such as dermatitis as well as acne.



Acne scars and dermatosis papulosa nigra before (left) and after two treatments with Fraxel re: Store 1,550 nm laser.

Photos: Vic Narurkar, M.D.

Q: Any nuances in the skin of South Asian men? Might it be different than Caucasian skin, for example?

A. Dr. Narurkar: The thing to remember is South Asian skin represents (many) different skin types and it ranges from being very fair to very dark. So, within South Asian skin, you have components of numerous ethnicities. An analogy I always use ... is in the United States you might see a blonde, blue-eyed woman and you perform say a procedure on her and (discover) she has some pigment. Later you find out that she has Native American heritage also. When you look at South Asian skin, you (should not assume) that it's supposed to behave in a particular way, as it is represents a diverse range of skin types.

Q: How do you treat South Asian men for the concerns you mentioned?

A. Dr. Narurkar: The number one treatment for under-eye circles, which is usually due to volume loss, is the use

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"When you look at South Asian skin, you (should not assume) that it's supposed to behave in a particular way, as it is represents a diverse range of skin types."

Vic Narurkar, M.D.
San Francisco

DISTINCTIONS:

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of hyaluronic acid fillers, such as Juvéderm (Allergan) and Restylane (Medicis). … And we perform Fraxel re:Store (Solta Medical) 1,550 nm nonablative laser resurfacing to improve the pigmentation. Sometimes, we also use a Q-switched 1,064 nm laser. In addition, we also recommend an under-eye cream such as the TNS Illuminating Eye Cream (SkinMedica) to hydrate the intraorbital area. We also recommend a broad-spectrum sunscreen. It's sort of a combination treatment, using fillers for loss of volume, Fraxel resurfacing and a skincare regimen.

For the second issue, postinflammatory hyperpigmentation, the main thing I always (recommend to patients is the) religious use of sunscreen, because the sun can make things darker.

Now we're also using a lot of alternatives to hydroquinone. … We're using products such as Lytera (SkinMedica) and Phloretin (SkinCeuticals), a topical vitamin C product that is particularly well-suited for dark complected skin. They are our go-to products in darker skin for issues of blotchiness and hyperpigmentation, particularly in men.

If they do have postinflammatory hyperpigmentation on the face (and) it has not responded to the sunscreen and the products, then we often do a series of light peels. Our peels of choice are Vitalize peels (SkinMedica), and they contain resorcinol and retinoic acid. Most recently we started using the Clear + Brilliant Permea laser (Solta Medical) in conjunction with C E Ferrulic (SkinCeuticals) and Lytera (SkinMedica) for enhanced permeation of topical products.

Q: What about psychosocial or cultural consideration when treating this population?

A: Dr. Narurkar: It's not just unique to this population, but men, regardless of their ethnicity, rarely like to talk about (these things). It's difficult to engage in discussions about appearance-related issues.

Make sure that any procedure done does not incur a lot of recovery. A lot of times, people don't want others to know anything has been done. We want to be sensitive to discretion. **DT**

Disclosures: Drs. Narurkar and Moy report no relevant financial interests. Dr. Alexis is a consultant for Galderma and Schick.

REFINING INJECTION TECHNIQUES

Lateral canthal rhytids treated with three injections of abobotulinumtoxinA (Dysport, Medicis) showed no statistically significant difference from those treated with one injection, according to a study in the August 2013 issue of *Journal of Drugs in Dermatology*.

The split-face study included 40 patients with moderate-to-severe hyperdynamic lateral canthal rhytids at maximal contracture who received one injection of 36 units of abobotulinumtoxinA into the middle of the lateral orbital rhytids on one side and three intradermal injections of 12 units each along the lateral canthal area on the contralateral side, according to the abstract. A blinded evaluator examined lateral orbital rhytids at rest and maximal contraction at baseline, seven, 42, 90, and 120 days post-treatment.

Reducing the number of injection sites can improve patient comfort during treatment and potentially decrease risk of bruising, according to Hema Sundaram, M.D., a Washington dermatologist and cosmetic surgeon in private practice and one of the researchers.

Ability to reduce the number of injection sites is a manifestation of enhanced spread of BoNT-A, which depends on factors including dosage, dilution (reconstitution volume) and injection technique, she says. What's important is that evidence level 2 studies have shown that spread is not a clinical problem for any of the available injectable BoNT-A products. Each one is comparable in safety and efficacy. Specifically, the incidence of upper eyelid ptosis after glabellar injection — an indicator of undesirable spread — is low and comparable for all three products.

"Studies like this one on reduction of injection sites help us to refine our techniques with BoNT-A and thereby apply individualized treatment strategies based on an understanding of what is happening functionally and how we can best correct it. It's a step forward that allows us to optimize treatment results for all our patients," Dr. Sundaram says. **DT**

DISCLOSURES: Dr. Sundaram serves as a clinical investigator and/or consultant for Allergan, Ipsen, Medicis/Valeant, Mentor/Johnson & Johnson, Merz and QMed/Galderma.

Fabi SG, Sundaram H, Guiha I, Goldman MP. A two-center, open-label, randomized, split-face study to assess the efficacy and safety of one versus three intradermal injection sites of abobotulinumtoxinA in the treatment of lateral periocular rhytids. *J Drugs Dermatol.* 2013;12(8):932-937

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Q&A HOW TO HANDLE CONSENT

quick read

Exercise caution, understand the law, and put patient safety first, panel advises

INFORMED CONSENT is a critical element of a strong physician-patient relationship. It is both a legal requirement and an ethical obligation that supports the physician in the face of litigation and protects the patient's autonomy in the decision-making process. It can, however, be challenging to manage due to time restraints and low patient information retention rates, among other issues. Studies have shown that patients forget as much as 75 percent of information disclosed. Poor recall increases the chance for litigation should complications arise. While consent itself is not absolute protection from litigation, there are best practices that can help to enhance patient care and reduce your risk of fighting a potentially losing legal battle.

Q: What, specifically, is on your consent form? What do you think are the important, poignant aspects that patients coming in for aesthetic fillers or neuromodulators need to know? And, do you have patients re-sign consent forms each time they return for a treatment?

Susan Weinkle, M.D.
Dermatologist, Bradenton, Fla.

Amy Taub, M.D., dermatologist, Chicago: I do have my patients renew a consent for each distinct procedure every six months. And on the consent form I have all the major things that can go wrong, although I am going to add blindness now (due to the information at this meeting that injection of filler into the nose can cause this rarely). I think that to be honest, we don't really take the time to go over every single thing on the consent form. We talk about bruises, swelling, overcorrection, asymmetry, and all the things that we can do to correct that. And I always have my initial patients — or in patients that we are injecting in a new area — come back in two weeks for evaluation.

Michael Persky, M.D., plastic surgeon, Encino Calif.: That was a great lead in, Amy, and I agree with everything you said. Practically, it's difficult to go over everything, every possible complication. I think that the medical consent form, no matter what procedure, treatment, or surgery that we do as physicians, is a medical legal document there to protect the physician. There's no worse feeling as a physician — and I'm sure all of us who have been practicing long enough have had some sort complication — where you want to go back to that consent form and make sure that it's written there and that the patient signed and dated it the consent.

I think everything you can possibly conceive of that could go wrong should be on that consent form. I think the injectable companies do a pretty good job of it and I don't know if blindness is on the company's form, but it's certainly on my form.

Rebecca Fitzgerald, M.D., dermatologist, Los Angeles: I (list) blindness and death on my consent forms. But what I tell patients is that if I really thought they were going to go blind and die, I wouldn't do this all day, every day, for a living, right? And then I tell them that there's inherent risk in everything. It's a lot like driving a car. Everybody's going to eventually get in a fender bender, but there are very few head-on collisions. The fender benders are the obvious stuff and the head-on collisions are blindness and death that are very unlikely to happen. But it's a risk, and if they're not willing to take any risk whatsoever they shouldn't do it.

I say it like that just because, you know who 95 percent of the crazy people are the minute you get your hand off the doorknob. It's those 5 percent that get you. So if I say that in kind of a stern voice in their face, if I can see them sort of break then I don't really want to treat them. It's just another way to divide who are the safer or more reasonable patients? They do have to know but, patients are in a highly suggestible state when they sign a consent form.

So I'm not talking about just a little anxiety. It's normal for everybody to be a little anxious. But I'm talking about the person who reads it line by line, wants to discuss the whole piece of paper, is flipping the sheet. "What about this one here that says...?" That does us a favor, right? It's just a way to look at who might not be ready to do those procedures. I think the length of time consent lasts varies from state to state. The staff watches that date, and whenever the date expires then we do it again. You can call your malpractice company and they'll tell you.

Ben Bassichis, M.D., plastic surgeon, Dallas: We have separate consents for neurotoxins and HA (hyaluronic acid) fillers. And we have a separate consent for the other fillers we do. We have patients sign every time: If they're going to do one filler one time and they do a different filler the next visit, they're going to sign a new

CONSENT see page 57

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(azelaic acid) Gel, 15%

INDICATION & USAGE

Finacea® (azelaic acid) Gel, 15% is indicated for topical treatment of inflammatory papules and pustules of mild to moderate rosacea. Although some reduction of erythema which was present in patients with papules and pustules of rosacea occurred in clinical studies, efficacy for treatment of erythema in rosacea in the absence of papules and pustules has not been evaluated.

IMPORTANT SAFETY INFORMATION

Skin irritation (e.g. pruritus, burning or stinging) may occur during use with Finacea®, usually during the first few weeks of treatment. If sensitivity or severe irritation develops and persists during use with Finacea®, discontinue use and institute appropriate therapy. There have been isolated reports of hypopigmentation after use of azelaic acid. Since azelaic acid has not been well studied in patients with dark complexion, monitor these patients for early signs of hypopigmentation.

Avoid contact with the eyes, mouth, and other mucous membranes. In case of eye exposure, wash eyes with large amounts of water. Wash hands immediately following application of Finacea®.

Avoid use of alcoholic cleansers, tinctures and astringents, abrasives and peeling agents. Avoid the use of occlusive dressings or wrappings.

In clinical trials with Finacea®, the most common treatment-related adverse events (AE's) were: burning/stinging/tingling (29%), pruritus (11%), scaling/dry skin/xerosis (8%) and erythema/irritation (4%). Contact dermatitis, edema and acne were observed at frequencies of 1% or less.

Finacea® is for topical use only. It is not for ophthalmic, oral or intravaginal use. Patients should be reassessed if no improvement is observed upon completing 12 weeks of therapy.

Please see Brief Summary of full Prescribing Information on adjacent page.

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1. According to IMS NPATM (National Prescription Audit) July 2010-August 2013

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BRIEF SUMMARY
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1 INDICATIONS AND USAGE
FINACEA® Gel is indicated for topical treatment of the inflammatory papules and pustules of mild to moderate rosacea. Although some reduction of erythema which was present in patients with papules and pustules of rosacea occurred in clinical studies, efficacy for treatment of erythema in rosacea in the absence of papules and pustules has not been evaluated.

5 WARNINGS AND PRECAUTIONS
5.1 Skin Reactions
Skin irritation (i.e. pruritus, burning or stinging) may occur during use of FINACEA Gel, usually during the first few weeks of treatment. If sensitivity or severe irritation develops and persists, discontinue treatment and institute appropriate therapy.

There have been isolated reports of hypopigmentation after use of azelaic acid. Since azelaic acid has not been well studied in patients with dark complexion, monitor these patients for early signs of hypopigmentation.

5.2 Eye and Mucous Membranes Irritation
Avoid contact with the eyes, mouth and other mucous membranes. If FINACEA Gel does come in contact with the eyes, wash the eyes with large amounts of water and consult a physician if eye irritation persists *[see Adverse Reactions (6.2)]*.

6 ADVERSE REACTIONS
6.1 Clinical Trials Experience
Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

In two vehicle-controlled and one active-controlled U.S. clinical trials, treatment safety was monitored in 788 subjects who used twice-daily FINACEA Gel for 12 weeks (N=333) or 15 weeks (N=124), or the gel vehicle (N=331) for 12 weeks. In all three trials, the most common treatment-related adverse events were: burning/stinging/tingling (29%), pruritus (11%), scaling/dry skin/xerosis (8%) and erythema/irritation (4%). In the active-controlled trial, overall adverse reactions (including burning, stinging/tingling, dryness/tightness/ scaling, itching, and erythema/irritation/redness) were 19.4% (24/124) for FINACEA Gel compared to 7.1% (9/127) for the active comparator gel at 15 weeks.

Table 1: Adverse Events Occurring in ≥1% of Subjects in the Rosacea Trials by Treatment Group and Maximum Intensity*

	FINACEA Gel, 15% N=457 (100%)			Vehicle N=331 (100%)		
	Mild n=99 (22%)	Moderate n=61 (13%)	Severe n=27 (6%)	Mild n=46 (14%)	Moderate n=30 (9%)	Severe n=5 (2%)
Burning/ stinging/ tingling	71 (16%)	42 (9%)	17 (4%)	8 (2%)	6 (2%)	2 (1%)
Pruritus	29 (6%)	18 (4%)	5 (1%)	9 (3%)	6 (2%)	0 (0%)
Scaling/ dry skin/ xerosis	21 (5%)	10 (2%)	5 (1%)	31 (9%)	14 (4%)	1 (<1%)
Erythema/ irritation	6 (1%)	7 (2%)	2 (<1%)	8 (2%)	4 (1%)	2 (1%)
Contact dermatitis	2 (<1%)	3 (1%)	0 (0%)	1 (<1%)	0 (0%)	0 (0%)
Edema	3 (1%)	2 (<1%)	0 (0%)	3 (1%)	0 (0%)	0 (0%)
Acne	3 (1%)	1 (<1%)	0 (0%)	1 (<1%)	0 (0%)	0 (0%)

* Subjects may have >1 cutaneous adverse event; thus, the sum of the frequencies of preferred terms may exceed the number of subjects with at least 1 cutaneous adverse event.

In patients using azelaic acid formulations, the following adverse events have been reported: worsening of asthma, vitiligo, depigmentation, small depigmented spots, hypertrichosis, reddening (signs of keratosis pilaris) and exacerbation of recurrent herpes labialis.

Local Tolerability Studies
FINACEA Gel and its vehicle caused irritant reactions at the application site in human dermal safety studies. FINACEA Gel caused significantly more irritation than its vehicle in a cumulative irritation study. Some improvement in irritation was demonstrated over the course of the clinical trials, but this improvement might be attributed to subject dropouts. No phototoxicity or photoallergenicity were reported in human dermal safety studies.

6.2 Post-Marketing Experience
The following adverse reactions have been identified post approval of FINACEA Gel. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate the frequency or establish a causal relationship to drug exposure:

Eyes: iridocyclitis upon accidental exposure of the eyes to FINACEA Gel

7 DRUG INTERACTIONS
There have been no formal studies of the interaction of FINACEA Gel with other drugs.

8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
Teratogenic Effects: Pregnancy Category B
There are no adequate and well-controlled studies in pregnant women. Therefore, FINACEA Gel should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Dermal embryofetal developmental toxicology studies have not been performed with azelaic acid, 15% gel. Oral embryofetal developmental studies were conducted with azelaic acid in rats, rabbits, and cynomolgus monkeys. Azelaic acid was administered during the period of organogenesis in all three animal species. Embryotoxicity was observed in rats, rabbits, and monkeys at oral doses of azelaic acid that generated some maternal toxicity. Embryotoxicity was observed in rats given 2500 mg/kg/day [162 times the maximum recommended human dose (MRHD) based on body surface area (BSA)], rabbits given 150 or 500 mg/kg/day (19 or 65 times the MRHD based on BSA) and cynomolgus monkeys given 500 mg/kg/day (65 times the MRHD based on BSA) azelaic acid. No teratogenic effects were observed in the oral embryofetal developmental studies conducted in rats, rabbits and cynomolgus monkeys.

An oral peri- and post-natal developmental study was conducted in rats. Azelaic acid was administered from gestational day 15 through day 21 postpartum up to a dose level of 2500 mg/kg/day. Embryotoxicity was observed in rats at an oral dose of 2500 mg/kg/day (162 times the MRHD based on BSA) that generated some maternal toxicity. In addition, slight disturbances in the post-natal development of fetuses was noted in rats at oral doses that generated some maternal toxicity (500 and 2500 mg/kg/day; 32 and 162 times the MRHD based on BSA). No effects on sexual maturation of the fetuses were noted in this study.

8.3 Nursing Mothers
It is not known whether azelaic acid is excreted in human milk; however, *in vitro* studies using equilibrium dialysis were conducted to assess the potential for human milk partitioning. The studies demonstrated that, at an azelaic acid concentration of 25 µg/mL, the milk/plasma distribution coefficient was 0.7 and the milk/buffer distribution was 1.0. These data indicate that passage of drug into maternal milk may occur. Since less than 4% of a topically applied dose of 20% azelaic acid cream is systemically absorbed, the uptake of azelaic acid into maternal milk is not expected to cause a significant change from baseline azelaic acid levels in the milk. Nevertheless, a decision should be made to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

8.4 Pediatric Use
Safety and effectiveness of FINACEA Gel in pediatric patients have not been established.

8.5 Geriatric Use
Clinical studies of FINACEA Gel did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects.

17 PATIENT COUNSELING INFORMATION
Inform patients using FINACEA Gel of the following information and instructions:

Use only as directed by your physician.
- For external use only.
- Before applying FINACEA Gel, cleanse affected area(s) with a very mild soap or a soapless cleansing lotion and pat dry with a soft towel.
- Avoid use of alcoholic cleansers, tinctures and astringents, abrasives and peeling agents.
- Avoid contact with the eyes, mouth and other mucous membranes. If FINACEA Gel does come in contact with the eyes, wash the eyes with large amounts of water and consult your physician if eye irritation persists.
- Wash hands immediately following application of FINACEA Gel.
- Cosmetics may be applied after the application of FINACEA Gel has dried.
- Avoid the use of occlusive dressings or wrappings.
- Skin irritation (e.g., pruritus, burning, or stinging) may occur during use of FINACEA Gel, usually during the first few weeks of treatment. If irritation is excessive or persists, discontinue use and consult your physician.
- Report abnormal changes in skin color to your physician.
- To help manage rosacea, avoid any triggers that may provoke erythema, flushing, and blushing. These triggers can include spicy and thermally hot food and drinks such as hot coffee, tea, or alcoholic beverages.

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CONSENT:

Exercise caution, understand law, put patient safety first

from page 54

consent. It goes over what we're going to do, and it offers documentation that, in the event there is a complication, there is a signed consent for that particular visit.

I think it just gives one more level of defense. So if I inject three different products in one visit, we'll circle which products we're injecting, where we're injecting. We have the complications in bold (type) that they have to initial, which includes blindness. And they also sign at the bottom of the form. So they initial the section that has the complications in bold.

Welf Prager, M.D., dermatologist, Hamburg, Germany: Before the malpractice companies will insure a new procedure, they require from the doctors, who perform the procedure to supply the informed consents for these treatments. There are organizations in Germany that distribute these inform consents. They make sure that all new legal issues are within these informed consents. I only use them, because they cover all the important issues. In our informed consents, blindness is included and I think that's a really important point, and it should be on the informed consent.

Derek Jones, M.D., dermatologist, Los Angeles: We have patients resign their consent each time they come in. The company-provided informed consents that I've seen in the U.S. are generally not as comprehensive as I'd like to see them.

Blindness has been reported frequently enough in the literature that it should be on there. Just a quick note about how blindness happens because it's kind of a hot topic these days. It is probably caused by accidentally injecting under high pressure into arteries in the glabella region and into facial artery branches in and around the nasal sidewall and dorsal nose, which causes retrograde flow to the retinal artery.

Products with a very high G prime and particulate products may carry a greater risk. Preventative techniques include a slow injection speed and a masterful knowledge of facial arterial anatomy.

Michael Kane, M.D., plastic surgeon, New York: I think embolic phenomenon theoretically can be greatly reduced, if not eliminated entirely, by slow flow rates. It's all about high flow rates when you've cannulated an artery. That being said, I've been in practice 22 years, and every consent that I've had has included blindness and death.

But I think it's more of a moral issue than a legal issue. Even if you had that in your consent, if you inject someone and they go blind they're probably going to win. It doesn't matter if it's in your consent. It doesn't matter if you talked it over with them. They're probably going to be compensated.

To me, it's more of a moral issue. I don't know if I could continue to practice if someone went blind. To me it's more about telling them that it's possible but extraordinarily unlikely. You've never had it your practice and you will do everything possible to make sure that doesn't happen.

A: Susan Weinkle, M.D., Bradenton, Fla.: I think we could say unanimously that we all feel quite strongly that the issue of blindness does need to be included in the consent form. You need to check with your malpractice company to find out how often you need to re-consent even when you're doing the same procedure with that patient so that we all know that we're working within what our regional variations may be. **DT**

VIDEO dermatologytimes.com/consent

Dermatology Times **presents a panel discussion (left) at the annual Vegas Cosmetic Surgery and Aesthetic Dermatology annual meeting. Here, panel members discuss best practices for patient consent.**

STEMULATION

Herbal toner works deep into skin

The new AHA Herbal Balancing Toner is designed to gently cleanse the skin and remove any unwanted buildup from throughout the day. The toner helps to remove residual traces of makeup and environmental pollutants that are left after cleansing, while maintaining skin's essenti moisture, according to the company.

The toner does not contain drying ingr dients such as alcohol, and contains a syr ergistic herbal complex including extracts of witch hazel, cucumber, grape seed, ginkgo biloba, lemongrass and green tea.

The AHA Herbal Balancing Toner is gentle enough to use once in the morning and at night on a daily basis, the company states.

FOR MORE INFORMATION:
www.stemulation.com

OLEHENRIKSEN

Wipes remove makeup, salt

The new Truth To Go Wipes are strong enough to remove runny makeup and salt after a dip in the ocean, as well as sweat, but gentle enough not to overdry skin, according to the company. Providing a pick-me-up with a bright citrus vanilla aroma, these portable wipes not only cleanse and refresh skin on-the-go, they also offer anti-aging benefits and antioxidant protection, the company claims.

Ingredient benefits include vitamin C, which brightens, lightens and tightens; micro algae, which firms skin and boosts collagen production; CoQ10, which boosts skin repair and regeneration, antioxidants; and green tea, which inhibits collagen breakdown.

OleHenriksen Truth To Go Wipes can be used on all skin types, the company states.

FOR MORE INFORMATION:
www.olehenriksen.com

LUTRONIC

Radiofrequency system uses 3-D energy

The Lutronic Infini 2-in-1 fractional radiofrequency system helps create targeted coagulation zones in aging, sagging skin with wrinkles. Infini's design delivers improved wrinkle reduction through three-dimensional energy delivery, according to the company.

Infini uses radiofrequency (RF) energy delivered via insulated gold-coated microneedles, which creates precise and controllable fractionated coagulation zones within a specific layer of dermis. Adjustable depth control allows for customized and reproducible treatments of delicate areas. Infini can be used on patients with melasma and other types of pigmented lesions.

Other Infini features include the ability to safely treat all skin types, results that are reproducible, deeper tissue effect than the conventional RF and fractional lasers, and a technology that treats more than 3.5 mm deep.

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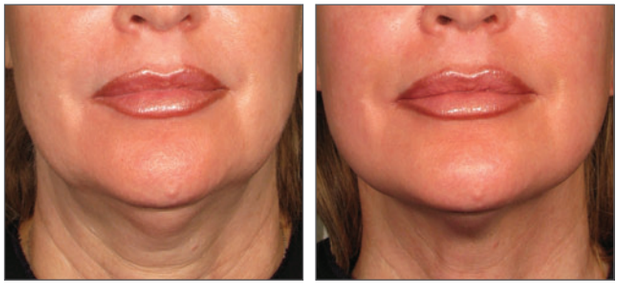
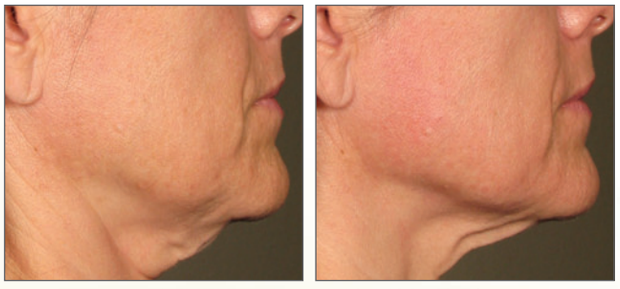
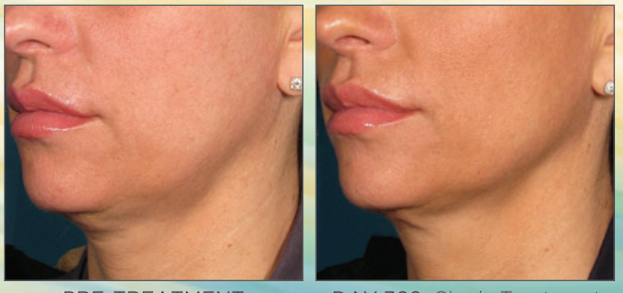


PRE-TREATMENT | DAY 90, *Single Treatment*



PRE-TREATMENT | DAY 180, *Single Treatment*



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ASSESSING METASTASIS

Investigators examine benefit of level 3 dissection in melanoma

BY LOUISE GAGNON | STAFF CORRESPONDENT

Banff, Alberta — Results of a retrospective chart review revealed patients with melanoma who present with bulky axillary disease develop distant metastases very quickly, prompting the plan for a prospective study to examine the preoperative impact of shrinking tumors through the use of systemic therapy.

The retrospective investigation aimed to look at the extent of surgery necessary for patients who presented in one of three ways, says Frances Wright, M.D., M.Ed., F.R.C.S.C., associate professor of surgery, University of Toronto, and director of surgical oncology fellowship program, University of Toronto.

Dr. Wright spoke here about how level 3 nodes, that is nodes medial to the insertion of pectoralis minor to the clavicular head, bear melanoma metastases and the effect on patient outcome at the annual Canadian melanoma conference.

"These were patients with melanoma who had either sentinel-positive disease, or disease that you can palpate, or a very amount of disease or bulky amounts of disease," says Dr. Wright, noting limited data exist on the need to resect level 3 nodes as part of an axillary dissection for melanoma.

QUICK READ

Level 3 nodes bear metastases more often in patients with palpable disease and in patients with bulky disease compared to sentinel lymph node positive patients.

Currently, in patients who have sentinel lymph node positive disease, complete lymphadenectomy is controversial and the clinical benefit is not known. This question is being addressed in the Multicenter Lymphadenectomy Trial Part 2 (MSLT 2).

There is also little evidence for benefit of level 3 dissection compared to a level 1/2 dissection. A study published in 2012 concluded that a level 3 dissection offered minimal benefit in melanoma patients with a positive axillary sentinel lymph node (Namm JP, Chang AE, Cimmino VM, et al. *J Surg Oncol*. 2012;105(3):225-228).

The study involved patients from two centers, Sunnybrook Odette Cancer Center/University of Toronto, and the Tom Baker Cancer Center/University of Calgary. All of the patients included in the review had undergone level 3 dissection for melanoma, with a goal to cure disease, between 2005 and 2011.

A total of 117 patients were included. A total of 65 patients were sentinel lymph node positive and had median age of 54, 44 had palpable disease and a median age of 61.5, and eight had palpable disease and a median age of 50.5.

The investigators found the median number of nodes of all three levels was 24, the median number of sentinel lymph nodes was three, and the median number of level 3 nodes was five.

Researchers found level 3 nodes bear metastases infrequently (3 percent) in sentinel lymph node positive patients, that they bear metastases more often (18 percent) in patients with palpable disease, and all level 3 nodes bear metastases in patients with bulky disease.

"Based on our findings, patients

PREDICTING RECURRENCE RISK

New York — A new genetic test can identify patients with nonmetastatic melanoma who are at high risk of recurrence, according to validation data presented at the 2013 summer meeting of the American Academy of Dermatology.

Using the DecisionDx-Melanoma test (Castle Biosciences), researchers with Northwestern Skin Cancer Institute, Northwestern University, Chicago, measured gene expression profiles of archived formalin-fixed, paraffin-embedded biopsies or wide excisions of primary melanoma tumors from 78 patients with stage 1 and stage 2 melanoma, according to a news release.

The DecisionDx-Melanoma test measures the expression levels of 31 genes in tumors and stratifies patients as either class 1 (low risk of metastasis) or class 2 (high risk of metastasis), based on which tumor genes are turned on and off. To date, the test has analyzed archived tumor samples from more than 400 patients with stage 1 and stage 2 melanoma.

Data from the latest study confirmed the test accurately stratifies metastatic risk for these patients, according to researchers. Investigators found that five-year metastasis free survival rates were 98 percent for class 1 and 37 percent for class 2 ($P<0.0001$), according to Kaplan-Meier analysis (accuracy = 85 percent, sensitivity = 86 percent). Cox proportional multivariate analysis found the test to be independent of Breslow, mitosis and ulceration as well as AJCC stage ($P<0.01$).

"The availability of a tool that helps predict future cancer behavior based on the tumor's biology, independent of and additive to current staging methods, is a welcomed advance," said study presenter Pedram Gerami, M.D., associate professor of dermatology at Northwestern University.

The company expects data to be published later this year. **DT**

who are sentinel lymph node positive don't need to have a formal level 3 dissection," says Dr. Wright, noting a level 1/2 dissection appears to be sufficient in patients with sentinel lymph node positive patients. "When you undergo a formal level 3 dissection, there is likely a small amount of additional morbidity and pain which, it looks like, we can avoid."

However, 20 percent of patients with palpable disease had level 3 disease and consequently a level 3 dissection is appropriate in these patients, according to Dr. Wright. In patients with bulky disease, level 3 is most commonly palliative as patients develop distant disease quickly.

> "Based on our findings, patients who are sentinel lymph node positive **don't need** to have a formal level 3 **dissection**."
>
> **Frances Wright, M.D.**
> Toronto

Dr. Wright says investigators found different survival and outcomes in terms of when the patient develops metastases.

Distant recurrence occurred with greater rapidity a with greater degree of disease: the median time to distant metastases was 13.6 months in patients with palpable disease and 2.1 months in patients with bulky disease. Patients with level 3 disease had a poorer overall survival than those who did not, 15.2 percent versus 61.1 percent, a difference that was statistically significant.

"It was a really surprising finding in terms of the rapidity with which patients develop distant metastases," Dr. Wright says. "It was much faster than we had anticipated. Even the median time for patients with palpable disease to develop distant metastases was fast at 13 months."

Dr. Wright and colleagues also measured the loco-regional recurrence rate and systemic recurrence rate, finding greater disease correlated with higher rates of both.

Dr. Wright and other investigators are launching a pilot study to assess the impact of preoperative administration of systemic therapy in patients with palpable and bulky disease.

"The goal is that we would shrink disease preoperatively to change outcomes," she says, noting vemurafenib would be administered to patients who are BRAF positive. **DT**

Disclosures: Dr. Wright reports no relevant financial interests.

Dermatology Times

SPEAKER DEVELOPMENT

Great lectures don't just happen

BY JOHN JESITUS | SENIOR STAFF CORRESPONDENT

Miami Beach, Fla. — Giving a great lecture requires ongoing refinement and the ability to be honest with one's audience and oneself, according to an expert.

When speaking at a conference, says Kanade Shinkai, M.D., Ph.D., half the challenge is presenting oneself. In this regard, "We would all like to think that we know our strengths and weaknesses. But they're not necessarily what other people perceive as our strengths and weaknesses as a speaker. It's not enough to be an expert on the content; it's about the delivery." Dr. Shinkai is assistant professor of dermatology, University of California, San Francisco, School of Medicine.

"And be very honest with yourself about it. For example, if you're incredibly charismatic onstage, and are able to grab the audience's attention and inspire them to participate, then that is the type of talk you should give," she says.

Conversely, "If you're quiet, conceptual and understated, emphasize those strengths. Don't try to do things that aren't your forte. For instance, if you're not a good joke-teller, don't feel obligated to tell jokes. Highlight your strengths instead and learn the essential skills of giving an effective talk. Giving a talk is a skill that can be learned."

KNOW YOUR AUDIENCE

Another critical challenge involves understanding your audience, Dr. Shinkai says.

Who are they, and what do they want or need to hear from you? This requires planning. Find out how you can tie your presentation into the conference experience as a whole and be certain to target the information to your audience. For example, presenting a topic to a group of non-dermatologists should be very different than presenting the same topic to a group of experts," she says.

Understanding the setting, time limits and format of your presentation are also important. "Are you speaking on a panel, leading a workshop, or lecturing to an audience of 1,000? And for how long?"

Presenting one's lecture content begins with capturing the audience. To that end, "I always like to tell a story, about why I became interested in the topic I'm speaking about, or why I believe it's important for people to learn about." Anecdotes and pictures of a memorable patient who had a particular disease also help to bring alive a speaker's connection to a topic, Dr. Shinkai adds.

Also at the beginning of a talk, she says, speakers should state the goals of their presentation. "You don't want there to be any surprises. You want people to understand what they're getting into. Provide a roadmap of what you will be discussing and how you will approach the information. But you don't have to give away all your punchlines up front."

Then, throughout the lecture, she recommends delivering information on your audience's level. "As specialists, we are at risk of scaring the audience or sounding 'high and

SPEAKER DEVELOPMENT see page 64

Quotable

"Social media is the ideal platform to ... connect directly with your target audience and influence their opinion about your practice."

Patricia Redsicker
Baltimore

On social media, page 66

DT Extra

Social media guidelines for physicians frequently focus on the need to separate personal from professional, but those types of policies **get social media all wrong**, according to a viewpoint recently published in *JAMA*. Instead, ask: **Is what you're about to say appropriate** for a doctor to talk about in public? Study authors stress they aren't proposing that doctors should "eliminate boundaries," or that "anything goes" on social media. Rather, the key is recognizing that **social media exist in primarily public spaces**, not in exclusively professional or exclusively personal ones.

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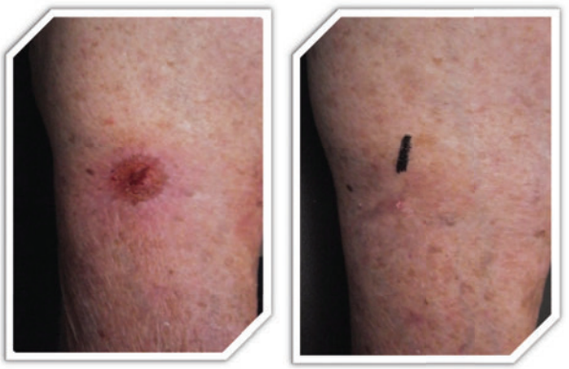

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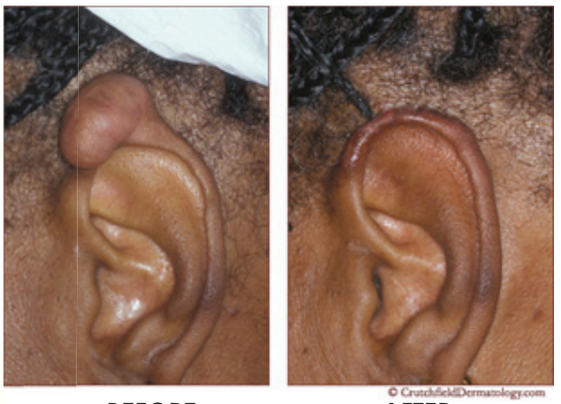
Keloid Scars - Left Ear Keloid



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voices from the industry

"Opinions vary on whether the Affordable Care Act will succeed, but **there is little debate it will forever change** the delivery of healthcare in the United States."

Jeffrey Bendix, Daniel R. Verdon, Rachael Zimlich, *Medical Economics* **page 72**

SPEAKER DEVELOPMENT:

Learn how to understand and captivate your audience from page 62

mighty' about our particular area of expertise. If you're speaking to non-dermatologists or nonspecialists, the last thing you want to do is alienate them by saying something like, 'If you miss this diagnosis, you're going to kill people.' Try to work with what they do know, avoid jargon, and address them in a positive, motivating fashion."

"Try to ... embrace each new talk as an opportunity to improve and practice your presentation skills."
Kanade Shinkai, M.D., Ph.D.
San Francisco

Dr. Shinkai suggests verbiage such as the following: "From my vantage point of having seen many cases of this entity, I want to share some clinical pearls about how to recognize this entity when it presents at your primary care clinic."

Moreover, she says, diagnoses that might seem obvious to the speaker may not be obvious to the audience. Therefore, "It's always good to say something like, 'This is very subtle information.' Rather than intimidating at audience, encourage them to recognize that it is a challenging diagnosis and lead them through the process of learning the information."

CATCH THEIR EYE

Regarding eye contact, says Dr. Shinkai, some inexperienced speakers literally lecture to one person in the audience. "Maybe it's somebody they know; maybe they always pick somebody in the middle section on the left side. And if you're not in that section, you don't feel as if the presenter is speaking to you."

At the other extreme, "Sometimes people overcompensate by scanning — looking quickly across the audience and never establishing eye contact with anyone. This makes people feel that you're unfocused. It's distracting."

To establish a happy medium, she recommends delivering each complete thought to a different person — and all those behind him or her. "When you direct your gaze at that person, it looks like you're looking down a line, at that row of people. Complete that thought, then move to another person on another side of the room, and again you're projecting toward a whole line of people. Shifting your gaze with each new thought or concept allows you to connect with a large number of people in a meaningful way."

Finally, learn from your experiences as a speaker.

"Reading your speaker evaluations or getting feedback from a trusted audience member is the single most important thing you can do to improve your presentation skills," she says. "Try to be as open as possible to suggestions, and embrace each new talk as an opportunity to improve and practice your presentation skills. It's a lifelong skill, and there's always room for improvement." **DT**

Disclosures: Dr. Shinkai reports no relevant financial interests.

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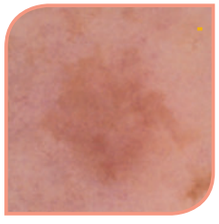

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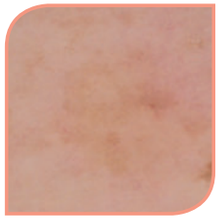

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*Clinical efficacy study on lentigo pigmentation with 58 women. D-Pigment RICH was applied once in the evening for 3 months. Chromametric measurements of ITA and dermatologist's opinion (DPGA score) were evaluated. p<0.0001.

Patricia Redsicker is a healthcare content marketing consultant and principal at Wordview Editing in Baltimore

THE PRACTICE BENEFITS OF GOING SOCIAL

Are you wondering how your dermatology practice can draw in more patients?

Social media is the ideal platform to share your brand's story, connect directly with target audiences and influence their opinion about your practice. For consumers at large, social media is not only a source of health information but also is representative of a growing movement in healthcare — one where the patient has more control of the conversation.

Social media networking has expanded the dialogue about health far beyond the doctor's office. Patients who share a particular health condition such as eczema, acne or even skin cancer can now talk directly to each other, share their experiences, encourage one another and even recommend doctors or treatments that have worked for them.

Dermatologists would do well to recognize the practical applications and benefits of using social media to influence patient perceptions about their practices.

BENEFITS FOR DERMATOLOGISTS

Here are some of the benefits for dermatologists who choose to use social media:

1. **Compelling numbers** With more than 1 billion active users on Facebook, 500 million on Twitter, 225 million on LinkedIn and 48.7 million on Pinterest, the chances that potential patients are hanging out on any of these platforms is very high and your chances of connecting directly with your ideal audience is guaranteed.

2. **Amplify your message** A recent study from Pew Research Center shows that 81 percent of adults in the United States use the Internet to look for health information. Even though they start their search on Google, they're more likely to find your online content if you have shared it on Facebook, Twitter, LinkedIn and especially Google+. In fact, the more others share your content on social media, the higher the visibility it will get on search engines, thus increasing your brand's exposure and potentially impacting a much wider audience.

3. **High traffic** When you post an interesting update on your social media networks and include a link back to your site, people will invariably click on the link to learn more about that topic. The more interesting the update the more people will click on it.

This means you will receive high referral traffic from those social platforms to your website. Make sure that your blog pages have social sharing buttons that allow visitors to share your content with their networks, thus increasing your Web traffic even more.

4. **Connect personally with target audience** Social media allows you to connect personally and directly with potential patients. In fact, on Facebook you can define your ideal target audience by age, gender, location educational status, interests, and even terms they have shared on Facebook. If you use these targeting options wisely you will see a big difference in the way people interact with your posts.

5. **Influence patients' perceptions** Whether you use social media or not, it's important to realize that your patients do, and may be talking about your practice whether you know it or not. When you participate in social media, you can join in those conversations and thus influence the way people think about your practice. Positive experiences can be reinforced, while negative experiences can be turned around.

TIPS TO GET STARTED

Blog: Blogging is associated with social media because blog articles, which represent your brand's message, are usually shared with a wider audience on platforms such as Facebook, Twitter and others.

Regular blogging can help people find your website faster when they look for a topic or solution that describes what you do. For SEO purposes, try to blog at least once or twice a week, focusing on topics that appeal to potential patients. Use simple, clear language and avoid using jargon or unexplained medical terms.

Facebook: Start out by posting two Facebook updates each day — morning and afternoon. Your morning post should consist of educational content such as a link to an article on your blog that explains "How to treat and manage acne."

Your afternoon post should be a more fun and engaging post to encourage interaction ("likes" and comments) from your audience. The more interactions you get on your Facebook page, the more visibility your social posts will get on your fans' news feed.

Twitter: Try to send out at least 10 to 15 tweets each day spaced out at regular intervals. Hashtags (symbol used for grouping online conversations) are becoming more ubiquitous, so try to find a hashtag that followers can use to identify your brand's message e.g. #exfoliation, #summerskin, etc.

If you're not familiar with hashtags, head on over to the Healthcare Hashtag Project (http://www.symplur.com/healthcare-hashtags/) and review some of the existing hashtags used to categorize healthcare conversations on Twitter. You can pick one or two that match the message your brand wants to be known for.

WRAP-UP

Active use of social media can help boost business for dermatology practices. If you're inexperienced with social media, begin with small steps (by starting a blog, and using at least Facebook and Twitter).

Try to observe what other brands similar to yours are doing online. You can also partner with social media consultants or marketing firms with exclusive focus on promoting healthcare brands. DT

App lets doctors securely share medical images

MICHELLE SPREHE | STAFF CORRESPONDENT

MANY ARE CALLING it an "Instagram for healthcare professionals," and one thing is for sure: Figure 1, a free social medical photo-sharing app available for iOS and available through the iTunes store, has been gaining attention since it debuted early this summer.

The app is the brainchild of Joshua Landy, M.D., a critical care specialist in Toronto and co-founder of the app.

Figure 1 is a crowd-sourced tool for healthcare professionals to share medical images and use them as a learning aid. Figure 1 gives image uploaders the ability to say something about the photo, add arrows to point out findings on the image, and add patient privacy with blurs and black-out boxes.

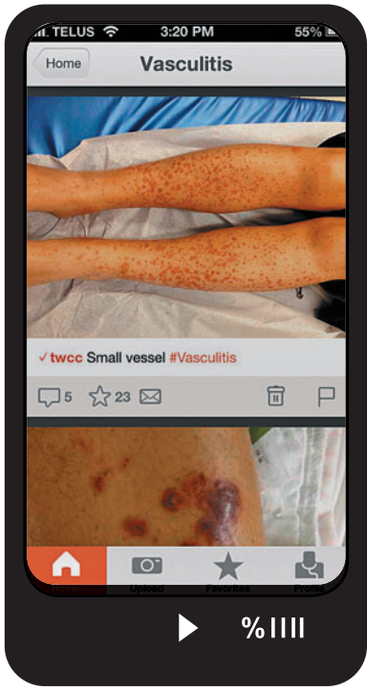

Photo: Figure 1

While you can find eye-catching images, perhaps the most notable part about the app is the medical dialogue found in the comment section of each image. Some physicians upload photos as pop-quizzes by asking others to guess what's wrong with the patient. Others simply share rare or interesting cases, and an educational discussion unfolds in the comments.

Although the app is not limited to healthcare professionals, when creating a profile you are asked to identify yourself by your profession, and then you are give the option to verify your credentials.

As for patient confidentiality and privacy, special considerations have been made in the app.

"We know that patient privacy is a priority for healthcare professionals, and we have designed Figure 1 with that firmly in mind," according to the Figure 1 website. "We take patient privacy extremely seriously, and we have worked hard to make sure that you don't breach privacy regulations while using Figure 1." **DT**

www.figure1.com

For more information about the app, or concerns about patient privacy, visit the app's FAQ page on its website

OMNIBUS:

Proactive steps may help prevent breaches of PHI from page 1

dollars of incentives to providers to adopt electronic health records (EHRs)," Mr. Tennant says. "The argument at the time was, if we're going to be storing and transmitting patients' data electronically, we need to ensure to a greater extent the privacy and security of that data."

"Electronic health data is **fundamentally different** from paper (data) ... there's more of it, and because **it's easier to lose and alter inadvertently.**"

Kenneth Rashbaum, J.D.
New York

"Electronic health data is fundamentally different from paper (data) both because there's more of it, and because it's easier to lose and to alter inadvertently. That's why HHS (the Department of Health and Human Services) is so adamant about enforcement," adds Kenneth Rashbaum, J.D., a health law attorney with Rashbaum Associates in New York.

The Office for Civil Rights (OCR) is responsible for enforcing the HIPAA privacy and security rules, which it does by investigating complaints and conducting compliance reviews — audits — of businesses and organizations covered by the rules. OCR has posted case examples and resolution agreements on its website. OCR also posts cases involving breaches of unsecured PHI affecting 500 or more individuals. The latter is sometimes referred to as the "wall of shame" by practice consultants and information technology (IT) security experts, Mr. Tennant says.

AVOIDING THE 'WALL OF SHAME'

So what can you do to keep your practice off the "wall of shame"? The short answer is, be proactive. "As they say in sports, the best defense is a good offense," Mr. Tennant says. "That's why we are encouraging our members to be really aggressive in taking the necessary steps to prevent that breach from occurring in the first place."

Although it is possible to hire a security expert to conduct a "soup to nuts" security risk assessment, the cost is usually prohibitive for a small medical practice. Mr. Tennant recommends instead that physicians use the wide variety of resources — many of them free — available through the government and professional societies and organizations to identify the steps they need to take to make their practices HIPAA-compliant.

SAFEGUARDING PHI

Broadly speaking, those steps fall into two categories. The first is safeguarding patients' PHI so that it is not lost, stolen, or otherwise subject to unauthorized access. In this, the biggest vulnerability most practices face comes from mobile devices such as smartphones, laptop computers and tablets ("anything that can store electronic information and is easily picked up and carried," Mr. Tennant says) because they are so easily lost or stolen.

Fortunately, a solution to the problem is readily available in the form of encryption software. In fact, Mr. Tennant says, under the HIPAA rules a lost or stolen mobile device is not treated as a breach as long as the PHI on it is encrypted. The software is relatively inexpensive and available at most places computers are sold. "It's a very reasonable step for a practice to take. There's really no excuse not to do this," Mr. Tennant says.

Beyond encryption software and other electronic protections such as firewalls, practices need to establish written policies and procedures describing how it safeguards PHI what remedial steps it will take if a breach occurs. Auditors look for results of HIPAA security assessments and concrete steps such as the appointment of an information security officer. In addition, "they've been looking for proof of implementation of policies and procedures. So it's not enough just to have the written documents, you have to prove that you've actually put them into practice," Mr. Rashbaum says.

A key element in the implementation process is making sure that staff members are trained in security measures. Angela Dinh Rose, director of health information management for the American Health Information Management Association, suggests ending HIPAA training sessions with a quiz, and putting the results in employees' files as proof that they've received the training.

Staff training may have the additional benefit of defusing patient concern over a privacy issue before it goes any further. A patient with such a concern likely will first speak to the practice

receptionist or other front-office staff person. The staff member needs to treat the complaint seriously, Mr. Tennant says, and have the patient speak with the office manager or privacy officer.

"Patients who feel they have not had their grievance addressed are the ones most likely to lodge a complaint with the government," Mr. Tennant says. "It's better to deal with the issue internally, and maybe issue an apology if appropriate, and of course identify and correct the problem."

BUSINESS ASSOCIATE AGREEMENTS

The second major area of vulnerability for many practices lies in relations with business associates — vendors and service providers — with access to patient PHI. These can range from billers and coders, to document shredders, and now health information exchanges. Under the new HIPAA rules, such business associates are considered covered entities, meaning they are responsible for securing and guarding PHI in the same way that practices are — and are subject to the same penalties for violations.

> "We are encouraging our members to **be really aggressive in taking the necessary steps to prevent that breach.**"
>
> **Robert Tennant, M.A.**
> MGMA-ACMPE

The extent of a medical practice's liability in case of a breach caused by a business associate has not yet been established, but Mr. Rashbaum recommends reviewing contracts with vendors that have PHI access to ensure it has all the elements HIPAA requires.

Vendors that service multiple physician practices may have standard agreements that they ask their customers to sign. An attorney should review any agreement to ensure HIPAA compliance before signing, Mr. Tennant

OMNIBUS see page 70

voice of the dermatologist

"If I do not mention or discuss alternative **approaches** with my patients, particularly those with a chronic and debilitating disease such as atopic dermatitis, **they will often be quickly discouraged and seek help elsewhere.**"

Peter Lio, M.D., Chicago **page 1**

OMNIBUS:

Proactive steps may help prevent breaches of PHI from page 69

says. Better yet, he adds, try to have the vendor sign your agreement and let them incur the cost of a lawyer's time.

CYBER INSURANCE POLICIES

Of course, even putting all the right safeguards in place can't guarantee that a breach won't occur or that a practice won't be fined after an audit. For such cases, insurance companies have recently started offering cyber insurance policies. Coverage under such policies varies depending on the type of business, says Dean Sorensen, chief executive officer of Sorensen Informatics in Lombard, Ill., and a licensed insurance agent. For small medical practices, he adds, the coverage areas to look for are:

- **business interruption** (if your practice has to cease or curtail operations while investigating the cause of the breach);
- **breach remediation**, such as notifying patients and the news media that a breach has occurred; fines or other monetary penalties; and legal expenses.

Policies currently are offered through the Beazley Group, The Hartford, The Travelers Insurance Group, and Zurich Insurance Group. Costs generally range from about $400 to $1,000 annually, Mr. Sorensen says, depending on the size of the practice and what is covered.

As with most other forms of insurance, obtaining a cyber insurance policy requires underwriting, usually in the form of a data security checklist.

"Basically it's saying 'I've done the following things to make my data secure. I have these procedures in place, I have these applications in place,'" Mr. Sorensen says.

Even though the underwriting process is time-consuming, it also benefits the practice by forcing it to look at all its security measures.

"They might see they're focusing on the wrong kinds of things, or overlooking something as simple as not locking the door at night," Mr. Sorensen says.

It also helps ensure that the practice's security measures are HIPAA-compliant, since there is considerable overlap between commercial underwriting and HIPAA security requirements.

Although it's not covered by HIPAA, Mr. Sorensen also recommends practices take steps to ensure they are following payment card industry-data security standard (PCI-DSS) when storing, processing, or transmitting patient credit/debit card information.

"The actual breach of the credit card information is not PHI, but if there's a breach on the PCI-DSS side, it shows someone can get into my system, which means I have exposure on the HIPAA side as well," Mr. Sorensen says. **DT**

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Making sense of the ACA

BY JEFFREY BENDIX, DANIEL R. VERDON AND RACHAEL ZIMLICH | MEDICAL ECONOMICS

THERE ARE THOUSANDS of pages of regulatory guidance on a slew of government-led mandates facing physicians this year and next. From sweeping revisions of the Affordable Care Act (ACA), to broad mandates of the Health Insurance Portability and Accountability Act of 1996 (HIPAA) to International Classification of Diseases, 10th revision's (ICD-10) colossal transition, this update will keep you informed about the many changes that will impact your practice.

The ACA represents vast changes in the way healthcare is financed in the United States. With a net cost estimated at $1.2 trillion between 2012 and 2021, with offsets due to cost cuts, savings, taxes, and other government-led initiatives, the overall theme is about improving quality and access to healthcare while lowering costs.

Opinions vary wildly on whether the ACA will succeed, but there is little debate that it will forever change the delivery of healthcare in the United States. In 2013, 14 provisions were slated to go into effect including increased Medicaid payments to primary care physicians (PCPs), a push to improve preventive healthcare by providing new funding to state Medicaid programs that choose to cover preventive services for patients at little or no cost, Medicare bundled payment initiatives, open enrollment in the health insurance exchanges (October 2013), and a Medicare tax increase. ACA will also provide bonus payments for PCPs in underserved areas and increase payments to rural healthcare providers.

Here are some of the key provisions that will impact every U.S. physician in 2014 and beyond.

› **Everyone must have insurance or face penalties** This provision mandates that U.S. citizens and legal residents have qualifying health coverage. For those people who opt out, there is a phased-in tax penalty. Some exceptions do apply. On Jan. 30, the Department of Health and Human Services (HHS) released a proposed rule on minimum essential coverage. The Internal Revenue Service (IRS) will enforce this provision. Implementation: Jan. 1, 2014.

› **Health insurance exchanges** Creates state-based American Health Benefit Exchanges and Small Business Health Options Program (SHOP) Exchanges, administered by a governmental agency or nonprofit organization. Individuals and small businesses with up to 100 employees can purchase qualified coverage. Subsequent to its passage, HHS finalized two rules detailing how states must set up the exchanges and standards related to risk adjustment, risk corridors, and reinsurance provisions. The federally-facilitated exchanges will be run by HHS in states that have not established an exchange or have elected to run a partnership exchange. Implementation: Jan. 1, 2014

› **Expanded Medicaid coverage** Expands Medicaid to people not eligible for Medicare under age 65 (children, pregnant women, parents, and adults without dependent children) with incomes up to 133 percent of the federal poverty line and provides enhanced federal matching payments for new eligibles. States may opt out of the increased income levels. Implementation: Jan. 1, 2014

› **Presumptive eligibility for Medicaid** Allows hospitals participating in Medicaid to make presumptive eligibility determinations for all Medicaid-eligible populations. Implementation: Jan. 1, 2014.

› **Health insurance premium, cost-sharing subsidies** Provides tax credits and cost sharing subsidies to eligible individuals. Premium subsidies are available to families with incomes between 133 and 400 percent of the federal poverty level to purchase insurance through the exchanges, while cost-sharing subsidies are available to those with incomes up to 250 percent of the poverty level. Implementation: Jan. 1, 2014

Note: On May 23, 2012, the IRS released final regulations related to the health insurance premium tax credits. Corrections to this regulation were published July 17, 2012. Additionally, on Jan. 30, 2013, the IRS released a final rule on the premium tax credit test for affordability of employer-sponsored insurance.

› **Guaranteed availability of insurance** Requires guarantee issue and renewability of health insurance regardless of health status and allows rating variation based only on age (limited to a 3 to 1 ratio), geographic area, family composition, and tobacco use (limited to 1.5 to 1 ratio) in the individual and the small group market and the exchanges. Implementation: Jan. 1, 2014

› **No annual limits on coverage** Prohibits annual limits on the dollar value of coverage. Implementation: Jan. 1, 2014

› **Essential health benefits** An essential health benefits package outlining a comprehensive set of services, limiting annual cost-sharing to Health Savings Accounts ($5,950/individual and $11,900/family). Creates four categories of plans that will be offered through the exchanges and in the individual and small group markets. Implementation: Jan. 1, 2014

› **Multi-state health plans** Requires the Office of Personnel Management to contract with insurers to offer at least two multi-state plans in each exchange. At least one plan must be offered by a nonprofit entity and at least one plan must not provide coverage for abortions beyond those permitted by federal law. Implementation: Jan. 1, 2014

› **Temporary reinsurance program for health plans** A temporary reinsurance program

AFFORDABLE CARE ACT see page 74

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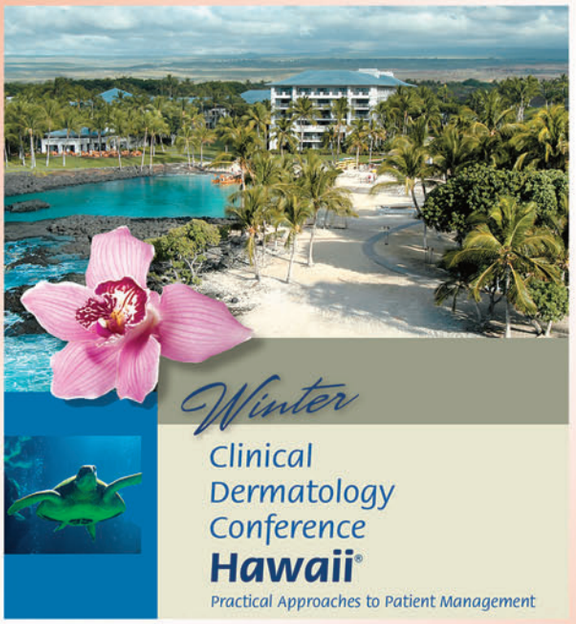

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AFFORDABLE CARE ACT:

Key provisions that will affect your practice in 2014 and beyond from page 72

will collect payments from health insurers in the individual and group markets to provide payments to plans in the individual market that cover high-risk individuals. On March 23, 2012, HHS issued a final rule implementing standards for states related to reinsurance and risk adjustment and for health insurance providers related to implementing reinsurance, risk corridors, and risk adjustment. Implementation: Jan. 1, 2014 through Dec. 31, 2016

› **Basic health plan** Allows states to create a basic health plan for uninsured individuals with incomes between 133 and 200 percent of the federal poverty level.

Implementation: HHS delayed implementation of the Basic Health Plan program until 2015 due to the scope of coverage changes being implemented on Jan. 1, 2014.

› **Employer requirements** Assesses a fee of $2,000 per full-time employee, excluding the first 30 employees, on employers with more than 50 employees that do not offer coverage and have at least one full-time employee who receives a premium tax credit. Last year, the Internal Revenue Service issued proposed regulations on the Employer Shared Responsibility provisions. Implementation: Jan. 1, 2014

› **Medicare Advantage plan loss ratios** Requires Medicare Advantage plans to have medical loss ratios not lower than 85 percent. Implementation: Jan. 1, 2014

› **Wellness programs** Permits employers to offer employees rewards of up to 30 percent, potentially increasing to 50 percent, of the cost of coverage for participating in a wellness program and meeting certain health-related standards; establishes 10 state pilot programs to permit participating states to apply similar rewards for participating in wellness programs in the individual market.

Implementation: Changes to employer wellness plans effective Jan. 1, 2014; 10-state pilot programs established by July 1, 2014

› **Quality of care** An ACA provision will tie physician payments to the quality of care they provide. Physicians will see their payments modified so that those who provide higher-value care will receive higher payments than those who provide lower-quality care. Implementation: January 2015.

Experts advise you to prepare your practice for increased call volume, understand how your state will operate its exchange, get ready for new administrative challenges related to insurance claims, become familiar with the new insurance plans, and prepare to handle increases in copays. Also, practice owners should evaluate purchasing options for employees. **DT**

(Source for 2014 provisions: Kaiser Family Foundation).

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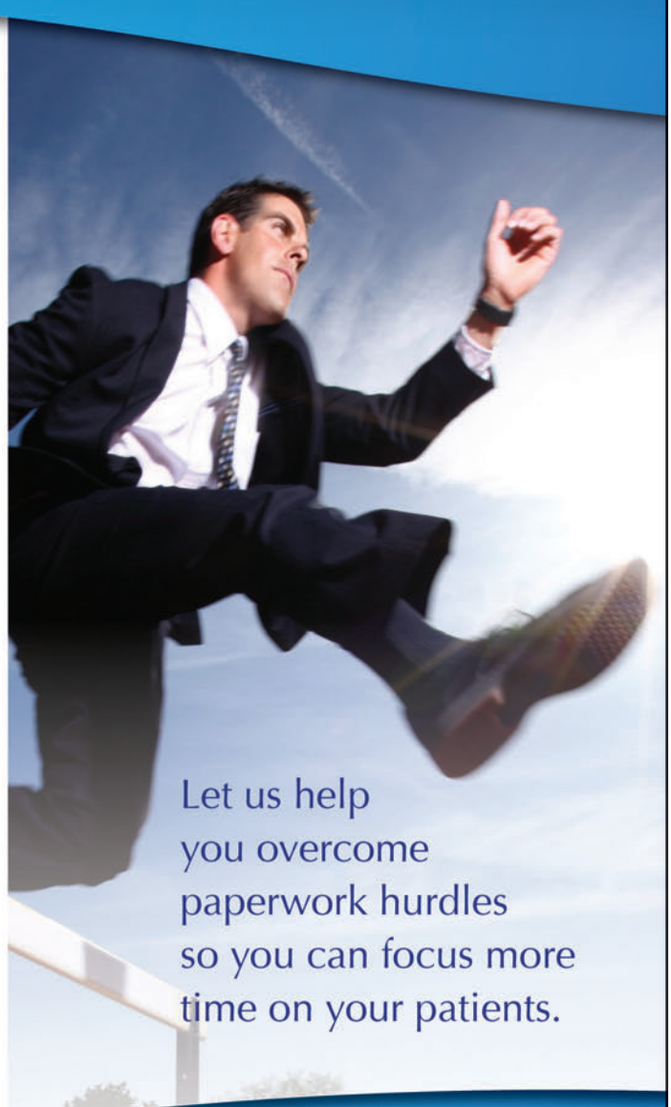

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3 TED TALKS TO REVIVE YOUR MEDICAL PRACTICE

When John Principe, M.D., got fed up with his standard primary care operations in Palos Heights, Ill., he made a radical change to his practice. Three years ago, he decided to add a kitchen and an educational center to help patients meet nutrition, weight and other wellness goals, renaming it WellBeingMD. A business associate encouraged him to apply for TEDx Naperville, and now Principe's November 2012 TED Talk has more than 2,000 views on YouTube.

"The TEDx talk has not only been integral both in telling my personal and professional journey, but sharing the crucial message that medicine can be delivered in a healthier and more sustainable way," Principe says. "(It) has been integral in revitalizing my practice."

Principe's TED Talk is one of hundreds uplifting and problem-solving lectures; many made for and by healthcare professionals. Below are three TED Talks that might help you revitalize your practice DT

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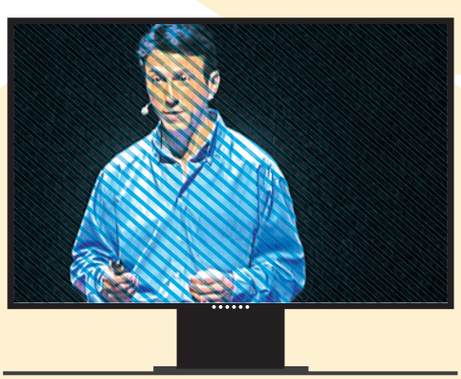

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