NEW

A CLASS 1, SUPER-POTENT SPRAY

For plaque psoriasis

Important Safety Information

- Topicort® Topical Spray is a topical corticosteroid indicated for the treatment of plaque psoriasis in patients 18 years of age or older.
- 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.
- Because of the potential for systemic absorption, use of topical corticosteroids may require that patients be periodically evaluated for HPA axis suppression.
- 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.

Topicort®
(desoximetasone)
Topical Spray 0.25%

0.25%
SPRAY

TaroPharma®

See brief summary of Prescribing Information on reverse side.

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Therapeutic approach for many women's skin conditions will require special considerations

By Lisette Hilton
Staff Correspondent

WOMEN & MEN are not always created equal when it comes to their dermatologic concerns, frequency and presentation of several dermatologic conditions, treatment options and outcomes.


Dr. Hordinsky

"Common dermatologic conditions may need to be addressed and thought about differently when they occur in women," says Maria Hordinsky, M.D., professor and chairwoman, department of dermatology, the University of Minnesota, Minneapolis. "People have to take into consideration the hormonal changes that go on in a woman over the lifespan. (Treating women requires) thinking

WOMEN see page 28

Healthcare reform requires novel approaches to patient care

By John Jesitus
Senior Staff Correspondent

Miami Beach, Fla. — To meet Affordable Care Act (ACA) goals regarding patient access and quality of care, an expert says, dermatologists are finding increasingly creative ways to deliver care where it's needed.

As healthcare reform proceeds, "There's a great concern among safety-net institutions and hospitals that we will see an increase in the number of patients who require services," says Miguel R. Sanchez, M.D., director of dermatology at Bellevue Hospital and associate professor of dermatology, New York University School of Medicine, New York.

23 MILLION
Americans the ACA won't cover

"Because few dermatologists take Medicaid in New York, and probably in most states, there's a lot of anxiety about reimbursement," and who will take care of the estimated 23 million Americans the ACA ultimately won't cover (*www.cbo.gov/sites/default/files/cbofiles/ftpdocs/121xx/doc12119/03-30-healthcarelegislation.pdf*), says Dr. Sanchez, who spoke at annual meeting of the American Academy of Dermatology.

Already, he says that with more than 27,000 visits annually, "Dermatology is the busiest specialty clinic in Bellevue Hospital. We've taken the initiative of providing care for several conditions that we believe we are the best people to treat, but that are not always treated in dermatology programs."

Along with phototherapy, the department offers clinics for woundcare, including

HEALTHCARE REFORM see page 32

ADVANSTAR MEDICAL COMMUNICATIONS GROUP

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.

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ADVANSTAR MEDICAL COMMUNICATIONS GROUP

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.

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5011975 January 2013

ONMEL™ (itraconazole)

Initial U.S. Approval: 1992

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

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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
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Greensboro, NC 27410

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Dermatology Times is the only clinical news resource serving a readership of more than 14,000 dermatologists and other professionals focused on skincare. Through unbiased reporting, we strive to help practitioners put into perspective developments that affect their business. Our goal is to provide practical information that will help them to better understand clinical, regulatory and financial issues, as well as chart business growth.

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RESOURCES IN DERMATOLOGY

Get up-to-date insight into new and emerging therapies for melanoma. Learn strategies for diagnosing, identifying appropriate treatment options and monitoring disease.
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Review a broad range of clinical, CME and digital information about psoriatic arthritis. Learn about treatment options to help reduce these symptoms in your patients.
dermatologytimes.com/PsoriaticArthritis

Trending FROM June

The Food and Drug Administration has approved Tafinlar (dabrafenib), Mekinist (trametinib) and a companion diagnostic for the treatment of advanced metastatic melanoma.
dermatologytimes.com/melanomadrugs

A new study indicates sun exposure may help to reduce blood pressure, demonstrating that the benefits of exposure to UV rays may be greater than the risk of getting skin cancer.
dermatologytimes.com/benefits

Comorbidities such as autoimmune diseases and mental health problems are common in patients with alopecia areata.
dermatologytimes.com/alopecia

Electrolysis provides a safe, permanent alternative for patients who don't want or are not appropriate for laser treatments.
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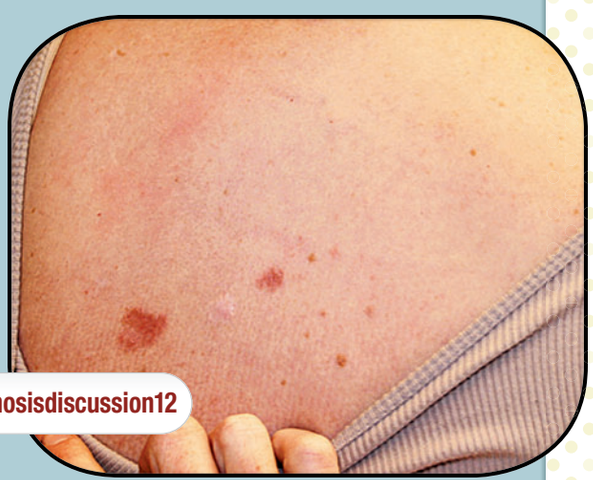
What's your diagnosis?

A healthy 19-year-old woman presents with two persistent, pearly red plaques on her back. The patient reports that they've been there for at least six months but they do not bother her. She is active in outdoor sports and works as a lifeguard and swimming instructor.



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The Business of Dermatology

Top 5 most-physician-used medical apps

A recent survey indicates doctors aren't too thrilled with the quality of apps available to the profession. Here are the top five used most frequently on smartphones and tablets.

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Electronic information exchange is slow but sure

The healthcare system and technology infrastructure has made slow but considerable progress toward being able to send patient data quickly, reliably, and securely between providers in different locations who use different EHR systems.

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How to select appropriate E/M levels and document patient care

You can obtain reimbursement at a higher level and overcome your fears of being audited by thoroughly and correctly documenting the care you provide to your patients. Here are some strategies:

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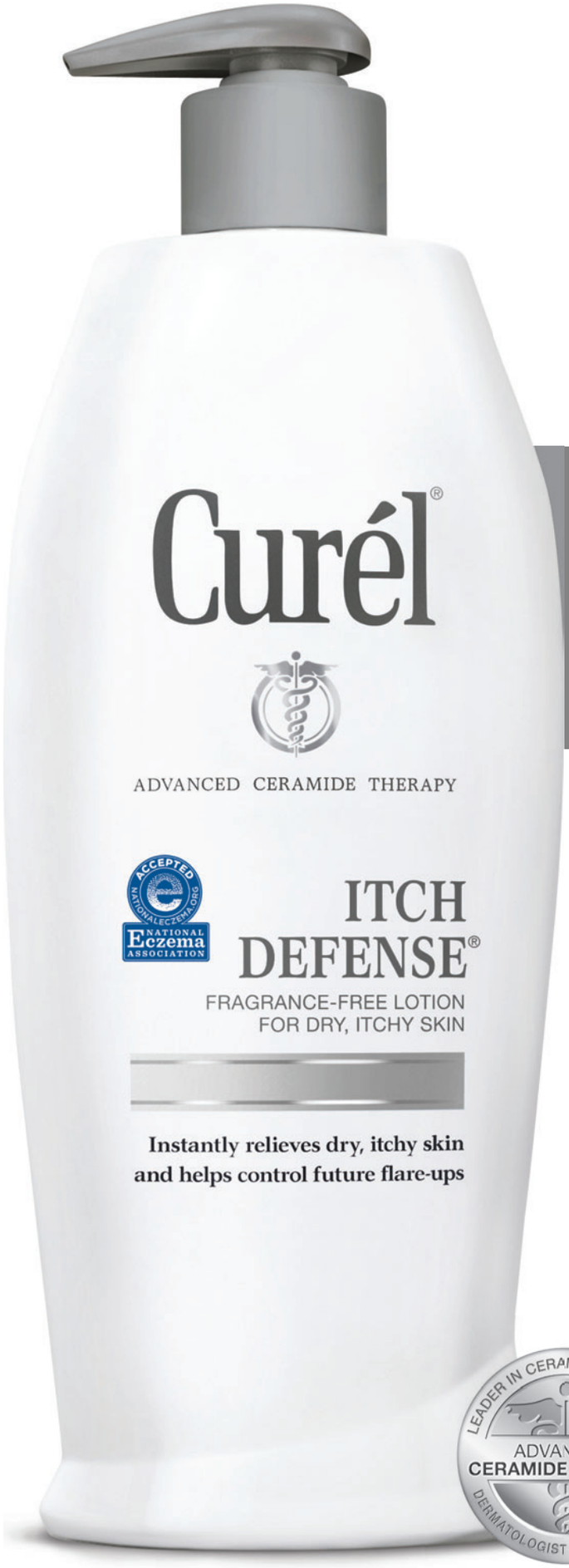

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Curbside consultation

This type of practice has value, is free of many administrative encumbrances

My hospital requires documentation of how I spend my time, tabulated in hours per week, for one representative week every month, an exercise related to Centers for Medicare and Medicaid Services (CMS) funding. The time can be allotted among only three mutually exclusive categories: "Hospital Activities," "Teaching Activities" and "Patient Care." My university also quantifies my productivity in relative value units (RVUs), clinical charges, grants submitted, grants awarded and publications.

I work a lot. I usually get to my office around 7:30 a.m. and leave about 12 or 13 hours later. I am on-call for ER and inpatients 24-7, and see scheduled clinic patients four days per week. But even my non-clinic days are consumed by multitasked attention to multiple simultaneous demands.

I rarely dedicate exclusive time for eating or attending to bodily functions. The pace often feels like taking a drink of water from a fire hose. But sometimes, at the end of a long day, when I haven't been able to focus on the task at the top of my to-do list, I take a mental inventory of how my time was spent.

Consultations catch on

One category requiring increasing attention — but largely unrecognized or quantified — is curbside consultation. A recent PubMed search on the topic yielded 42 articles since 1984. The majority addressed the problem as an occupational hazard of hospital-based subspecialists, especially infectious diseases. Several publications focused on inadequate compensation and medicolegal liability. Only one mentioned dermatology.[1] This is not surprising, because prior to cell phone cameras, an in-the-flesh exam was an important dermatologic diagnostic prerequisite.

Phone or email advice supports the primary care physician, strengthens the medical home, and **avoids overburdening my staff.**

The one dermatology-related publication was a recent "Dermatoethics Consultation" from the *Journal of the American Academy of Dermatology*. The editorial discussed various pitfalls that can result when either laypeople or colleagues want off-the-record advice. It was illustrated by a clinical scenario that one of the authors endured "many years ago."

I was confronted by a similar experience in the pre-digital era, when a male acquaintance asked me to "look at something" and led me to a private, poorly-lit space (in my case, a hospital stairwell) where he proceeded to drop his drawers to show me an inguinal skin lesion.

Fortunately, the curbsides I get these days are less uncomfortable, and more clinically rewarding. But they are also much more frequent. My hospital actually encourages these calls with an established "Access Center," marketed to community physicians as a direct line to subspecialists.

Last month, I started a tally of every phone call, email, text and hallway consult. Not a day goes by that doesn't include at least one. The total for the month was 72. The series included an email about an infant seen by a colleague in an African clinic; a phone call from a physician who works at my institution (but I have never met), for my opinion about a picture of his daughter's armpit; cell phone images of two patients by their dermatologist attending Grand Rounds with me; and texted images from my cousin and college roommate.

EDITORIAL ADVISORY BOARD UPDATE see page 10

Are curbside consultations a quiet reward or a thorn in your side? Tell us why: twitter.com/DermTimesNow

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INSTRUCTIONS FOR USE: Apply liberally to the affected areas three times daily or as needed. If skin is broken, cover Eletone® Cream with a dressing of choice.

INGREDIENTS: Eletone® Cream contains petrolatum, purified water, mineral oil, cetostearyl alcohol, ceteth-20, citric acid, sodium citrate, propylparaben, and butylparaben.

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CAUTION: Rx only. Federal law restricts this device to sale by or on the order of a physician.

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ELE-13801

Advisory board update from page 8

Effective and efficient

Many of the consults provided advice to a local physician in lieu of an urgent work-in appointment, because my clinics are too full to accommodate one more patient. Curbside consultation is an efficient and effective way to provide access to dermatologic care for the 50 percent of children in the United States who are Medicaid-insured.[2] Phone or email advice supports the primary care physician, strengthens the medical home, and avoids overburdening my staff and generating patient dissatisfaction with unpredictable wait times.

For the great majority of my curbsides, I believe I am able to help. And that feels good. Added bonuses are that I don't have to document my advice in Epic (electronic health record system) — making sure to include "a key portion of two of three key elements" so diligently sought by the university compliance auditor — detail my recommendations in eighth-grade language and do "feedback" teaching, all within a 10-minute time slot, or decide how to code the bill, submit a prior authorization for medication or worry about fitting a follow-up appointment into my packed clinic schedule.

In a fee-for-service world, curbside consultation is often viewed as a convenience by the requestor, and exploitation by the consultant, because the work is not formally recognized or reimbursed. But having enough expertise to be able to make a positive impact on a patient's course is one of the main reasons that doctors choose a career in medicine. Being able to do so without the administrative encumbrances that often dominate daily clinical practice is a chance to rediscover the joy in patient care. For me, curbside consultation is so rewarding that if money were not an issue, I would love to do it full-time.

Fortunately, experts across many specialties seem to share my sentiments. Some are co-workers who give and take curbside advice with me, others I may have met briefly or know only by national reputation. But when I have contacted them for help with clinical conundrums, they have been genuinely interested in the patients and solving the problem, generous with their wisdom and their time, and are eager to help, seemingly unaware they are paying it forward. Most, but not all, of these mensches are salaried physicians who work full-time in the knowledge-sharing environment of academic institutions: microbiologists, immunologists, rheumatologists, oncologists, gynecologists, gastroenterologists, geneticists, cardiologists, child abuse specialists, social workers, otolaryngologists, plastic surgeons, ophthalmologists, infectious disease specialists, pediatricians, anesthesiologists, pharmacologists, statisticians.

This network of expertise is the underappreciated scaffolding of excellent and cost-effective tertiary healthcare. I have high hopes that the future accountable care world will recognize, value and support curbside consultation as an efficient complement to primary care. DT

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Elaine Siegfried, M.D.

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Non-compete clarifications

Can physicians enforce restrictive covenants?

Dr. Derm has a large dermatology practice with eight employee dermatologists. Each employee physician has signed an agreement that stipulates his/her duties, salary and benefits. Each agreement also has a restrictive covenant that states that if the employee physician chooses to leave, he/she cannot practice within 10 miles for two years after the separation from Dr. Derm's practice.

Dr. Disgruntled signed such an agreement, chose to leave Dr. Derm's practice and opened up his own practice one mile away. Dr. Derm filed a lawsuit against Dr. Disgruntled alleging breach of the restrictive covenant. He seeks not only monetary damages but also an injunction against Dr. Disgruntled that prohibits his practicing dermatology within the 10-mile radius of Dr. Derm's office. Will the restriction hold up?

Doctors frequently sign non-compete agreements. This is an inherent part of most physician employment agreements and physician employees should expect to sign them. Ever since the famous case of *Carlin v. Weinberg*, most reasonable physician employee restrictive covenants have been held up by many state courts.

Time, distance restrictions

In *Carlin v. Weinberg*, two New Jersey dermatologists were in practice together — one as an employer and one as an employee. The employee left and opened a new office within his employment contract stipulated geographically prohibited area. The employer dermatologist sued. The court looked at the restrictive covenant and said that as long as the "time" and "distance" restriction were reasonable, the restrictive covenant was enforceable. Therefore where a 10-mile restriction in New Jersey might be reasonable, a similar 10-mile restriction in New York City (with its dense population) would not be.

Although *Carlin v. Weinberg* is an often-quoted case, today every state treats such restrictions differently. In California, for example, most are unenforceable. In North Carolina, on the other hand, if the agreement is not unduly restrictive, it is upheld. Today the healthcare landscape has dramatically changed. As doctors sell their practices, restrictive covenants become part of the process. The subtext is that if you are fired or leave, you will need to exit the community. You will be forced to sell your house, uproot your children from their schools and start over. However, a recent ruling may change this.

The Federal Trade Commission (FTC) recently weighed in and the ripple effect has yet to be understood.

Decision on monopolies

On Dec. 4, 2012, the FTC formally voted to approve a settlement of a complaint they brought against Renown Health, a healthcare system in Nevada. The complaint alleged that the three-hospital system established some type of illegal monopoly for heart-care services. Renown had bought two cardiology groups, whose 31 doctors gave Renown control over 88 percent of the market for cardiology, the FTC stated. The FTC ruled that such a monopoly controlled market share. Monopolies are often not allowed by the FTC.

Rather than ordering Renown to unwind the acquisitions, the FTC voted unanimously to allow up to 10 of its Renown cardiologists to disregard the non-compete language in their employment contracts. The FTC said voiding 10 non-compete agreements would restore competition for cardiology in the Reno metro area.

Non-compete agreements … are an inherent part of most physician employment agreements and physician employees should **expect to sign them.**

Eight physicians have already notified Renown they intend to work for other area hospitals, and two others are planning to move into private practice. The CEO of Renown Health said: "We understand the pressures the FTC is under, but it would be helpful to the industry if various government agencies would speak with one voice on whether or not consolidation is a good thing in the era of healthcare reform. On the one hand, we are being pressed to consolidate and integrate, and on the other we are being restrained by outdated laws regulating physician and hospital relationships."

What is clear is that the enforceability of non-compete agreements will likely continue to evolve as healthcare keeps changing. At this point the enforceability of the restriction on Dr. Disgruntled is likely to be determined by which state he chooses to practice in. DT

Research stat

ABSTRACTS FROM THAT PILE OF PEER-REVIEWED JOURNALS ON YOUR DESK

CLINICAL DERMATOLOGY

Combined therapy for psoriasis more individualized

Journal of Drugs in Dermatology MAY 2013

THE EXTENSIVE ASSORTMENT of combination treatment options for psoriasis in the United States can lead to more customized treatment that matches specific patient needs, according to a study published in the May issue of *Journal of Drugs in Dermatology*.

Researchers at Wake Forest School of Medicine, Winston-Salem, N.C., evaluated how often calcipotriene was prescribed in combination with other psoriasis treatments. Using 1990-2010 data from the National Ambulatory Medical Care Survey, study authors reviewed patient visits that resulted in only one psoriasis diagnosis. They documented the number of combination treatments used, principal treatments in each medication class, and the foremost types used in combination.

Of 20.3 million psoriasis visits, 10.2 million of those involved more than one treatment. Six topical steroids, two topicals, calcipotriene, and methotrexate rounded out the top 10 treatments used for psoriasis. Combinations most often used were topical steroid and other topical (15 percent), various topical steroids (11.5 percent), topical steroid and vitamin D analogue (9.7 percent), and topical steroid plus systemic treatment (6.9 percent).

Over time, vitamin D analogues and systemic treatments were administered more often, while topical steroids were prescribed less often.

http://jddonline.com/articles/dermatology/S1545961613P0546X

Nickel-plated coins may increase allergy risk

Contact Dermatitis JUNE 2013

COINS THAT ARE NICKEL-PLATED leave behind higher nickel levels on the skin, compared to cupronickel coins, raising allergy risk, according to findings published in the June issue of *Contact Dermatitis*. To measure the risk of using objects that have high nickel release and are exposed to the skin, researchers determined that the one-week artificial sweat release is not suitable. Instead, the nickel skin dose is advised for risk assessment.

The study was designed to assess the allergy risk of nickel-plated coins in the United Kingdom (five and 10 pence) compared to cupronickel coins that will no longer be used. Enrolling six volunteers, study authors used coin handling studies assessing skin exposure and metal release in artificial sweat.

In a one-hour period, nickel levels remaining on the skin while handling the nickel-plated coin were 7.5 µg/cm^2, four times greater than that of cupronickel coins. The nickel content in the oxidized surface of nickel-plated coins was higher. Researchers noted short, frequent contact with nickel-plated coins can lead to high levels of nickel exposure.

http://onlinelibrary.wiley.com/doi/10.1111/cod.12092/abstract

Migraine, rosacea may have ties in older female patients

Journal of the American Academy of Dermatology MAY 2013

WOMEN 50 YEARS OR OLDER who experience severe migraines may have a slightly higher risk of having rosacea, according to a study published in the May issue of the *Journal of the American Academy of Dermatology*.

Investigators with the University of Basel, Switzerland, and University Hospital Basel, evaluated via a case-control study the link between migraine or triptan exposure and rosacea risk in patients in the United Kingdom. Researchers culled data from the General Practice Research Database in the U.K. to pinpoint patients with incident rosacea from 1995 to 2009 (cases); one rosacea-free control was matched to each case.

Prevalence of diagnosed migraine and triptan exposure before the first-time rosacea diagnosis was compared between cases and controls with multivariate conditional logistic regression. There were 53,927 cases and the same number of controls. There was a slight overall link between rosacea and migraine in women; no link was found in men. Women who used triptan also showed marginally greater risk estimates as women got older, especially age 60 and older.

http://www.jaad.org/article/S0190-9622%2813%2900308-3/abstract

SIBO patients with cutaneous lesions may benefit from rifaximin

Journal of the American Academy of Dermatology MAY 2013

RIFAXIMIN TREATMENT MAY completely clear up cutaneous lesions in patients with small intestinal bacterial overgrowth (SIBO), according to research published in the May issue of the *Journal of the American Academy of Dermatology*.

Investigators suggested SIBO can affect immunity and lead to rosacea by elevating tumor necrosis factor-alpha (TNF-alpha) or other cytokines, suppressing interleukin-17, and boosting the T helper 1-mediated immune response. Researchers analyzed prevalence of SIBO in patients with rosacea who received treatment at a gastroenterology clinic and measured effectiveness of rifaximin in patients with secondary SIBO evidence (such as a positive result on lactulose breath test).

Gastroenterologists identified most patients with rosacea during physical exam before patients had screening colonoscopy. In 57 cases, rosacea was diagnosed by a dermatologist. Ophthalmologists referred four patients with medicine-refractory ocular rosacea. Two rosacea cases were identified. Aside from the ocular cases (three patients had facial erythema), nine patients had papulopustular and 50 had erythematotelangiectatic rosacea, according to the study.

Each patient received a lactulose breath test. Positive test results for SIBO meant there was an increase in hydrogen or methane levels >20 ppm from baseline within 90 minutes. SIBO prevalence was compared with two control groups. For 10 days, patients with SIBO received 400 mg of rifaximin three times a day. Ten days after stopping rifaximin, patients answered a self-report four-point rosacea improvement scale questionnaire. For 70 percent of patients treated with rifaximin, they had a repeat physical exam.

SIBO was named as a diagnosis for 32 of 63 rosacea patients (51 percent; six male and 26 female) compared to seven of 30 general-population control subjects (23%) and 3 of 30 entirely healthy control subjects (10 percent). Of the SIBO patients, 28 were given rifaximin, 46 percent reported cleared or markedly improved rosacea, 25 percent reported moderately improved rosacea, and 11 percent reported mildly improved rosacea. All four patients with ocular rosacea and SIBO noted significant improved improvement. Only 18 percent of patients said their rosacea symptoms were unchanged.

http://www.jaad.org/article/S0190-9622%2812%2902330-4/fulltext#article-outline

Rosacea subtypes vary, impact characteristics of disorder

British Journal of Dermatology APRIL 2013

WHEN DISCUSSING ROSACEA, there are sizeable differences between the subtypes, erythematotelangiectatic and papulopustular, in rosacea-related characteristics and in subtype associations, according to a study published in the April issue of the *British Journal of Dermatology*. Also, some rosacea patients may advance between subtypes.

For the cross-sectional study, researchers measured relationships among the four rosacea

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subtypes: erythematotelangiectatic, papulopustular, phymatous, and ocular. Investigators reviewed criteria pertaining to primary and secondary rosacea traits. The authors measured the possibility of movement between subtypes. There were 135 rosacea patients from northern Germany for which dermatologists provided clinical evaluations. Researchers also incorporated a demographics survey and appearance of rosacea-related symptoms.

More often, phymatous rosacea was linked with papulopustular rosacea than erythematotelangiectatic rosacea. Compared to erythematotelangiectatic rosacea, papulopustular rosacea was significantly tied to facial burning/stinging, phymas and edema; and during flushing bouts, it was more frequently related to burning, skin tension and itching.

Erythematotelangiectatic rosacea was more frequently connected to dry facial skin. Sixty-six percent of patients indicated flushing of the cheeks in particular (100 percent). Papulopustules were brief in 42 percent of patients and the most often reported sites were cheeks (80 percent) and nose (67 percent). For patients with criteria for at least two subtypes, 66 percent developed erythematotelangiectatic rosacea before papulopustular rosacea; 92 percent developed erythematotelangiectatic rosacea before phymatous rosacea; 83 percent developed papulopustular rosacea before phymatous rosacea; and the majority presented with cutaneous rosacea-associated features before ocular sign/symptoms.

http://onlinelibrary.wiley.com/doi/10.1111/bjd.12385/abstract

Idiopathic facial aseptic granuloma patients prone to rosacea

Pediatric Dermatology APRIL 2013

THERE IS A RISK OF ROSACEA in pediatric patients who have idiopathic facial aseptic granuloma, according to research published in the April issue of *Pediatric Dermatology*.

The retrospective multicenter study aimed to identify potential associations between idiopathic facial aseptic granuloma and childhood rosacea. Patients (n=38; 20 girls and 18 boys; median age at time of idiopathic facial aseptic granuloma diagnosis: 43 months) came from four French dermatologic centers and had been diagnosed with idiopathic facial aseptic granuloma between October 2000 and July 2007. The median follow-up was 3.9 years.

Childhood rosacea symptoms that were noted included flushing, lasting or repeat erythema; facial telangiectasia; facial papules and pustules without comedones or microcysts; lesions primarily on the convexity of the face; and ophthalmologic-related rosacea (recurrent chalazions, conjunctival hyperemia, and keratitis).

Sixteen patients (42.1 percent) had two or more childhood rosacea criteria, 11 of 32 (34.4 percent) had a single lesion and five of six (83.3 percent) had multiple lesions.

http://onlinelibrary.wiley.com/doi/10.1111/pde.12137/abstract

COSMETIC DERMATOLOGY

Hypocollagenesis' effects may aid in customized treatment

Journal of Cosmetic Dermatology JUNE 2013

HYPOCOLLAGENESIS MAY BE the No. 1 factor in predicting anti-aging cosmeceutical treatment outcome, findings published in the *Journal of Cosmetic Dermatology* suggest. Understanding this may provide a basis for future cosmetic testing and customized skincare, according to researchers.

Investigators conducted a meta-analysis to discern what triggers a reaction or response to various cosmeceuticals. One hundred patients in five cosmeceutical studies that focused on either: L-ascorbic acid, pentapeptide, alpha-lipoic acid, yeast extract, or 1 percent idebenone. In each of the groups, 16 to 20 people used one cosmeceutical on their photodamaged forearms for a few weeks. Investigators took punch biopsies of the patients pre- and post-treatment, looking for type I procollagen by enzyme-linked immunosorbent assay (ELISA).

Researchers found that hypocollagenesis is related to severity of photoaging, regardless of age or gender. Results from treatment were all over the board among subjects, ranging from no change to a seven-fold increase in collagenesis. Researchers then led a retrospective meta-analysis to figure out whether cosmeceutical type, gender, age, or hypocollagenesis evidence with untreated skin could measure how a person responds to cosmeceuticals. People with hypocollagenesis had a reaction 6.4 times more than those with normocollagenesis.

Researchers noted that hypocollagenesis was the only trigger to impact treatment results.

http://onlinelibrary.wiley.com/doi/10.1111/jocd.12037/abstract

Hyaluronic acid's unwanted effects warrant swift treatment

Journal of Drugs in Dermatology APRIL 2013

PHYSICIANS MUST BE IN TUNE to unwanted effects of hyaluronic acid (HA) (immediate, early or late-onset) to treat appropriately and limit scarring or other sequelae. Many times, treating HA-related adverse events can lead to swift improvement, according to a study published in the April issue of the *Journal of Drugs in Dermatology*.

Study authors at the University of Seville, Spain, sought to establish what type and how to manage unwanted effects of nonanimal reticulated or stabilized HA. Study patients, all of whom received treatment, were placed in one of three categories based on when adverse events occurred: immediate, early and late-onset complications.

There were 23 patients who visited the clinic and who noted adverse effects related to soft tissue augmentation with HA. Of those, 10 had immediate-onset complications, eight had early-onset complications, and five reported late-onset complications. The immediate-onset group was treated with hyaluronidase injection, massage and topical antibiotics. Early- and late-onset issues were managed with intralesional triamcinolone acetonide. Every patient experienced improvement, except for one patient who had recurrent granulomas.

http://jddonline.com/articles/dermatology/S1545961613E0059X

Clinical characteristics impact distribution patterns in vitiligo

Journal of the European Academy of Dermatology and Venerology MAY 2013

CLINICAL CHARACTERISTICS SUCH AS age, gender or association with autoimmune disease may impact distribution patterns in vitiligo patients. Koebner's phenomenon may also play a role in how the disorder is distributed, according to findings published in May issue of the *Journal of the European Academy of Dermatology and Venerology*.

Researchers with Ghent University Hospital, Belgium, evaluated whether vitiligo's distribution pattern is affected by clinical characteristics in this 700-patient study (all with generalized vitiligo).

Areas most prominently affected were the face (87 percent), acral areas (76.3 percent), and extremities (59.7 percent). In women, joints, hips, trunk and body folds (such as axilla) were more frequently affected compared with men. Men experienced increased depigmentation in the beard and genital areas. In young persons, vitiligo tends

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to be more concentrated in the lower extremities; upper extremities are more vulnerable when older. The face's periocular area is more vulnerable at younger ages, contrasted to the perioral area. Acral areas were more frequently affected in patients with autoimmune disorders (in particular thyroid disease).

http://onlinelibrary.wiley.com/doi/10.1111/jdv.12171/abstract;jsessionid=9E8E9E38A03769DF5932C0E299E6D180.d03t02

ONCOLOGY

Mohs efficacious for squamoid eccrine ductal carcinoma

Journal of Clinical Aesthetic Dermatology APRIL 2013

MOHS MICROGRAPHIC SURGERY may be an efficacious surgical option when treating squamoid eccrine ductal carcinoma, according to a

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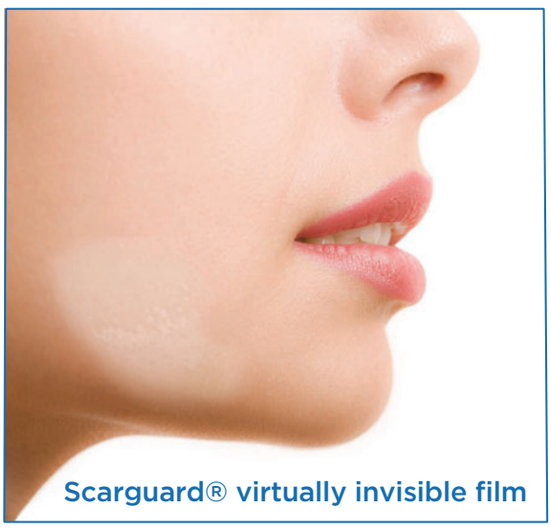

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study published in the April issue of the *Journal of Clinical Aesthetic Dermatology*. The report analyzed data on squamoid eccrine ductal carcinoma and Mohs micrographic surgery as a therapeutic option. The authors detailed the ninth reported case of squamoid eccrine ductal carcinoma and the third report of Mohs micrographic surgery for complete lesion extirpation. Because the natural history of squamoid eccrine ductal carcinoma has not been sufficiently studied, and the lesion's etiology and malignant classification is not definite, study authors advised adequate follow-up.

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3638851/

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RESEARCH NEWS

Stem cells in nails give clues to limb regeneration

New York — A signaling pathway in the stem cells of nails is a crucial component of the process of regrowth after amputation, a discovery that could help to facilitate research into limb regeneration.

Investigators from New York University Langone Medical Center identified a population of stem cells under the base of the nail that helps to promote the regrowth of partially amputated digits. The process can only occur, however, if there is sufficient nail epithelium, according to study findings.

Studying mice, the investigators performed toe amputations in a group of normal mice and in a group of mice that had been treated with a drug rendering them unable to make signals for nail cells to grow. The signals that helped stem cells develop into nail cells were critical for the regeneration of amputated digits, researchers found.

"These results establish a link between NSC (nail stem cell) differentiation and digit regeneration, and suggest that NSCs may have the potential to contribute to the development of novel treatments for amputees," study authors concluded.

The study was published online June 12 in *Nature*. **DT**

Melanoma detectable through skin odor

Philadelphia — An odor emitted by melanoma through skin cells allows the disease to be detectable noninvasively, results of a recent study indicate.

Researchers from the Monell Chemical Senses Center, Philadelphia, and colleagues used sampling and analytical techniques to identify volatile organic compounds (VOCs), which are chemical molecules that give off an odor. The VOCs were identified in three stages of melanoma and in normal melanocytes, according to a news release.

Using an absorbent device, researchers collected chemical compounds from the air and housed them in containers that held the various types of cells. Investigators used gas chromaphotography-mass spectrometry techniques to analyze compounds and identify various profiles of VOCs emitted by both cancer and normal cells.

The melanoma cells emitted compounds different than those of normal cells. The different types of melanoma cells were also distinguishable by the type of chemical compounds they released.

To make this discovery useful in the clinical setting, investigators began analyzing VOCs from the cells with a nanosensor made of nano-sized tubes that were coated with DNA strands. The portable nanosensor device proved useful for deciphering differences in VOCs from cancerous cells versus those from normal melanocytes.

"This study demonstrates the usefulness of examining VOCs from diseases for rapid and noninvasive diagnostic purposes," said A.T. Charlie Johnson, Ph.D., professor of physics, University of Pennsylvania, who helped develop the nanosensor.

The findings were published online in *Journal of Chromatography B*. **DT**

QUICKTAKES

DEVICE DOESN'T BEAT SHAVING FOR HAIR REMOVAL

Nashville, Tenn. — A home-use hair removal device was no better than shaving in terms of improving hair density and reducing hair regrowth rate. Researchers examined high-resolution photographs taken at baseline, once a week during treatment and monthly during follow-up, according to the study abstract. The shaving group had a mean baseline hair count of 79.4. After stopping treatment, it climbed to 98.8, 100.1 and 104.6 at months one, two and three post-treatment, respectively. The active group (the no!no! hot wire device) showed a mean baseline count of 86.0 which rose to 104.0, 106.4 and 109.0 at one, two and three months post-treatment, respectively. During treatment, shaving proved to be slightly more effective at removing hair than the hot wire device with weak statistical significance ($P<0.05$ at five of seven time points). Shaving and the hot wire device were statistically indistinguishable at one, two and three months. The study was published online June 5 in *Lasers in Surgery and Medicine*.

NEVADA BANS MINORS FROM TANNING BEDS

Carson City, Nev. — Nevada is the latest state to prohibit minors under age 18 from using indoor tanning beds, joining California, Vermont and New Jersey to block adolescents from using the devices. Nevada Gov. Brian Sandoval signed into law a bill that was sponsored by Sen. Joyce Woodhouse, D-Las Vegas, and had the backing of the American Academy of Dermatology Association, the American Society for Dermatologic Surgery Association, the Dermatology Nurses Association and several other groups, according to a news release. The ban follows a recent recommendation by the Food and Drug Administration that indoor tanning beds include warning labels that describe the risk of skin cancer associated with using the devices. The FDA is accepting comments on that proposal, which would reclassify tanning beds from class 1 to class 2, for 90 days. Nevada's tanning bed restrictions go into effect July 1.

FDA CLEARS SOLTA MEDICAL'S DUAL DEVICE

Washington — The Food and Drug Administration has cleared Solta Medical's Fraxel DUAL 1550 nm/1927 nm laser system for the treatment of pigmented lesions, including lentigos, solar lentigos and ephelides, the company announced in a news release. The fractional laser system already is indicated for soft tissue coagulation and skin resurfacing procedures in the treatment of actinic keratosis, melasma, periorbital wrinkles, and acne and surgical scars, according to the company. "The Fraxel DUAL 1550/1927 provides patients superior anti-aging results, specifically when treating pigmentation of the skin caused by sun exposure," Roy G. Geronemus, M.D., director of the Laser & Skin Surgery Center of New York and clinical professor of dermatology at New York University Medical Center, said in the news release.

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Reference:

1. Data on file. Ranbaxy Laboratories, Inc. Princeton, NJ.

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KENALOG® SPRAY

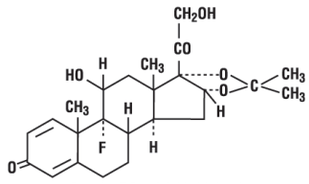
Rx only

Triamcinolone Acetonide Topical Aerosol, USP (0.147 mg/g)

For dermatologic use only
Not for ophthalmic use

DESCRIPTION

The topical corticosteroids constitute a class of primarily synthetic steroids used as anti-inflammatory and antipruritic agents. The steroids in this class include triamcinolone acetonide. Triamcinolone acetonide is designated chemically as 9-fluoro-11β, 16α, 17, 21-tetrahydroxypregna-1, 4-diene-3, 20-dione cyclic 16, 17- acetal with acetone. The structural formula is:



$C_{24}H_{31}FO_6$, MW 434.50

A two-second application, which covers an area approximately the size of the hand, delivers an amount of triamcinolone acetonide not exceeding 0.2 mg. After spraying, the nonvolatile vehicle remaining on the skin contains approximately 0.2% triamcinolone acetonide. Each gram of spray provides 0.147 mg triamcinolone acetonide in a vehicle of isopropyl palmitate, dehydrated alcohol (10.3%), and isobutane propellant.

CLINICAL PHARMACOLOGY

Topical corticosteroids share anti-inflammatory, antipruritic and vasoconstrictive actions.

The mechanism of anti-inflammatory activity of the topical corticosteroids is unclear. Various laboratory methods, including vasoconstrictor assays, are used to compare and predict potencies and/or clinical efficacies of the topical corticosteroids. There is some evidence to suggest that a recognizable correlation exists between vasoconstrictor potency and therapeutic efficacy in man.

Pharmacokinetics

The extent of percutaneous absorption of topical corticosteroids is determined by many factors including the vehicle, the integrity of the epidermal barrier, and the use of occlusive dressings.

Topical corticosteroids can be absorbed from normal intact skin. Inflammation and/or other disease processes in the skin increase percutaneous absorption.

Once absorbed through the skin, topical corticosteroids are handled through pharmacokinetic pathways similar to systemically administered corticosteroids. Corticosteroids are bound to plasma proteins in varying degrees. Corticosteroids are metabolized primarily in the liver and are then excreted by the kidneys. Some of the topical corticosteroids and their metabolites are also excreted into the bile.

INDICATIONS AND USAGE

Kenalog Spray (Triamcinolone Acetonide Topical Aerosol, USP) is indicated for relief of the inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses.

CONTRAINDICATIONS

Topical corticosteroids are contraindicated in those patients with a history of hypersensitivity to any of the components of the preparations.

PRECAUTIONS

General

Systemic absorption of topical corticosteroids has produced reversible hypothalamic-pituitary-adrenal (HPA) axis suppression, manifestations of Cushing's syndrome, hyperglycemia, and glucosuria in some patients.

Conditions which augment systemic absorption include the application of the more potent steroids, use over large surface areas, prolonged use, and the addition of occlusive dressings.

Therefore, patients receiving a large dose of any potent topical steroid applied to a large surface area or under an occlusive dressing should be evaluated periodically for evidence of HPA axis suppression by using the urinary free cortisol and ACTH stimulation tests, and for impairment of thermal homeostasis. If HPA axis suppression or elevation of the body temperature occurs, an attempt should be made to withdraw the drug, to reduce the frequency of application, substitute a less potent steroid, or use a sequential approach.

Recovery of HPA axis function and thermal homeostasis are generally prompt and complete upon discontinuation of the drug. Infrequently, signs and symptoms of steroid withdrawal may occur, requiring supplemental systemic corticosteroids.

Children may absorb proportionally larger amounts of topical corticosteroids and thus be more susceptible to systemic toxicity (see **PRECAUTIONS, Pediatric Use**).

If irritation develops, topical corticosteroids should be discontinued and appropriate therapy instituted.

In the presence of dermatological infections, the use of an appropriate antifungal or antibacterial agent should be instituted. If a favorable response does not occur promptly, the corticosteroid should be discontinued until the infection has been adequately controlled.

Information for the Patient

Patients using Kenalog Spray 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 eyes and inhalation of the spray.
2. Patients should be advised not to use this medication for any disorder other than for which it was prescribed.
3. The treated skin area should not be bandaged or otherwise covered or wrapped as to be occlusive unless directed by the physician.
4. Patients should report any signs of local adverse reactions.
5. Parents of pediatric patients should be advised not to use tight-fitting diapers or plastic pants on a child being treated in the diaper area, as these garments may constitute occlusive dressings.
6. Do not use Kenalog Spray on the underarms or groin areas unless directed by your physician.
7. If no improvement is seen within 2 weeks, contact your physician.
8. Do not use other corticosteroid-containing products while using Kenalog Spray without first consulting your physician.
9. Kenalog Spray is flammable. Avoid heat, flames or smoking when applying Kenalog Spray.

Laboratory Tests

A urinary free cortisol test and ACTH stimulation test may be helpful in evaluating HPA axis suppression.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term animal studies have not been performed to evaluate the carcinogenic potential or the effect on fertility of topical corticosteroids.

Studies to determine mutagenicity with prednisolone and hydrocortisone showed negative results.

Pregnancy: Teratogenic Effects

Category C. Corticosteroids are generally teratogenic in laboratory animals when administered systemically at relatively low dosage levels. The more potent corticosteroids have been shown to be teratogenic after dermal application in laboratory animals. There are no adequate and well-controlled studies in pregnant women on teratogenic effects from topically applied corticosteroids. Therefore, topical corticosteroids should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Drugs of this class should not be used extensively on pregnant patients, in large amounts, or for prolonged periods of time.

Nursing Mothers

It is not known whether topical administration of corticosteroids could result in sufficient systemic absorption to produce detectable quantities in breast milk. Systemically administered corticosteroids are secreted into breast milk in quantities not likely to have a deleterious effect on the infant. Nevertheless, caution should be exercised when topical corticosteroids are administered to a nursing woman.

Pediatric Use

Pediatric patients may demonstrate greater susceptibility to topical corticosteroid-induced HPA axis suppression and Cushing's syndrome than mature patients because of a larger skin surface area to body weight ratio.

HPA axis suppression, Cushing's syndrome, and intracranial hypertension have been reported in children receiving topical corticosteroids. Manifestations of adrenal suppression in children include linear growth retardation, delayed weight gain, low plasma cortisol levels, and absence of response to ACTH stimulation. Manifestations of intracranial hypertension include bulging fontanelles, headaches, and bilateral papilledema.

Administration of topical corticosteroids to children should be limited to the least amount compatible with an effective therapeutic regimen. Chronic corticosteroid therapy may interfere with the growth and development of children.

ADVERSE REACTIONS

The following local adverse reactions are reported infrequently with topical corticosteroids, but may occur more frequently with the use of occlusive dressings (reactions are listed in an approximate decreasing order of occurrence): burning, itching, irritation, dryness, folliculitis, hypertrichosis, acneiform eruptions, hypopigmentation, perioral dermatitis, allergic contact dermatitis, maceration of the skin, secondary infection, skin atrophy, striae, and miliaria.

OVERDOSAGE

Topically applied corticosteroids can be absorbed in sufficient amounts to produce systemic effects (see **PRECAUTIONS, General**).

DOSAGE AND ADMINISTRATION

Directions for use of the spray can are provided on the label. The preparation may be applied to any area of the body, but when it is sprayed about the face, care should be taken to see that the eyes are covered, and that inhalation of the spray is avoided.

Spray is flammable; avoid heat, flame or smoking when using this product.

Three or four applications daily of Kenalog Spray (Triamcinolone Acetonide Topical Aerosol) are generally adequate.

HOW SUPPLIED

Kenalog Spray (Triamcinolone Acetonide Topical Aerosol, USP)

63 g (NDC 10631-093-62) aerosol can.

100 g (NDC 10631-093-07) aerosol can.

Storage and Handling

Store at room temperature; avoid excessive heat. Contents under pressure; do not puncture or incinerate. Keep out of reach of children.

To report SUSPECTED ADVERSE REACTIONS, contact the FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

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REGULATORY NEWS

Providers stumble after HIPAA audits

Washington — When it comes to securing and protecting patient health information, physician practices with fewer than 50 providers fared the worst in a recent audit by the Department of Health and Human Services' Office for Civil Rights (OCR).

In fact, Linda Sanches, M.P.H., an OCR senior adviser, reports that only two of the 64 healthcare providers in the audit passed without problems.

While OCR's audit on privacy and security also included health plans and healthcare clearinghouses, the report says that significant compliance issues exist among physician practices.

OCR evaluated practices related to security (administrative, physical and technical safeguards), breach notification, and privacy [access to patient health information (PHI), administrative requirements, uses and disclosures of PHI, etc.]. Security problems accounted for 60 percent of the findings and observations. Data privacy problems were noted in 30 percent of the audits, while only 10 percent were attributed to data breach notifications.

Small practices, OCR notes, "struggled with all three audit areas."

Nearly 50 percent of the smaller practices posted negative findings and observations related to compliance of uses and disclosure of PHI, another 30 percent were dinged for not having acceptable administrative requirements in place, 30 percent had compliance problems related to patient access, and another 31 percent had findings and observations related to notice of privacy practices for PHI.

Many of the audit problems, Ms. Sanches says, were triggered simply because providers were unaware of the requirements. She urged physicians to evaluate the regulations and conduct a compliance assessment to help protect PHI from breaches. **DT**

App lets users submit device reports to FDA

Washington — The MedWatcher mobile application allows physicians and other users to submit voluntary reports of serious medical device problems to the Food and Drug Administration using a smartphone or tablet. Although not intended to fulfill mandatory reporting requirements, the app is designed to improve patient safety more quickly by speeding the reporting process compared with traditional reporting done via mail, telephone, or Web.

Users can:

- report serious adverse events, therapeutic failures, use errors, and product quality issues;
- upload photos to help identify visible problems; and
- receive safety alerts, safety communications, recall information, and more.

A built-in firewall means that information is not vulnerable after it has been received, according to the agency. The app does not store personal information from a user's mobile device, nor does it store reports once they are submitted.

MedWatcher is available for download in the iTunes and Google Play stores. For more information contact HealthMap; (800)463-6332; www.medwatcher.org. **DT**

REGULATORY NEWS

IRS staffs up for start of ACA

Washington — The Internal Revenue Service has 700 full-time staffers devoted to the implementation of the Affordable Care Act (ACA), and some pundits believe that number may grow to a minimum of 5,000 employees, according to a recent report in *Forbes*.

The IRS's new role will be to verify eligibility and monitor whether a business carries qualifying health coverage or remains exempt from the law's penalties, *Forbes* reports.

The American Association of Family Physicians says the IRS's role in implementing ACA will not involve physicians directly. And their oversight authority will not involve access to a physicians' medical records as some news organizations implied.

Nonetheless, the IRS will administer 47 tax provisions related to ACA including "the right to levy a penalty against businesses and individuals who don't provide or acquire insurance." **DT**

Congress forms caucus on skin cancer

Washington — A bipartisan caucus comprised of congressional leaders and dermatology groups will focus on addressing the epidemic of skin cancer in the United States.

The Congressional Skin Cancer Caucus was established by Reps. Jim Cooper (D-Tenn.), Carolyn Maloney (D-N.Y.), Peter Roskam (R-Ill.) and Charlie Dent (R-Pa.) with the help of the American College of Mohs Surgery (ACMS) and support from the American Academy of Dermatology Association (AADA).

The caucus will support legislative activities and public policies that are aimed at raising skin cancer awareness, promoting skin screening and early detection of the disease, and improving access to skin cancer treatment.

"We are delighted to see this new caucus come to fruition," said Dirk M. Elston, M.D., president of the AADA. "This bipartisan group has the potential to not only save lives but decrease skin cancer-related healthcare costs in the future."

Brent Moody, M.D., chairman of the ACMS, said, "Mohs surgeons are excited to see the skin cancer epidemic taking a more prominent place in the eyes of our federal policymakers. The Mohs College, in partnership with the AADA and other advocates, including federal agencies, will work with the caucus to identify opportunities to further the mission of this new organization". **DT**

RESEARCH NEWS

Mohs best for high-risk facial cancers

Charlottesville, Va. — Mohs micrographic surgery is the ideal treatment option for high-risk skin cancers occurring on the face, results of a study show.

Investigators from the University of Virginia, Charlottesville, reviewed 495 lesions that were removed with Mohs surgery from 180 male and 119 female patients between 2005 and 2011. The size and final defect size were compared to calculate the margins needed. Lesions were categorized based on their histological characteristics.

Mean margins for low-risk basal cell carcinomas (BCC) were 2.4 mm, 3.7 mm for high-risk basal cell, 2.6 mm for low-risk squamous cell (SCC) and 5.3 mm for high-risk squamous cell, according to the study abstract.

The established high-risk zones for BCC and SCC were not associated with larger margins. The margins required to excise completely 95 percent of all the low-risk BCCs, high-risk BCCs, low-risk SCCs and high-risk SCCs were 4.75 mm, 8 mm, 5 mm and 13.25 mm, respectively.

"When primary excision instead of Mohs micrographic surgery is the only option, the aforementioned margins may be considered guidelines," the study authors noted. "The relevance of this study is to guide future management and margins for primary excision."

The study was published online June 6 in *JAMA Facial Plastic Surgery*. **DT**

BUSINESS NEWS

Two-thirds of physicians in ACOs say they've not benefited financially

Alpharetta, Ga. — A new survey suggests that accountable care organizations (ACOs) won't create any financial benefit for physicians — what many doctors have feared.

More than two-thirds (67 percent) of physicians who participated in an ACO last year reported no personal financial benefit, such as a bonus or shared savings agreement, as a result of their participation, according to a survey of about 3,500 physicians by staffing firm Jackson Healthcare.

That compares with 19 percent of ACO participants who weren't sure if they'd benefitted financially, and 14 percent who said they had. The roughly 3,500 respondents were self-selected from a group of about 225,000 doctors who received the survey via email. Of those respondents, 25 percent said they were currently participating in an ACO. With the latest round of ACO approvals from the Centers for Medicare and Medicaid Services earlier this year, physician-led organizations pulled ahead of hospitals 202 to 189.

ACOs are relatively new, so it's possible that they could offer financial benefit to physicians in the future, and that it's simply too early to have expected that to happen yet. **DT**

RESEARCH NEWS

Virus targets melanoma in mice

New Haven, Conn. — A virus injected into mice with melanoma proved effective for prompting an immune system response that killed the virus and the tumor, a recent study demonstrated.

Researchers with Yale School of Medicine and Yale Cancer Center, New Haven, Conn., injected the vesicular stomatitis virus into mice, and determined that the fast-acting virus bypassed healthy melanocytes but found 19 melanoma tumors, according to a news release.

In 70 percent of the tumors that investigators tested, the disease was destroyed, while the remainder demonstrated a limited response to the virus. The immune system's response in attacking the virus may also allow it to target and destroy the tumor cells, according to the report. Researchers said the study results merit further study of the virus "for its oncolytic and vaccine potential."

The findings were published in the *Journal of Virology*. **DT**

Comorbidities accompany alopecia areata

New Haven, Conn. — Comorbidities such as autoimmune diseases and mental health problems are common in patients with alopecia areata, study results suggest.

Researchers from Brigham and Women's Hospital, Boston, reviewed the medical files of 350 randomly selected patients with alopecia areata who were part of the Partners healthcare system in Boston.

Common comorbid conditions among the patients were autoimmune diagnoses such as thyroid disease in 14.6 percent, diabetes mellitus in 11.1 percent, inflammatory bowel disease in 6.3 percent, systemic lupus erythematosus in 4.3 percent and rheumatoid arthritis in 3.9 percent. Additionally, psoriasis and psoriatic arthritis were found in 2 percent of the patients. Mental health problems such as anxiety and depression were in 25.5 percent.

In the patients with alopecia areata, researchers also noted a high prevalence of hyperlipidemia (24.5 percent), hypertension (21.9 percent) and gastroesophageal reflux disease (17.3 percent). The investigators suggested that clinicians treating patients who have alopecia areata consider screening these patients for comorbid conditions.

The study was published online May 22 in *JAMA Dermatology*. **DT**

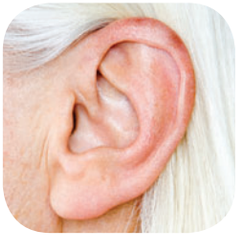
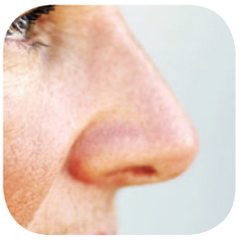
High Clearance[1*]

Low Down Time[†]

Monitored Completion[**]

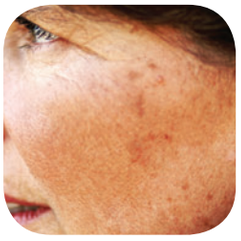
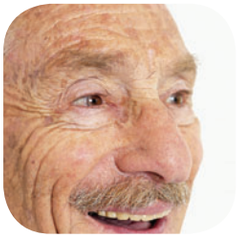
Few AKs

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® and BLU-U® are registered trademarks of 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.

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26 ISOTRETINOIN INSIGHTS
Responsibility lies with dermatologists to promote best practices for this drug

Game-changers

Physicians refine treatment strategies using biologic agents

By John Jesitus
Senior Staff Correspondent

Miami Beach, Fla. — As the use of therapy for moderate-to-severe psoriasis grows, an expert says, physicians continue refining treatment strategies.

"Biological therapies have been a major advance in psoriasis treatment," says Robert E. Kalb, M.D., clinical professor of dermatology, State University of New York, Buffalo, School of Medicine. Patients who have severe psoriasis and fail conventional therapies can choose from this new armamentarium, he says, using regimens that increasingly match drug attributes with individual patient characteristics.

If the efficacy of a tumor necrosis factor (TNF) blocker starts waning, which suggests autoantibodies to the drug, dermatologists should consider switching TNF agents, says Dr. Kalb, who spoke at the 71st annual American Academy of Dermatology meeting. "The autoantibodies will not affect the second agent." Another option, he says, is increasing the patient's dose or dosing frequency if feasible.

Some experts recommend adding methotrexate when a biologic's efficacy begins to wane. In this regard, "There's no right or wrong answer. Others have argued that you should always consider using methotrexate with a biologic drug to prevent autoantibodies."

A recent study in patients with psoriasis shows for the first time that such a combination works better than etanercept alone (Gottlieb AB, Langley RG, Strober BE, et al. *Br J Dermatol.* 2012;167(3):649-657).

Conversely, Dr. Kalb says, if a patient fails to respond to an initial TNF therapy, data suggest switching to a drug with a different mechanism, such as the interleukin (IL)-12/IL-23 blocker ustekinumab. A recent five-year ustekinumab study showed no significant safety issues, including cancer or major adverse cardiovascular events (Papp KA, Griffiths CE, Gordon K, et al. *Br J Dermatol.* 2013 Jan 10. [Epub ahead of print]).

Presently, Dr. Kalb adds, three IL-17 blockers (brodalumab, Amgen; secukinumab, Genzyme; ixekizumab, Eli Lilly) are in phase 2/3 clinical trials. Among small-molecule drugs, he says, "Tofacitinib (Pfizer), a Janus activated kinase (JAK) inhibitor, was recently approved in rheumatoid arthritis." Also, the phosphodiesterase 4 inhibitor apremilast (Celgene) recently completed phase 3 trials for psoriasis and psoriatic arthritis.

More conventional options

For phototherapy, he says, narrowband 311 nm UVB (NBUVB) repre-

GAME CHANGERS see page 31

QUICK READ

Biologic drugs for psoriasis allow increasingly individualized treatment.


Dr. Kalb

Patients taking finasteride consume **less** alcohol

DT Extra Patients taking the hair loss treatment finasteride (Propecia, Merck) may drink less alcohol than they were consuming before they began taking the medication, according to researchers with George Washington University School of Medicine & Health Sciences. In standardized interviews with 83 otherwise healthy male patients, investigators found that of 63 men who had consumed at least one alcoholic drink per week before taking the medication, 65 percent had a decrease in their level of consumption after stopping treatment with finasteride. Thirty-two percent saw no change in their consumption and 3 percent reported an increase in how much they drank.

Source: George Washington University School of Medicine & Health Sciences

Quotable

"Patients with substantial acne, independent from being treated with isotretinoin ... have a much higher rate of suicidal ideation."

Shannon Humphrey, M.D.
Vancouver, British Columbia

On best practices with isotretinoin

See story, page 26

Isotretinoin INSIGHTS

Responsibility lies with derms to promote best practices for this drug

By John Jesitus
Senior Staff Correspondent

Miami Beach, Fla. — With isotretinoin disappearing from continuous medical education (CME), an expert says, dermatologists must take the initiative in promoting best practices for this indispensable acne drug.

Dr. Humphrey

In recent years, says Shannon Humphrey, M.D., "Isotretinoin has been relatively absent from the CME agenda." Dr. Humphrey is director of CME and clinical instructor, department of dermatology and skin science, University of British Columbia, Vancouver.

"It's important that we keep ourselves abreast of the most recent evidence, as well as best practices in terms of safety and patient outcomes," says Dr. Humphrey, who spoke at the annual meeting of the American Academy of Dermatology. "As dermatologists, it's even more important that we stay on the cutting edge of the evidence base behind isotretinoin — so we can model the safest and best practices for our colleagues, and maintain our ability to prescribe it. As we've seen in other countries, the process of accessing this medication has become increasingly legislated and regulated. But there's really nothing like it in terms of efficacy for acne."

Far-reaching results

Accordingly, Dr. Humphrey says isotretinoin's real-world indications go well beyond its labeled indications (severe, recalcitrant nodular acne). "Patients with scarring, even if their acne is milder, and patients who have psychological distress resulting from any degree of acne may warrant this particularly aggressive treatment."

QUICK READ

To maintain access and model best practices, an expert says, dermatologists must take the lead in isotretinoin-related education.

In this regard, she notes, "The impact of acne on quality of life and psychosocial functioning does not necessarily correlate with acne severity. Sometimes, patients with milder disease may have the most significant quality-of-life impairment."

Patients with postinflammatory hyperpigmentation, those who have failed copious conventional treatments, and those with widespread disease unsuited to topical treatment also may warrant isotretinoin, she says.

Standard isotretinoin doses range from 0.5 mg/kg daily to 1 mg/kg daily for up to 20 weeks, for a cumulative dose of 120 mg/kg to 150 mg/kg. Conversely, she says, "Some dermatologists use a long-term low dose; for example, 10 mg three times a week. This practice has not been well studied, and we don't know clearly the side effect profile if we prescribe this for many years at a time." But at any dose, she says, "The most significant side effect to remember is teratogenicity. Even a tiny dose can cause retinoid embryopathy."

Particularly intriguing to Dr. Humphrey are studies of shorter courses that give a lower cumulative dose. In one such study, investigators treated patients with milder acne for an additional four weeks after their acne cleared (using an average cumulative dose of 80.92 mg/kg). Ultimately, patients thusly treated had a two-year relapse rate of 9.35 percent, the same as those who had undergone standard isotretinoin treatment (Borghi A, Mantovani L, Minghetti S, et al. *J Eur Acad Dermatol Venereol*. 2011;25(9):1094-1098).

Analyzing adverse events

Meanwhile, in the media, controversy swirls around the drug's association with adverse events, including depression and suicidal ideation. "However," Dr. Humphrey says, "the weight of the evidence does not support a causal association."

Regarding either of these adverse events and isotretinoin, "Most dermatologists and experts agree that there's been a failure to demonstrate a causal association. But this does not preclude the possibility of an extremely rare, idiosyncratic reaction of depressive symptoms," she says.

According to a recent population-based study, "Patients with substantial acne — independent from being treated with isotretinoin — actually have a much higher rate of suicidal ideation and social impairment (Halvorsen JA, Stern RS, Dalgard F, et al. *J Invest Dermatol*. 2011;131(2):363-270)." Specifically, researchers found that 24.1 percent of patients with substantial acne experienced suicidal ideation, versus 18.6 percent of those with moderate acne. "Therefore, these patients at baseline are at much higher risk, which helps to explain some of the patterns that have been reported."

Regarding inflammatory bowel disease (IBD), Dr. Humphrey says that as in depressive symptoms, "There are so many confounders in both the population and the treatments they've had that it's very difficult to produce a clear, final conclusion. But in a recent meta-analysis that pooled data from four large-scale epidemiologic, case-controlled studies, investigators did not find any indication that isotretinoin confers an increased risk of IBD (Etminan M, Bird ST, Delaney JA, et al. *JAMA Dermatol*. 2013;149(2):216-220). That's ultimately very reassuring." DT

Disclosures: Dr. Humphrey reports no relevant financial interests.

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WOMEN

Some women's skin conditions require special considerations from page 1

about pregnancy and the potential for pregnancy in the early years. Then, later on, thinking about the dynamics of potential drug-drug interaction in an older woman's life."

Dr. Schlosser

Dr. Hordinsky says hot dermatology-related topics for women include aging's effects on hair and skin, as well as skin changes associated with pregnancy and menopause.

Acne, rosacea and hormonal therapy

While acne affects the majority of male and female adolescents, adult women are more often affected by acne than are men, according to Bethanee J. Schlosser, M.D., Ph.D., assistant professor, departments of dermatology and obstetrics/gynecology, Northwestern University Feinberg School of Medicine, Chicago.

"Adult women with acne can present with different clinical features compared to adolescents and men with acne," Dr. Schlosser says. "Adult women may preferentially develop acne lesions on the lower one-third of the face … and upper-neck which consist of tender nodules under the skin."

Dr. Schlosser says acne often worsens around the time of menstruation.

"Such features suggest that adult women with acne may benefit from hormonal therapy rather than oral antibiotics and other acne treatments," she says.

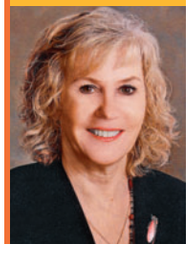
Women are more commonly affected by rosacea, but men with rosacea have been shown to have more severe rosacea and are at greater risk of developing phymatous rosacea, she says.

"Rosacea most often begins in the fourth decade of life … and many women report fluctuation of their rosacea symptoms and skin lesions with regards to the menstrual cycle and in the context of hormonal medication like oral contraceptive pills," Dr. Schlosser says.

Similarities in psoriasis

Psoriasis presents similarly and affects both men and women nearly equally, according to Erin Boh, M.D., Ph.D., chairwoman and professor of dermatology, Tulane University Health Sciences Center, New Orleans. But women may have different concerns from the psychosocial, as well as physical perspectives, she says.

Dr. Boh



"There are a few unique issues for women — the most obvious being in those of childbearing age," Dr. Boh says. "For instance, I recommend phototherapy (narrowband UVB) more frequently to women who are actively trying to get pregnant, or if they are pregnant. There are few safe medications for pregnant women but, if a patient absolutely needs one, I use cyclosporine A."

For non-pregnant, non-lactating patients, sex is not a strong factor for treatment choices, except that dermatologists should not give oral retinoids to women of childbearing age, if possible, according to Dr. Boh.

Autoimmune issues and more

Women are more likely than men to get lupus and dermatomyositis. And there is an increasing incidence and prevalence of autoimmune blistering diseases seen in women, according to Victoria Werth, M.D., professor of dermatology and medicine, University of Pennsylvania, Philadelphia.

Dr. Werth

"There are specific issues about safety of medications in women of child-bearing potential, some of which are also relevant to men. In particular, women who require steroids and might benefit from bisphosphonates to prevent bone loss usually must avoid these if they plan to have children," Dr. Werth says. "In addition, although hydroxychloroquine and azathioprine are used routinely during pregnancy in women with a variety of autoimmune problems, drugs like chloroquine, quinacrine, methotrexate and mycophenolate should be avoided."

Another important issue for dermatologists treating these women to consider: quality of life among women with cutaneous lupus is worse than for men, Dr. Werth says.

"The disease activity particularly affects the emotional component of quality of life," she says.

Another concern for women: lichen sclerosis, which affects the vulvar area. Clinically, patients present with white, atrophic, shining cigarette-paper-like plaques in the vulva, perianal area and ecchymosis, says A. Mary Guo, M.D., assistant professor, department of dermatology, Saint Louis University, St. Louis.

Dermatologists should watch for a secondary change of excoriation, erosion, ulceration and hyperkeratosis when treating lichen sclerosis, Dr. Guo says.

"Patients need to have long-term follow-up to monitor the effectiveness of treatment, as well as any changes of malignancy. Rarely, patient may have lichen sclerosis and morphea overlapping, which may require systemic treatment," she says.

Another condition affecting the vulva area, lichen simplex chronicus, results from chronic rubbing, scratching or both.

"Often, it is difficult to find out the original trigger of local pruritus. Most of these patients do have an atopic diathesis in my opinion," Dr. Guo says.

Pregnancy concerns

Medication safety in female patients who are pregnant, nursing or trying to conceive is important. Pregnancy also can affect psoriasis, eczema and other common skin diseases, according to Dr. Schlosser.

Dr. Guo

"Pregnancy presents unique changes in the hormonal composition and immune system activity of women," she says.

According to Dr. Schlosser, psoriasis may improve, remain stable worsen during pregnancy; however, having psoriasis can influence a woman's risk of delivering her baby prematurely.

Eczema often worsens during pregnancy.

"Many women experience eczema for the first time during pregnancy, and atopic dermatitis in pregnancy accounts for half of pregnant patients that present with an itchy skin rash," Dr. Schlosser says.

There are several skin conditions

that are unique to pregnancy. The most common, Dr. Schlosser says, is polymorphic eruption of pregnancy.

"Fortunately, polymorphic eruption of pregnancy does not carry any risks for either the pregnant woman or her fetus," Dr. Schlosser says. "Pemphigoid gestationis, cholestasis of pregnancy and impetigo herpetiformis … all have potential negative consequences for the pregnant woman and her fetus."

Pigmentary disorders

The pigmentary issues most likely to occur in women, according to Philadelphia dermatologist Susan Taylor, M.D., are solar lentigines, melasma and postinflammatory hyperpigmentation.

Dr. Taylor

"Men do develop solar lentigines but do not seem as bothered by them and usually do not seek treatment for them. Melasma rarely occurs in men," Dr. Taylor says. "Since fewer adult men experience acne as compared to adult women, we see less post-inflammatory hyperpigmentation in men."

Again, the emotional component appears to be more pronounced among women. Dr. Taylor says men seem less concerned if pigmentary issues develop. Men are also less willing to use a topical medication daily or twice-daily to address the problem.

For women, pigmentary issues are more than a cosmetic problem. They affect women's self-esteem and work and social interactions, according to Dr. Taylor, who published findings in the September 2008 issue of the *Journal of Cosmetic Dermatology* about how pigmentary disorders impact life quality.

Cosmetic nuances

There are nuances between especially cosmetic male and female patients, according to Heidi A Waldorf, M.D., director of laser and cosmetic dermatology at Mount Sinai Medical Center, New York.

Dr. Waldorf

"Female patients are generally more apologetic about 'being vain' and feel guilty about spending on themselves instead of their families. I've never heard a male patient voice those concerns," Dr. Waldorf says. "The men in my practice more commonly ask to treat specific brown spots or red vessels while more women ask to look younger."

In some cases, Dr. Waldorf's approach to cosmetic treatments is different for women and men.

"I had one man who wanted his lips augmented, and that was tricky without feminizing him," Dr. Waldorf says. "It is important to remember that the ideal male face is more angular than the ideal female face. The overall face shape should be a rectangle or rhomboid for a man, versus an upside down egg or heart for a woman."

Dermatologists also should be careful when treating men versus women with neuromodulators.

"A man's brow should remain straight and

WOMEN see page 30

WOMEN

Some women's skin conditions require special considerations from page 29

can even be heavy. A woman's must have some arch," Dr. Waldorf says.

Handling hair loss

Hair loss in women affects many women emotionally not only because they might have less hair but also because their hair-styling suffers, according to Dr. Hordinsky.

"The hairstyle that a man is usually simple compared to a lot of women," she says.

Female patients might consider not taking their medications if a drug has the potential to affect hair loss or hair growth, Dr. Hordinsky says. One of the challenges in treating the aging female patient experiencing hair loss is to step back and take a look at the mechanisms of action of medications that patient is taking, she says.

"Weigh the risks and benefits. If it's a non-scarring type of hair loss problem, talk about the tools we do have to maintain the hair follicle in a growth phase, so the patient can continue the medication … prescribed for the underlying medical problem," Dr. Hordinsky says.

Many women have a deep emotional concern with their hair quality throughout their lives.

"It is not uncommon to see women in their 70s, 80s and even early 90s coming to the clinic with the chief complaint of hair loss, where they are seeking to improve their hair density because that is part of their image," Dr. Hordinsky says. "And they will work very hard with the tools that we have to try and get the best clinical result possible."

An issue for dermatologists, however, is there are few studies available to refer to on the efficacy of some devices or products on hair loss in aging women, she says.

A hair loss issue that dermatologists might see increasingly among women, according to Dr. Hordinsky, is frontal fibrosing alopecia, a condition first recognized in the mid-'80s.

"In the past three to five years, there has been a dramatic increase in the number of patients with this entity. It seems to primarily affect postmenopausal women," she says.

At this point, there are only hypotheses, including hormonal and inflammatory causes, and how best to manage frontal fibrosing alopecia remains a mystery. However, Duke University researchers have started a cross-country epidemiologic study to understand what might be behind this "epidemic" among postmenopausal women, Dr. Hordinsky says. **DT**

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References: 1. Bissett D. Topical niacinamide and barrier enhancement. *Cutis.* 2002;70(suppl 6):8-12. **2.** Dow G, Basu S. A novel aqueous metronidazole 1% gel with hydrosolubilizing agents (HSA-3). *Cutis.* 2006;77(suppl 4):18-26. **3.** Data on file. Galderma Laboratories, L.P. **4.** Clinical study. Data on file. Galderma Laboratories, L.P.

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GAME CHANGERS:

Biologics provide refined treatment options for psoriasis from page 25

sents the gold standard. Combining it with low-dose acitretin rivals the efficacy of biologics, Dr. Kalb adds. The mechanism of action of phototherapy is still not entirely clear, but recent data suggest NBUVB suppresses the IL-23/IL-17 axis (Johnson-Huang LM, Suárez-Fariñas M, Sullivan-Whalen M, et al. *J Invest Dermatol.* 2010;130(11):2654-2663).

"Additionally, low-dose acitretin has far fewer side effects than we've been led to believe" by labeled data based on high-dose acitretin monotherapy. Furthermore, he says, patients who respond well to NBUVB plus acitretin often can decrease or eliminate one of the treatments over time.

> "Low-dose acitretin has **far fewer side effects** than we've been led to believe."
>
> **Robert Kalb, M.D.**
> Buffalo, N.Y.

"Don't forget about home phototherapy units," Dr. Kalb says. In a randomized NBUVB trial, in-office treatments and home-based treatments showed similar results and costs, although patients preferred the home unit (Koek MB, Sigurdsson V, van Weelden H, et al. *BMJ.* 2010;340:c1490). "If a person is responding well and would consider a home device, it requires effort on the physician to obtain the necessary insurance authorization."

Methotrexate and cyclosporine

As for methotrexate, Dr. Kalb says, five recent placebo-controlled studies show that it typically achieves psoriasis area severity index (PASI) 75 results in 40 percent of patients. Efficacy becomes apparent in 12 to 16 weeks, he says.

"If there is not an adequate response, then a biologic agent can be added while continuing methotrexate (to improve efficacy and prevent autoantibodies)," Dr. Kalb says.

Folic acid supplementation (1 mg daily) reduces methotrexate's hepatic, gastrointestinal and hematologic toxicity without compromising efficacy (Prey S, Paul C. *Br J Dermatol.* 2009;160(3):622-628). Similarly, Dr. Kalb says, patient self-administered subcutaneous methotrexate provides increased efficacy in arthritis and perhaps psoriasis, while improving tolerance.

Moreover, "If you select patients properly, without significant risk factors, the vast majority won't need serial liver biopsies. It could be argued that methotrexate itself does not cause liver fibrosis without contribution from other risk factors." Primary risk factors include obesity, diabetes and excess alcohol use, he adds.

Conversely, Dr. Kalb says that hematologic toxicity is the most serious adverse event associated with methotrexate use in psoriasis, and the likelihood of hematologic toxicity increases in patients with decreased creatinine clearance.

"Cyclosporine can provide a quick fix," often providing initial relief within days to weeks, Dr. Kalb says. He suggests beginning with high doses (4 mg/kg to 5 mg/kg), then lowering the dose if feasible. "Because of the long-term renal toxicity and hypertension, it's sometimes not practical long-term. But in low doses, it can be combined with other treatments and often is very effective."

> "In low doses, (**cyclosporine**) can be combined with other treatments and **often is very effective**."
>
> **Robert Kalb, M.D.**
> Buffalo, N.Y.

European physicians commonly prescribe cyclosporine for intermittent courses of three to four months, he says. "It's also used as a bridging agent between therapies," and to help quell flares. DT

Disclosures: Dr. Kalb is an investigator, speaker and/or consultant for Abbott, Amgen, Janssen, Leo, GlaxoSmithKline/Stiefel. His group practice provides phototherapy and infusion services for psoriasis.

HEALTHCARE REFORM

Dermatologists find creative ways to deliver care where it's needed from page 1

chronic leg ulcers; leprosy and tropical diseases; sexually transmitted diseases; vulvar conditions and connective tissue diseases.

Specialty strategies

The dermatology department runs many of these clinics in conjunction with other departments such as obstetrics and gynecology. Still, as a resident-run clinic, dermatology faces challenges including maintaining appropriate ratios of attending physicians to residents, which can be as high as 1:1 in areas such as surgery.

In this regard, Dr. Sanchez says, "Our strategy is to use volunteer attending physicians to supplement the ones that are paid for by the hospital. This is made possible through the hospital's affiliation with the medical school." He is the department's only full-time employee, he adds, along with two full-time equivalent attendings and 27 volunteer attending physicians who each work approximately one shift weekly.

In working with volunteer dermatologists, he says, "My philosophy is if someone becomes available, I find out what their interests are, and I find use for them." If someone is interested in hair and nails, for example, this could mean starting a hair and nail clinic, if needed.

Broader solutions to the shortage of dermatology providers include partnering with primary care physicians (PCPs) interested in dermatology, Dr. Sanchez says. In 2012, Bellevue's dermatology department implemented a program to train PCPs how to evaluate skin problems, particularly pigmented lesions. So far, he says, two local internists have completed the program and are now training other community internists and residents.

Utilizing teledermatology

Regarding teledermatology, the department recently began a program to serve inmates at nearby Rikers Island correctional facility, where there is a 10-month waiting list to see a dermatologist. Now, a physician assistant (PA) trained by the department forwards photos from the forensic clinic where inmates are seen, to Bellevue's dermatologists when needed.

It's too soon to gauge the program's impact, Dr. Sanchez says. "However, we noticed right away that the type of visits we're seeing really require a dermatologist, because patients might require a procedure" or complex diagnostic skills.

Ultimately, he adds, the program will eliminate prisoner transport — which costs the state thousands of dollars per hospital visit — wherever possible. Along with incorporating teledermatology, this might require training PAs or physicians working at the prison to diagnose and treat skin problems there, and/or sending Bellevue dermatologists to the prison occasionally, he says.

In short, "The ACA is saying that rather

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

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than the patient always coming to the hospital, the practitioner should be going to the community, providing and promoting good care." In this climate, Dr. Sanchez says, periodically transporting specialists including dermatologists to understaffed facilities, perhaps in Brooklyn on the Bronx, likely will grow in popularity. Alternately, dermatology departments like Bellevue's may equip vehicles to host remote patient visits on board.

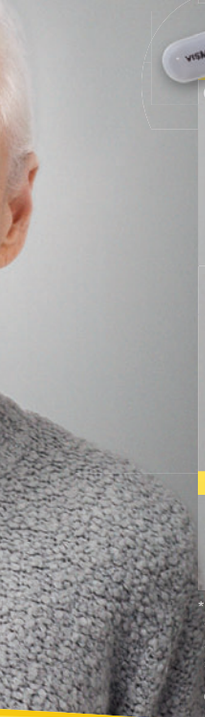
"We're trained that we have to work in hospitals" or dedicated offices, he says, but that won't necessarily be the case going forward.

Skin problems cause patients significant anxiety, whether through symptoms or worries about contagion or skin cancer, he says. "So people don't want to wait to see a dermatologist. Often they'll go to emergency rooms. Therefore, we must make every effort to see people on a timely basis. Under the ACA, you'll have to be accessible to patients when they need you."

Together, the initiatives undertaken by Bellevue's dermatology department mean that new patients wait only two to three weeks for an appointment, versus up to six months in other Bellevue clinics, Dr. Sanchez says. DT

Disclosures: Dr. Sanchez reports no relevant financial interests.

TRANSFORM THE TREATMENT OF DIFFICULT ADVANCED BASAL CELL CARCINOMA (aBCC)



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ERIVEDGE IS A UNIQUE ORAL THERAPY

- Due to the nature of aBCC and its clinical factors (ie, lesion recurrence, location/size, and invasiveness), some patients may not be candidates for surgery or radiation[1,2]
- Erivedge is an oral treatment option dosed as a 150-mg capsule once daily until disease progression or unacceptable toxicity[3]
- Erivedge reduced lesions in patients with aBCC[1,3]

Objective response rates (ORR) by IR from ERIVANCE[1,3*]

	laBCC (n=63)	mBCC (n=33)
ORR (95% CI)	43% (n=27) (30.5-56.0)	30% (n=10) (15.6-48.2)
Complete response	21% (n=13)	0%
Partial response	22% (n=14)	30% (n=10)
Median duration of response (months) (95% CI)	7.6 (5.7-9.7)	7.6 (5.6-NE)

Indication

Erivedge® (vismodegib) capsule is a hedgehog pathway inhibitor 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.

*Patients received at least 1 dose of Erivedge with independent pathologist-confirmed diagnosis of BCC. Response in laBCC: absence of disease progression and either ≥30% reduction in lesion size (sum of the longest diameter) from baseline in target lesions by radiography or in externally visible dimension (including scar tissue); or complete resolution of ulceration in all target lesions. Complete responders also had no residual BCC on sampling biopsy and partial responders had residual BCC on sampling biopsy. Response in mBCC: assessed by the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.0.

IR=Independent Review; laBCC=locally advanced BCC; ORR=objective response rate; CI=confidence interval; NE=not estimable; mBCC=metastatic BCC.

Adverse Reactions

- The most common adverse reactions (≥10%) were muscle spasms, alopecia, dysgeusia, weight loss, fatigue, nausea, diarrhea, decreased appetite, constipation, arthralgias, vomiting, and ageusia
- In clinical trials, a total of 3 of 10 premenopausal women developed amenorrhea while receiving Erivedge
- 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%)

You may report side effects to the FDA at (800) FDA-1088 or www.fda.gov/medwatch. You may also report side effects to Genentech at (888) 835-2555.

Please see Brief Summary of Prescribing Information on following page.

Erivedge® (vismodegib) capsule

Treatment Transformed

See what you can offer your patients with aBCC at www.Erivedge.com

References: 1. Sekulic A, Migden MR, Oro AE, et al. *N Engl J Med.* 2012;366:2171-2179. **2.** Walling HW, et al. *Cancer Metastasis Rev.* 2004;23:389–402. **3.** Erivedge® (vismodegib) capsule Prescribing Information. Genentech, Inc. January 2012.

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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
South San Francisco, CA 94080-4990

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39 MAKING A CASE
Botulinum toxin treatments safe; lawsuits, adverse events relatively uncommon

SCRATCHING the surface

Many potential indications for botulinum toxin formulations have yet to be realized

By Ilya Petrou, M.D.
Senior Staff Correspondent

Vancouver, British Columbia — The emergence of new formulations of botulinum toxin and other neuromodulators in the pipeline awaiting approval by the Food and Drug Administration signal a need for clinicians to stay abreast of the various uses and potential adverse events.

Since the start of its therapeutic use in the medical arena decades ago, the utilities for botulinum toxin have been expanding for clinical as well as cosmetic indications.

"Botulinum toxin has shown to be a very useful therapeutic tool in medicine employed for the treatment of varying indications including eye disorders, pain and neuromuscular disorders, but perhaps its most popular applications are seen in the field of aesthetic medicine for the treatment of frown lines," says Alastair Carruthers, M.D., clinical professor, department of dermatology and skin science, Vancouver, British Columbia. "Despite its extensive use for numerous medical and aesthetic indications, I believe that we have only scratched the surface of its potential."

QUICK READ

An ever-increasing number of indications for neurotoxins and neuromodulators continue to come to light. The sky appears to be the limit for this versatile treatment modality.

Currently, four botulinum toxin serotype A (BoNTA) and B (BoNTB) formulations are approved by the FDA, namely onabotulinumtoxinA (Botox, Allergan), abobotulinumtoxinA (Dysport, Medicis), incobotulinumtoxinA (Xeomin, Merz) and rimabotulinumtoxinB (Myobloc, Solstice Neurosciences). Of these, the BoNTA preparations are the most widely used worldwide and the only ones FDA-approved for aesthetic use.

Formulation nuances

Dr. Carruthers and colleagues recently performed a comprehensive review of the current evidence regarding the FDA-approved botulinum toxin formulations. They found that there are very fine nuances that discern the different neuromodulators. According to Dr. Carruthers, these small differences can give clinicians the opportunity to personalize and individualize treatment approaches according to the intended treatment indication.

All botulinum toxin serotypes demonstrate the same basic mechanism of action, Dr. Carruthers says; however, the intracellular targets vary among them. While BoNTA cleaves synaptosomal-associated protein 25, BoNTB cleaves a vesicle-associated membrane protein, or synaptobrevin. The effects of botulinum toxin intoxication are not permanent in nature and, similarly, neither are the effects of botulinum toxin injection, with facial cosmetic treatment results lasting anywhere from three to six months or longer, Dr. Carruthers says.

Each commercially available BoNTA formulation is unique and the most basic difference among them is

SCRATCHING THE SURFACE see page 36

Sunscreen use slows skin aging

DT Extra Daily sunscreen use by middle-aged men and women helps to prevent skin aging, according to a study led by researchers with University of Queensland, Brisbane, Australia. Analyzing data from 903 adult patients ages 55 and younger from a community register, investigators found that those who used a broad-spectrum sunscreen daily demonstrated no detectable increase in skin aging after four and a half years. Skin aging from baseline to the end of the trial was 24 percent less in the daily sunscreen group than in the discretionary sunscreen group.

Source: *Annals of Internal Medicine*

Quotable

"We could only find 24 cases related to botulinum toxin complications, which is relatively quite a small number."

John B. Korman, M.D.
Boston

On lawsuits related to adverse events

See story, page 39

SCRATCHING THE SURFACE:

The sky's the limit for indications for botulinum toxin formulations

from page 35

seen in complex size and structure, he says. While onabotulinumtoxinA and abobotulinumtoxinA are formulated complexes and differ from one another in size and composition, incobotulinumtoxinA is unique in that it is the first BoNTA formulated with no complexing proteins.

Botulinum toxin treatments are generally considered to be safe and adverse events are extremely rare, particularly at the doses in which they are given cosmetically and when a precise injection strategy is employed, according to Dr. Carruthers.

Ongoing research

Although incobotulinumtoxinA is free of complexing proteins, it still remains to be seen whether the product's supposed decreased immunogenicity is of an advantage compared to onabotulinumtoxinA and abobotulinumtoxinA, which have complexing proteins in their formulation.

"A **topical neurotoxin** that can target the sweat glands, sebaceous glands and vasculature could help to **treat numerous dermatologic conditions**."

Alastair Carruthers, M.D.
Vancouver, British Columbia

"I believe there are only five cases of resistance that have been reported with BoNTA with complexing proteins following cosmetic treatment, but when you look at the millions of BoNTA treatments performed around the world, five cases could be considered negligible. It may take decades before we see another five such cases, or other issues with any of these complexing and noncomplexing protein BoNTA formulations," he says.

According to Dr. Carruthers, all toxins diffuse upon injection because diffusion is a natural process to attain equilibrium. Although the conventional wisdom is that smaller complexes allow for a greater diffusion, past studies have shown mixed results in terms of how differing toxin formulations spread following injection regardless of complex size.

"Further research is necessary to clarify the differences between study results and the nuances of how formulations may differ in terms of spread," Dr. Carruthers says.

Bright future

The future of botulinum toxin therapies is very exciting, as new and innovative toxin delivery modalities are developed, such as the topical RT001 cream (Revance Therapeutics), which has yet to be approved by the FDA. This uncomplexed BoNTA topical product has been shown to traverse intact skin and achieve a result, Dr. Carruthers says, that could open doors for novel clinical applications, such as the reduction of redness, oiliness and sweating after a brief application of the neurotoxin.

"A topical neurotoxin that can target the sweat glands, sebaceous glands and vasculature could help to treat numerous dermatologic conditions. Although I don't think that this is going to significantly impact the injectable market, such a topical modality may expand the market dramatically," Dr. Carruthers says.

Injectable neurotoxins have been shown to be effective in the treatment of headaches and migraines, and topical neurotoxin products such as Revance have also been shown to improve this condition, representing a novel treatment option for patients.

Other evolving indications for neurotoxin therapy in medicine could be the treatment of depression. According to Dr. Carruthers, there is an increasing number of studies being reported demonstrating that the use of botulinum toxin in frown lines can help improve depression in many affected individuals. Other changes being made to the botulinum toxin molecule could result in radical changes in the treatment of pain syndromes in the future. Novel neurotoxin formulations in the works could significantly help alleviate the pain typically associated with those syndromes, he says.

Studies have shown mixed results in terms of **how differing toxin formulations spread** following injection regardless of complex size.

"I have had experience with all of the available neurotoxins and though there are fine differences among them, I find them all to be effective. As we get to know these products better and learn from personal experiences and future studies, we may begin to distinguish areas for which one may be more suitable than the other for a given indication," Dr. Carruthers says. **DT**

Disclosures: Dr. Carruthers is a consultant and researcher for Merz and Allergan.

CONTINUING TO SUPPORT YOUR PATIENTS WITH COPAY SAVINGS

For mild to moderate rosacea

The **first and only gel** approved to treat all 3 symptoms

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.

3 Symptoms, 1 Medicine for clearer-looking skin

- **61% of patients** achieved treatment success in 12-week clinical studies[1]

Finacea®
(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

FINACEA Gel, 15% is contraindicated in individuals with a history of hypersensitivity to propylene glycol or any other components of the formulation. 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, these patients should be monitored for early signs of hypopigmentation. FINACEA and its vehicle caused irritant reactions at the application site in human dermal safety studies. 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/or persists during use with FINACEA, discontinue use and institute appropriate therapy.

In clinical trials with FINACEA, the most common local adverse events (AE's) (inclusive of mild, moderate and severe categories) 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.

Rarely reported AE's included: worsening of asthma, vitiligo depigmentation, small depigmented spots, hypertrichosis, reddening (signs of keratosis pilaris) and exacerbation of recurrent herpes labialis. Post-marketing safety information: Skin (facial burning and irritation); Eyes (iridocyclitis on accidental exposure with FINACEA to the eyes). **To report SUSPECTED ADVERSE REACTIONS, contact Bayer HealthCare at 1-866-463-3634 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.**

FINACEA is for topical use only. It is not for ophthalmic, oral or intravaginal use. In case of accidental eye exposure, wash eyes with large amounts of water and consult a physician if eye irritation persists. Wash hands following application of FINACEA.

See adjacent page for Brief Summary of full Prescribing Information.

Model used for illustrative purposes only.

Reference: 1. FINACEA [package insert]. Morristown, NJ: Intendis, Inc; 2010.

Bayer HealthCare

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Finacea®
(azelaic acid) Gel, 15%

For Dermatologic Use Only–Not for Ophthalmic, Oral, or Intravaginal Use

Rx only

BRIEF SUMMARY
CONSULT PACKAGE INSERT FOR FULL PRESCRIBING INFORMATION

INDICATIONS AND USAGE

FINACEA 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. Patients should be instructed to avoid spicy foods, thermally hot foods and drinks, alcoholic beverages and to use only very mild soaps or soapless cleansing lotion for facial cleansing.

CONTRAINDICATIONS

FINACEA Gel, 15%, is contraindicated in individuals with a history of hypersensitivity to propylene glycol or any other component of the formulation.

WARNINGS

FINACEA Gel, 15%, is for dermatologic use only, and not for ophthalmic, oral or intravaginal use. 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, these patients should be monitored for early signs of hypopigmentation.

PRECAUTIONS

General: Contact with the eyes should be avoided. If sensitivity or severe irritation develops with the use of FINACEA Gel, 15%, treatment should be discontinued and appropriate therapy instituted.

In a transgenic mouse study, chronic use of FINACEA Gel led to an increased number of animals with papillomas at the treatment site [**see PRECAUTIONS: Carcinogenesis, Mutagenesis, and Impairment of Fertility**]. The clinical relevance of the findings in animal studies to humans is not clear.

Information for Patients: Patients using FINACEA Gel, 15%, should receive the following information and instructions:

- FINACEA Gel, 15%, is to be used only as directed by the physician.
- FINACEA Gel, 15%, is for external use only. It is not to be used orally, intravaginally, or for the eyes.
- Cleanse affected area(s) with a very mild soap or a soapless cleansing lotion and pat dry with a soft towel before applying FINACEA Gel, 15%. Avoid alcoholic cleansers, tinctures and astringents, abrasives and peeling agents.
- Avoid contact of FINACEA Gel, 15%, with the mouth, eyes and other mucous membranes. If it does come in contact with the eyes, wash the eyes with large amounts of water and consult a physician if eye irritation persists.
- The hands should be washed following application of FINACEA Gel, 15%.
- Cosmetics may be applied after FINACEA Gel, 15%, has dried.
- Skin irritation (e.g., pruritus, burning, or stinging) may occur during use of FINACEA Gel, 15%, usually during the first few weeks of treatment. If irritation is excessive or persists, use of FINACEA Gel, 15%, should be discontinued, and patients should consult their physician [See **ADVERSE REACTIONS**].
- Avoid any foods and beverages that might provoke erythema, flushing, and blushing (including spicy food, alcoholic beverages, and thermally hot drinks, including hot coffee and tea).
- Patients should report abnormal changes in skin color to their physician.
- Avoid the use of occlusive dressings or wrappings.

Drug Interactions: There have been no formal studies of the interaction of FINACEA Gel, 15%, with other drugs.

Carcinogenesis, Mutagenesis, Impairment of Fertility:

Systemic long-term animal studies have not been performed to evaluate the carcinogenic potential of azelaic acid. In a 26-week dermal carcinogenicity study using transgenic (Tg.AC) mice, FINACEA Gel, 15%, and the gel vehicle, when applied once or twice daily, did not increase the number of female Tg.AC animals with papillomas at the treatment site. No statistically significant increase in the number of animals with papillomas at the treatment site was observed in male Tg.AC animals after once daily application. After twice daily application, FINACEA Gel, 15%, and the gel vehicle induced a statistically significant increase in the number of male animals with papillomas at the treatment site when compared to untreated males. This suggests that the positive effect may be associated with the vehicle application. The clinical relevance of the findings in animals to humans is not clear.

Azelaic acid was not mutagenic or clastogenic in a battery of *in vitro* (Ames assay, HGPRT in V79 cells {Chinese hamster lung cells}, and chromosomal aberration assay in human lymphocytes) and *in vivo* (dominant lethal assay in mice and mouse micronucleus assay) genotoxicity tests.

Oral administration of azelaic acid at dose levels up to 2500 mg/kg/day (162 times the maximum recommended human dose based on body surface area) did not affect fertility or reproductive performance in male or female rats.

Pregnancy: *Teratogenic Effects: Pregnancy Category B*

There are no adequate and well-controlled studies of topically administered azelaic acid in pregnant women. The experience with FINACEA Gel, 15%, when used by pregnant women is too limited to permit assessment of the safety of its use during pregnancy.

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 based on body surface area), rabbits given 150 or 500 mg/kg/day (19 or 65 times the maximum recommended human dose based on body surface area) and cynomolgus monkeys given 500 mg/kg/day (65 times the maximum recommended human dose based on body surface area) 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 that generated some maternal toxicity (2500 mg/kg/day; 162 times the maximum recommended human dose based on body surface area). 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 maximum recommended human dose based on body surface area). No effects on sexual maturation of the fetuses were noted in this study.

Because animal reproduction studies are not always predictive of human response, this drug should be used only if clearly needed during pregnancy.

Nursing Mothers: Equilibrium dialysis was used to assess human milk partitioning *in vitro*. 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, indicating that passage of drug into maternal milk may occur. Since less than 4% of a topically applied dose of azelaic acid cream, 20%, 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. However, caution should be exercised when FINACEA Gel, 15%, is administered to a nursing mother.

Pediatric Use: Safety and effectiveness of FINACEA Gel, 15%, in pediatric patients have not been established.

Geriatric: Clinical studies of FINACEA Gel, 15%, did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects.

ADVERSE REACTIONS

Overall, treatment related adverse events, including burning, stinging/tingling, dryness/tightness/scaling, itching, and erythema/irritation/redness, were 19.4% (24/124) for FINACEA Gel, 15%, and 7.1% (9/127) for the active comparator gel at 15 weeks.

In two vehicle controlled, and one active controlled U.S. clinical studies, treatment safety was monitored in 788 patients who used twice daily FINACEA Gel, 15%, for 12 weeks (N=333) or for 15 weeks (N=124), or the gel vehicle (N=331) for 12 weeks.

Table 3. Cutaneous 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.

FINACEA Gel, 15%, and its vehicle caused irritant reactions at the application site in human dermal safety studies. FINACEA Gel, 15%, caused significantly more irritation than its vehicle in a cumulative irritation study. Some improvement in irritation was demonstrated over the course of the clinical studies, but this improvement might be attributed to subject dropouts. No phototoxicity or photoallergenicity were reported in human dermal safety studies.

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

Post-marketing safety-Skin: facial burning and irritation; Eyes: iridocyclitis on accidental exposure with FINACEA Gel, 15%, to the eye [see **PRECAUTIONS**].

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MAKING A CASE

Botulinum toxin treatments safe, but as utility expands, so should caution

By Ilya Petrou, M.D.
Senior Staff Correspondent

Boston — Botulinum toxin treatments are considered to be safe, particularly when used for on-label indications and in the cosmetic arena. A recent study finds, however, that lawsuits associated with botulinum toxin treatments make headlines and some generate multimillion dollar judgments, underscoring the need for physicians to "handle with care."

"The troves of clinical data gathered following millions of treatments suggest that botulinum toxin products are exceptionally safe, especially for cosmetic applications. Nevertheless, botulinum toxin lawsuits alleging complications from its clinical use are making headlines and given how ubiquitous these treatments have become in our specialty, practicing dermatologists may want to carefully consider how and in which scenarios they use the toxin," says John B. Korman, M.D., department of dermatology, Massachusetts General Hospital, Harvard Medical School, Boston.

Dr. Korman

Adverse event cases

Dr. Korman recently conducted a review study to identify and assess lawsuits involving complications from the clinical administration of botulinum toxin products. Using the LexisNexis Academic online database, he conducted a search for federal and state cases filed between 1985 and 2012. He also performed a second search of newspapers and wires in the United States using the same research database.

QUICK READ

As the utilities of botulinum toxin expand, clinicians must exercise caution when employing these treatments. Lawsuits can generate multimillion dollar judgments.

Only cases that involved alleged adverse events arising from the cosmetic or therapeutic use botulinum toxin type A or botulinum toxin type B products approved by the Food and Drug Administration were included in the study. In total, 24 relevant cases were identified, of which three were tried in federal courts, while 21 remained at the state level.

"Of the 27 years of data reviewed, we could only find 24 cases related to botulinum toxin complications, which is relatively quite a small number. However, two of the 24 cases have resulted in multimillion-dollar jury verdicts in favor of the plaintiffs," Dr. Korman says.

Study data showed that all 24 cases alleged adverse effects from onabotulinumtoxinA, and each named its manufacturer, Allergan, as a defendant. Most of the lawsuits against Allergan were dismissed or settled. Sixteen cases involved therapeutic uses of onabotulinumtoxinA, including treatment of migraine headaches, cervical dystonia, limb spasticity and hyperhidrosis.

The data also showed that physicians, including a dermatologist, were codefendants in three cases. None of the lawsuits named a dermatologist when the complication arose from on-label indications and cosmetic use.

Landmark case

Two of the cases generated multimillion-dollar judgments, Dr. Korman says, one of which was named by Lawyers Weekly USA as one of the top 10 jury verdicts of 2011, after a federal district court jury found Allergan liable for $212 million. This case involved the therapeutic use of botulinum toxin that resulted in alleged severe immune reaction and brain injury.

"Looking at our own experiences as well as the study data, it must be said that botulinum toxin treatments are safe, especially for cosmetic applications, which is what is very pertinent for dermatologists," he says. "However, it is important to remember that trial lawyers only have to convince a jury of peers and not a panel of physician scientists. Having said that, the facts do matter, but so does perception."

Since the FDA initially approved the use of onabotulinumtoxinA in 1989 for the treatment of strabismus and blepharospasm — and approved its cosmetic application in 2002 for the correction of glabellar lines — the potential utilities for the toxin have been ever expanding.

Dr. Korman says the relatively small number of lawsuits could be related to the overall low rate of serious adverse events associated with botulinum toxin treatments, or to the transient nature of toxin effect that typically results in time-limited adverse events that partially or completely resolve before legal action can be initiated. According to Dr. Korman, though, caution is warranted.

"Though lawsuits have been brought, their small numbers are reassuring. With the ever-increasing interest in cosmetic and medical botulinum toxin treatments, physicians should be informed about the medical-legal issues surrounding this very commonly performed treatment across different specialties," Dr. Korman says. **DT**

> "Troves of clinical data ... suggest that **botulinum toxin products** are **exceptionally safe**."
>
> **John B. Korman, M.D.**
> Boston

Disclosures: Dr. Korman reports no relevant financial interests.

Dermatology Times

EYEING BRAF inhibitors

Targeted therapy, immunotherapy transform treatment of metastatic melanoma

By Louise Gagnon
Staff Correspondent

Banff, Alberta — There has been a rapid revolution in the treatment of metastatic melanoma since the identification of driver oncogenes such as BRAF and its mutations more than a decade ago, according to a clinical researcher at the Vanderbilt-Ingram Cancer Center, Nashville, Tenn.

Speaking at the annual Canadian melanoma conference about lessons learned from the use of BRAF inhibitors to treat metastatic melanoma, Igor Puzanov, M.D., M.S.C.I., F.A.C.P., associate director of phase 1 drug development, clinical director, Renal Cancer Melanoma/Renal Cancer Program, division of hematology-oncology, Vanderbilt University Medical Center, noted that melanoma is a mix of subtypes characterized by specific mutations and about 50 percent carry BRAF mutations.

"BRAF kinase is an important mediator of cellular proliferation," Dr. Puzanov says. "A therapy such as vemurafenib is a selective RAF inhibitor and effective in this subgroup."

QUICK READ

The detection of BRAF and its mutations has transformed the treatment of metastatic melanoma, producing improvements in overall and progression-free survival.

Optimizing the impact

In general, two approaches can be taken to treat metastatic melanoma: immunotherapy, which targets the host, and targeted therapy, which targets the tumors.

There may be numerous combinations of treatment options at the beginning of therapy, but once patients experience disease progression, the options become more limited, Dr. Puzanov says.

Inhibition of BRAF(V600E) has demonstrated anti-melanoma activity in both cell and animal-based models (Tsai J, Lee JT, Wang W, et al. *Proc Natl Acad Sci U S A*. 2008;105(8):3041-3046).

A pivotal phase 3 trial in 2010 compared vemurafenib with dacarbazine in 675 patients with metastatic melanoma. The BRAF inhibitor produced significant gains in terms of the relative reduction in the risk of either death or disease progression. In addition, vemurafenib-treated patients had greater progression-free survival (Chapman PB, Hauschild A, Robert C, et al. *N Engl J Med*. 2011;364(26):2507-2516).

Optimizing the impact of the BRAF inhibitor in patients with metastatic melanoma will require investigation to find the best dosing regimen to achieve objectives such as regression and stasis, according to Dr. Puzanov.

Anticipating AEs

A limitation of BRAF inhibitor therapy with vemurafenib or dabrafenib, another highly selective

BRAF INHIBITORS see page 47

Quotable

"Mathematical proof ... supports the reality of the current melanoma epidemic."

Darrell Rigel, M.D.
New York

On evidence of an epidemic of melanoma

See story, page 42

Melanoma **deadlier** for young **men** than for women

DT Extra

Young men with melanoma are up to 55 percent more likely to die of the disease than women in the same age group, according to researchers from Stanford University, Palo Alto, Calif. They analyzed survival rates in 26,107 adolescent and young adult patients with primary invasive melanoma of the skin. Among those patients, 1,561 died from melanoma, with adolescent and young adult males accounting for 63.6 percent of melanoma-specific deaths. Males were 55 percent more likely to die from melanoma than female patients of the same age.

Source: *JAMA Dermatology*

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Please see Brief Summary of Prescribing Information.

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CURBING DISEASE

Primary, secondary prevention address melanoma epidemic

By Ilya Petrou, M.D.
Senior Staff Correspondent

Miami Beach, Fla. — The epidemic of melanoma is real and the alarming increase in the incidence of the disease is worrisome. While new and evolving therapies for melanoma are continually being researched and come to light, one expert says efforts in primary and secondary prevention must be stepped up to get a better handle on this deadly form of skin cancer.

"There are several groups that suggest the current epidemic in melanoma to be fiction, and they try to back their claims with different arguments. However, their hypotheses remain just that, as there is compelling evidence that support the reality of the ongoing epidemic in melanoma," says Darrell S. Rigel, M.D., clinical professor of dermatology, Ronald O. Perelman department of dermatology, New York

QUICK READ

The epidemic of melanoma is real. Increased efforts must be taken in terms of primary and secondary prevention in order to help curb the rising incidence of this disease.

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BRIEF SUMMARY

1 INDICATIONS AND USAGE
Locoid Lotion is a corticosteroid indicated for the topical treatment of mild to moderate atopic dermatitis in patients 3 months of age and older.

4 CONTRAINDICATIONS
None.

5 WARNINGS AND PRECAUTIONS
5.1 Hypothalamic-pituitary-adrenal (HPA) Axis Suppression Systemic effects of topical corticosteroids may include reversible HPA axis suppression, manifestations of Cushing's syndrome, hyperglycemia, and glucosuria.
Studies conducted in pediatric subjects demonstrated reversible HPA axis suppression after use of Locoid Lotion. Pediatric patients may be more susceptible than adults to systemic toxicity from equivalent doses of Locoid Lotion due to their larger skin surface-to-body-mass ratios *[see Use in Specific Populations (8.4)]*.
Patients applying a topical corticosteroid to a large surface area or to areas under occlusion should be considered for periodic evaluation of the HPA axis. This may be done by using cosyntropin (ACTH1-24) stimulation testing (CST).
If HPA axis suppression is noted, the frequency of application should be reduced or the drug should be withdrawn, or a less potent corticosteroid should be substituted. Signs and symptoms of glucocorticosteroid insufficiency may occur, requiring supplemental systemic corticosteroids.
5.2 Concomitant Skin Infections If skin infections are present or develop, an appropriate antifungal, antibacterial or antiviral agent should be used. If a favorable response does not occur promptly, use of Locoid Lotion should be discontinued until the infection has been adequately controlled.
5.3 Skin Irritation Locoid Lotion may cause local skin adverse reactions *[see Adverse Reactions (6)]*.
If irritation develops, Locoid Lotion should be discontinued and appropriate therapy instituted. Allergic contact dermatitis with corticosteroids is usually diagnosed by observing a failure to heal rather than noticing a clinical exacerbation. Such an observation should be corroborated with appropriate patch testing.

6 ADVERSE REACTIONS
The following adverse reactions are discussed in greater detail in other sections of the labeling:
- HPA axis suppression. This has been observed in pediatric subjects using Locoid Lotion *[see Warnings and Precautions (5.1) and Use in Specific Populations (8.4)]*
- Concomitant skin infections *[see Warnings and Precautions (5.2)]*
- Skin irritation *[see Warnings and Precautions (5.3)]*

6.1 Clinical Trials Experience The safety data derived from Locoid Lotion clinical trials reflect exposure to Locoid Lotion twice daily for up to four weeks in separate clinical trials involving pediatric subjects 3 months to 18 years of age and adult subjects 18 years and older with mild to moderate atopic dermatitis. Because clinical trials are conducted under widely varying conditions, the adverse reaction rates observed cannot be directly compared to rates in other clinical trials and may not reflect the rates observed in clinical practice.
Adverse reactions shown in the tables below include those for which there is some basis to believe there is a causal relationship to Locoid Lotion. Although the rates of application site reactions in the vehicle group were greater than those in the Locoid group in both studies, these rates are included in the tables (Table 1 and Table 2) because skin irritation is a known adverse reaction of topical corticosteroids.
TABLE 1. Frequency of adverse reactions in pediatric subjects with mild to moderate atopic dermatitis

	Locoid Lotion (n=139) n (%)	Vehicle (n=145) n (%)
Application site reactions, including application site burning, pruritus, dermatitis, erythema, eczema, inflammation, or irritation	2 (1)	20 (14)
Infantile acne	1 (1)	0 (0)
Skin depigmentation	1 (1)	0 (0)

TABLE 2. Frequency of adverse reactions in adult subjects with mild to moderate atopic dermatitis

	Locoid Lotion (n=151) n (%)	Vehicle (n=150) n (%)
Application site reactions, including application site burning, dermatitis, eczema, erythema, or pruritus	5 (3)	7 (5)

The following additional local adverse reactions have been reported infrequently with topical corticosteroids, and they may occur more frequently with the use of occlusive dressings and higher potency corticosteroids. These reactions included: irritation, folliculitis, acneiform eruptions, hypopigmentation, perioral dermatitis, allergic contact dermatitis, secondary infection, skin atrophy, striae, miliaria and telangiectasia.

7 DRUG INTERACTIONS
There are no known drug interactions with Locoid Lotion.

8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy Pregnancy Category C. Corticosteroids have been shown to be teratogenic in laboratory animals when administered systemically at relatively low dosage levels. Some corticosteroids have been shown to be teratogenic after dermal application in laboratory animals.
There are no adequate and well-controlled studies in pregnant women. Therefore, Locoid Lotion should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.
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 human milk. Because many drugs are excreted in human milk, caution should be exercised when Locoid Lotion is administered to a nursing woman.
8.4 Pediatric Use Safety and efficacy in pediatric patients below 3 months of age have not been established.
Because of higher skin surface-to-body-mass ratios, pediatric patients are at a greater risk than adults of HPA axis suppression when they are treated with topical corticosteroids. They are therefore also at a greater risk of glucocorticosteroid insufficiency after withdrawal of treatment and of Cushing's syndrome while on treatment.
8.5 Geriatric Use Clinical studies of Locoid Lotion did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects.

17 PATIENT COUNSELING INFORMATION
Patients using Locoid Lotion should receive the following information and instructions:
- Apply a thin layer to the affected skin two times daily.
- Rub in gently.
- Discontinue Locoid Lotion when control is achieved.
- Do not use for longer than 4 weeks.
- Avoid contact with the eyes.
- Do not bandage, otherwise cover, or wrap the affected skin area so as to be occlusive unless directed by your physician.
- Do not use Locoid Lotion in the diaper area, as diapers or plastic pants may constitute occlusive dressings.
- Do not use Locoid Lotion on the face, underarms, or groin areas unless directed by your physician.
- If no improvement is seen within 2 weeks, contact your physician.
- Do not use other corticosteroid-containing products while using Locoid Lotion without first consulting your physician.

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BS-LOL Rev 09/12

University School of Medicine, New York.

Some physicians claim the rise in incidence of melanoma is just artifact, Dr. Rigel says, noting that the primary increase is mostly occurring with thin lesions. These skeptics argue that because dermatologists are much more focused on finding primary melanoma lesions — and/or that pathologists are loosening their diagnostic criteria and may be more inclined to commit to a melanoma diagnosis when evaluating a suspicious lesion — more melanoma lesions are being detected earlier as a result.

Reviewing cases

Speaking against the argument of changes in the interpretation of histological criteria in malignancy, Dr. Rigel cites a study in which 2,665 pigmented lesion cases from 1930 to 1980 were reviewed by pathologists from Australia, France, Italy, New Zealand, Norway, Sweden, the U.K., Russia and the U.S. (Van Deresch EP, Muir CS, Nectoux J, et al. *Int J Cancer.* 1991;47(4):483-489). All pathologists were blinded to the actual diagnosis of the lesions evaluated, which included junctional and intradermal pigmented nevi, as well as malignant melanoma.

Results of the study showed that there was a 2.6 percent net shift of cases from malignant to benign, suggesting that the pathologists, irrespective of geographic location, are using common criteria.

"Their findings clearly argue against changes in histological interpretation as being responsible for the continuous increase of some 3 percent to 8 percent per year observed in malignant melanoma incidence," Dr. Rigel says.

The rising incidence in melanoma also cannot be explained by increased awareness, and the screening and surveillance programs currently in place. According to Dr. Rigel, there have been significant increases in melanoma incidence rates observed in many different countries worldwide. Even in countries with a low frequency of melanoma that have not had organized early detection programs in place — such as in the U.S. — Dr. Rigel says increased numbers of melanoma have been reported.

Rate continues to rise

Skeptics of the melanoma epidemic also argue that many more melanomas are being diagnosed perhaps because of the increase in the number of biopsies being performed. According to Dr. Rigel, an equally if not more plausible theory would be that there are simply more suspicious lesions that are being scrutinized, which actually turn out to be melanomas, and that is why the biopsies are being performed in the first place.

2.6 PERCENT net shift of cases from malignant to benign

It may be true that the majority of diagnosed melanoma cases are thin lesions, Dr. Rigel says; however, the absolute number of thick melanoma lesions also continues to rise. Some may argue that melanoma *in situ* is being over-diagnosed; however, it is interesting that none of the skeptics seem to be arguing that invasive melanoma is being over-diagnosed, which, according to Dr. Rigel, is telltale of the true epidemic in melanoma.

Another argument supporting the current melanoma epidemic is that although the survival rate of melanoma is improving, meaning that lesions are detected earlier, leading to higher survival rates after appropriate therapy, Dr. Rigel says the mortality rate is still rising.

"The only way that the survival percentage can be increasing at the same time that the mortality rate is also increasing, is that the incidence has to be increasing even faster. That is mathematical proof that supports the reality of the current melanoma epidemic," he says.

While research is still looking for a silver bullet therapy to treat melanoma, Dr. Rigel says efforts in primary and secondary prevention must be increased significantly. Currently, the five-year survival rate is approximately 93 percent for patients with invasive melanoma, which, according to Dr. Rigel, is very likely due to early detection. Stepping up primary prevention measures coupled with an even higher awareness for early detection could be key in bringing the incidence of melanoma down.

"While practicing strict primary prevention can help bring down the incidence of melanoma, secondary prevention or early detection can significantly impact mortality," he says. "Though much has been accomplished in primary and secondary prevention, there is still room for improvement and ideally, efforts should be focused in both of these areas." **DT**

"Secondary prevention or early detection can significantly impact mortality."

Darrell Rigel, M.D.
New York.

Disclosures: Dr. Rigel reports no relevant interests.

POTENTIAL FOR SEQUENTIAL

PD-1, PD-L1 pathway inhibition represent melanoma treatment strategy

By Louise Gagnon
Staff Correspondent

Banff, Alberta — New research suggests that there are some potential predictive biomarkers relating to the efficacy and toxicity of emerging treatments for metastatic melanoma.

Speaking here at the annual Canadian Melanoma conference, Jeffrey Weber, M.D., Ph.D., a medical oncologist and director of the Donald A. Adam Comprehensive Melanoma Research Center, Moffitt Cancer Center, Tampa, Fla., discussed the potential for sequential treatment of metastatic melanoma that will have a significant impact on the number of responders to treatment.

"They (ipilimumab and anti-PD-1 antibody) appear to have two separate modes of action, and you can fail one and respond to another, which would set up a sequential strategy which would make sense and which everyone is interested in now," Dr. Weber says.

Studies are pointing to the importance of the programmed death-1 (PD-1) pathway and antibodies that target the PD-1 pathway. There is recognition that PD-1, a checkpoint protein expressed on T lymphocytes, plays a key role in immune tolerance.

Data are suggesting that PD-1 and PD-L1 pathway inhibition are clinically effective strategies to manage disease, and some have even put forth the idea that immunotherapy that targets the PD-1 pathway may serve as the backbone of cancer treatment in the future.

Study results

Research presented at last year's scientific meeting of the American Society of Clinical Oncology (ASCO) revealed about a third of metastatic melanoma patients, who had failed at least one other therapy but had not received ipilimumab (Bristol-Myers Squibb), had an objective response, either partial or complete, with the administration of a PD-1 antibody.

"We have now shown that it is safe to give (anti) PD-1 antibody after ipilimumab, which provoked a newly initiated international phase 3 study of PD-1 versus chemotherapy in patients that have failed ipilimumab," Dr. Weber says. "We have defined further a number of biomarkers for outcomes with (anti) PD-1 antibodies as part of our trial."

Recent data indicate an association between PD-L1 expression and clinical outcome. More specifically, metastatic lesions that were positive for PD-L1 were linked to improved survival in patients with stage 3 and stage 4 melanoma. Lesions were biopsied and immunohistochemical staining was performed to detect whether lesions were positive or negative for PD-L1 (Taube JM, Anders RA, Young GD, et al. *Sci Transl Med*. 2012;4(127):127ra37).

"You can treat patients with the vaccine and the PD-1 antibody and can define endpoints relating to changes in antigen-specific T cells and T-regulatory cells," Dr. Weber adds.

Unknown adverse effects

The possibility for sequential or simultaneous treatment may mean that patient response rates rise from 15 to as high as 50 percent, but the side effect profile of the sequential or simultaneous regimens remain to be determined, Dr. Weber says. "The question is what will the toxicity look like," he says.

Ipilimumab and an anti-PD-1 antibody have not been compared head-to-head, but the toxicities associated with ipilimumab and an anti-PD-1 antibody are different, which stands to reason given they target different biological pathways. Mild infusion reactions have been more frequently reported with the use of an anti-PD-1 antibody. Severe colitis has been reported with the use of ipilimumab, but it is infrequent in patients who have been administered an anti-PD-1 antibody.

Other anti-PD-1 antibodies being explored include Merck's MK-3475, which, like BMS-936558, is being tested in patients who have failed ipilimumab, Dr. Weber notes. The limitation of the sequential treatment approach is that patients who have a history of autoimmune disease or who have conditions requiring immunosuppressive therapies are not suitable candidates.

The next step in treating metastatic melanoma will be the application of checkpoint protein inhibition to adoptive cell therapies, Dr. Weber says. DT

Disclosures: Dr. Weber has received honoraria from Bristol-Myers Squibb for his attendance at advisory board meetings.

QUICK READ

Ongoing research suggests therapies that involve the PD-1 and PD-L1 pathways may be offered to patients with metastatic melanoma.

There is **recognition that PD-1**, a checkpoint protein expressed on T lymphocytes, **plays a key role in immune tolerance**.

The Importance of the Unique MetroGel® (metronidazole) Gel 1% HSA-3® Vehicle on Skin Barrier Function for Patients With Rosacea

COMPROMISED SKIN BARRIER OF ROSACEA PATIENTS

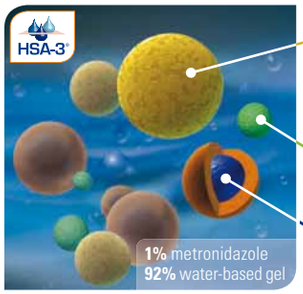
The skin of patients with rosacea is extremely sensitive and sufferers frequently experience physical discomfort, burning sensation, facial itching, stinging, and swelling.[1-4] Research shows that a deficient stratum corneum (SC) may be responsible for many of the signs and symptoms of rosacea. It is essential to select a topical rosacea treatment that enhances SC barrier function as it may help improve skin sensitivity and reactivity, and help reduce sensory rosacea symptoms such as facial burning/stinging.[1,4,5]

THE IMPORTANCE OF THE VEHICLE IN TOPICAL ROSACEA TREATMENT SELECTION

The vehicle of a topical rosacea therapy can be as important as the active ingredient. In fact, **the vehicle may account for 50% to 75% of treatment efficacy**. The vehicle should: **1. Maintain activity of the medication; 2. Repair and/or not further damage the skin barrier; 3. Allow penetration of the active ingredient; 4. Deliver the correct dose; 5. Be easy to use and well tolerated**. A vehicle that carries out all of these activities will help optimize the efficacy and tolerability of the therapy, which may help increase patient comfort and compliance.[1,2]

THE TECHNOLOGICALLY ADVANCED METROGEL 1% HSA-3 VEHICLE PROVIDES MOISTURIZING BENEFITS

MetroGel 1% is the only topical rosacea treatment with a vehicle that contains HSA-3—the hydrosolubilizing agents niacinamide, propylene glycol, and beta cyclodextrin (betadex)—to help protect the skin barrier and facilitate drug delivery.[1]



Niacinamide (vitamin B3) is believed to have broad effects in facilitating normal skin metabolism. Niacinamide has been shown to improve skin barrier function by increasing epidermal lipid and protein production, reducing transepidermal water loss (TEWL) and increasing the skin's resistance to common irritants and barrier-damaging agents. Niacinamide is an essential component of metabolic pathways involved in both cellular survival and cellular death, and has been shown to improve skin texture, blotchiness, and uneven pigmentation.[1,2,6]

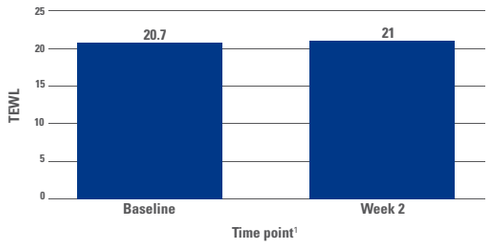
Propylene glycol promotes permeation and penetration of the SC by diffusing into the SC and changing the skin's solubility properties. It has been shown that propylene glycol is important for maximizing metronidazole penetration through the SC.[2,7-9]

Betadex has a polyhydric hydrophilic exterior, resulting in good water solubility and skin moisturization, and helps to reduce irritation after topical drug administration.[1,2]

METROGEL 1% IN UNIQUE HSA-3 VEHICLE HELPS PROTECT BARRIER FUNCTION

A study* evaluating the impact this topical treatment has on skin barrier function demonstrated that MetroGel 1% and its novel HSA-3 vehicle did not damage the skin barrier and may have additional barrier-enhancing effects on skin. This was evidenced by no increase in TEWL and no decrease in corneometry (skin hydration).[1]

The study revealed no damage to the skin barrier following 2 weeks of treatment with MetroGel 1%, as reflected by no worsening of TEWL or corneometry measurements. In fact, there was a trend toward statistically significant improvement in skin corneometry at the end of the 2-week study period (P=.052).[1]



> *Studies have shown the scientifically advanced HSA-3 vehicle of MetroGel 1% does not disrupt the already compromised skin barrier and may enhance barrier function by increasing skin hydration. This may help reduce skin sensitivity, burning, stinging, and other symptoms of rosacea.*
>
> —*Patricia K. Farris, MD*
> *Metairie, Louisiana*

HSA-3: NOT ALL VEHICLES ARE CREATED EQUALLY

The technologically advanced vehicle of MetroGel 1% does more than simply function as an inert drug carrier; this active vehicle has increased hydration and no disruption of the skin barrier, which enhances this topical treatment. Generic forms of the active drug are available but the vehicles are not standardized, which may change the efficacy and tolerability of a product.[1,2]

CONCLUSION

MetroGel 1% is the only topical rosacea therapy in a measured-dose pump with the scientifically advanced HSA-3 vehicle—providing a combination of efficacy, tolerability, and convenience for rosacea patients. There is no generic substitute for MetroGel 1% 55-gram Pump.[1,2,10]

Important Safety Information

Indication: METROGEL® 1% is indicated for the topical treatment of the inflammatory lesions of rosacea. **Adverse Events:** In controlled clinical studies, the most commonly reported adverse events (>2%) in patients treated with METROGEL® 1% were nasopharyngitis, upper respiratory tract infection, and headache. Other adverse experiences reported when using topical metronidazole include skin irritation, transient redness, metallic taste, tingling or numbness of the extremities and nausea. **Warnings/Precautions:** METROGEL® 1% should not be used by patients who are allergic to metronidazole or any ingredient in METROGEL® 1%. Avoid contact of METROGEL® 1% with the eyes as it may cause tearing. METROGEL® 1% should be used with caution in patients with evidence of, or a history of, blood dyscrasia, and with patients taking blood thinning agents as they may experience prolonged prothrombin times. METROGEL® 1% treatment should be discontinued if numbness or paresthesia of any extremity should occur.

You are encouraged to report negative side effects of prescription drugs to the FDA.
Visit *www.fda.gov/medwatch* or call 1-800-FDA-1088.

Please see brief summary of Prescribing Information on adjacent page.

*A total of 25 female subjects ranging from 20 to 75 years of age with mild to moderate rosacea were assessed by the investigator to determine the effect of MetroGel 1% in the HSA-3 vehicle on skin barrier function.[1]

Dr Farris is a paid consultant for Galderma Laboratories, L.P.

IMPORTANT INFORMATION ABOUT

METROGEL®

(metronidazole) gel, 1%

BRIEF SUMMARY

This summary contains important information about METROGEL Gel. It is not meant to take the place of your doctor's instructions. Read this information carefully before you start taking METROGEL Gel. Ask your doctor or pharmacist if you do not understand any of this information or if you want to know more about METROGEL Gel. For full Prescribing Information and Patient Information please see the package insert.

WHAT IS METROGEL GEL?

METROGEL® (metronidazole) Gel, 1% is a prescription topical medication to treat the bumps and blemishes (inflammatory lesions) on the face caused by a condition called rosacea.

WHO IS METROGEL GEL FOR?

METROGEL Gel is for use in adults. The safety and effectiveness of METROGEL Gel in pediatric patients has not been established.

You **should not** use METROGEL Gel if you are allergic to metronidazole or to any other ingredient of the formulation. If you are not sure, talk to your doctor or pharmacist.

WHAT SHOULD I TELL MY DOCTOR BEFORE USING METROGEL GEL?

Tell your doctor about all your health conditions and medications, especially if you

- are pregnant or planning to become pregnant.
- are breastfeeding.
- have or had a central nervous system disease.
- have a blood disorder.
- are taking blood thinners (anticoagulants).

WHAT SHOULD I AVOID WHILE USING METROGEL GEL?

Topical metronidazole has been reported to cause tearing of the eyes. Therefore, contact with the eyes should be avoided.

WHAT ARE THE MOST COMMON SIDE EFFECTS OF METROGEL GEL?

The most common side effects of METROGEL Gel are

- sore throat / nasal congestion.
- upper respiratory tract infections.
- headaches.

METROGEL GEL may also cause

- skin irritation.
- transient redness.
- metallic taste.
- tingling or numbness of extremities.
- nausea.
- tearing of the eyes.

These are not all of the possible side effects of METROGEL Gel. For more information, ask your doctor or pharmacist.

You are also encouraged to report negative side effects of prescription drugs to the FDA. Visit *www.fda.gov/medwatch* or call 1-800-FDA-1088. You may also contact GALDERMA LABORATORIES, L.P. AT 1-866-735-4137.

HOW SHOULD I USE METROGEL GEL?

- Use METROGEL Gel exactly as prescribed by your doctor.
- Unless you have been instructed otherwise, apply and rub in a thin film of METROGEL Gel once daily to affected area(s).
- A gentle cleanser should be used before the application of METROGEL Gel.
- Cosmetics may be applied after the application of METROGEL Gel.
- For external use only. Not for oral, ophthalmic or intravaginal use.

WHERE SHOULD I GO FOR MORE INFORMATION ABOUT METROGEL GEL?

- Talk to your doctor or pharmacist
- Go to **www.metrogel.com** or call **1-866-735-4137**

GALDERMA LABORATORIES, L.P.,
Fort Worth, Texas 76177 USA

Revised: February 2013

References: 1. Draelos ZD. Assessment of skin barrier function in rosacea patients with a novel 1% metronidazole gel. *J Drugs Dermatol.* 2005;4(5):557-562. **2.** Jackson JM, Pelle M. Topical rosacea therapy: the importance of vehicles for efficacy, tolerability and compliance. *J Drugs Dermatol.* 2011;10(6):627-633. **3.** National Rosacea Society. New survey documents prevalence of burning, stinging and itching. *Rosacea Review.* http://www.rosacea.org/rr/2006/winter/article_3.php. Accessed April 3, 2013. **4.** Farris PK. Skin care based on science: improving outcomes in rosacea. *Cosmetic Dermatol.* 2012;25(2):72-78. **5.** National Rosacea Society. Treating rosacea and seborrhea. *Rosacea Review.* http://www.rosacea.org/rr/2012/summer/article_4.php. Accessed April 3, 2013. **6.** Bissett D. Topical niacinamide and barrier enhancement. *Cutis.* 2002;71:8-12. **7.** Otto A, du Plessis J, Wiechers JW. Formulation effects of topical emulsions on transdermal and dermal delivery. *Int J Cosmet Sci.* 2009;31:1-19. **8.** Fisher AA. Reactions to popular cosmetic humectants. Part III. Glycerin, propylene glycol, and butylene glycol. *Cutis.* 1980;26:243-244, 269. **9.** Wagner N, Berthaud C, Laffet G, Caron JC. Differential penetration of skin by topical metronidazole formulations. *Adv Ther.* 1998;15:197-205. **10.** Data on file. Galderma Laboratories, L.P.

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"The process of accessing [isotretinoin] has become increasingly legislated and regulated. But there's really nothing like it in terms of efficacy for acne."

Shannon Humphrey, M.D.
page 26

BRAF INHIBITORS:

Detection of BRAF and mutations transforms cancer treatment

from page 40

RAF inhibitor, is the development of cutaneous adverse events such as keratoacanthomas, with some side effects developing as early as one week after initiation of therapy (Chu EY, Wanat KA, Miller CJ, et al. *J Am Acad Dermatol*. 2012;67(6):1265-1272).

Other side effects that have been reported with BRAF inhibitor therapy include rash, photosensitivity, fatigue, pruritus, fever, elevated liver function tests, and palmar-plantar dysesthesia.

A survey of physicians' perceptions about unmet needs in the treatment of metastatic melanoma presented at this year's annual meeting of the American Society of Clinical Oncology in Chicago found the majority of respondents, consisting of oncologists and dermatologists, had used ipilimumab and vemurafenib and cited toxicity and tolerability as challenges with these treatments.

Toxicity and tolerability of treatments is of particular concern in pediatric patients. A current study is enrolling patients with surgically incurable melanoma that harbors BRAF(V600) mutations.

The study will examine various dose cohorts in patients ages 12 to 17 being treated with vemurafenib. The goal is to determine the maximum tolerated dose/recommended dose, as well as the efficacy and tolerability of vemurafenib in these patients. The amount of dosage administered daily will vary depending on the weight of the patient.

While BRAF inhibitors are very effective when they are administered, patients typically develop resistance to the therapies within a year. Resistance is brought on by several means including activation of alternative signaling pathways and reactivation of the MAP kinase pathway.

Battling resistance

Faced with the challenge of resistance, clinicians are devising other treatment strategies such as adding immunotherapy in the form of ipilimumab, anti- PD-1/PDL-1 antibodies, PEG-IFN with or without another targeted therapy such as a MEK inhibitor.

Future combination regimens will likely be based on mechanisms of resistance and/or activation of oncogenic pathways. Anti-angiogenic agents such as bevacizumab may possibly be part of the combination treatments.

To respond to the issue of resistance that develops to BRAF inhibitor therapy, investigators are studying *in vitro* modeling of resistance using patient tumor or peripheral blood circulating tumor cells, with a goal to develop promising therapies to overcome the challenge of resistance.

"BRAF kinase is an **important** mediator of **cellular proliferation.**"

Igor Puzanov, M.D.
Nashville, Tenn.

Monitoring response and monitoring relapse would be part of the strategy to avoid or delay the development of resistance. The use of circulating tumor cells instead of serial tumor biopsies would also be beneficial if the cells prove comparable in their resistance mechanisms. DT

Disclosures: Dr. Puzanov is a consultant for Roche, Genentech and GlaxoSmith-Kline.

Dermatology Times

ACOs: Taking aim at the economic impact

By Beth Thomas Hertz
Staff Correspondent

The payer system is changing and physicians face a fundamental choice when it comes to joining an accountable care organization (ACO) — get involved now and influence the outcome, or simply abdicate the role and let hospitals and payers determine the future.

That's the message from Randall Curnow, M.D., M.B.A., chief medical officer, Summit Medical Group based in Tennessee. Still, although even nationally recognized Harvard Business School professor Clayton Christensen and others predict the model will ultimately fail, the ACO trend is changing healthcare delivery. And the number of ACOs keeps climbing.

In March 2012, hospital-led ACOs outnumbered those headed by doctors nearly two to one (91 to 45), says Neil Kirschner, Ph.D., senior associate of regulatory and insurer affairs for the American College of Physicians (ACP). But with the latest round of ACO approvals from the Centers for Medicare and Medicaid Services (CMS) earlier this year, physician-led organizations pulled ahead of hospitals (202 to 189).

While physician-led ACOs are currently the most numerous, however, they are generally smaller than those run by hospitals. According to CMS, roughly half of all ACOs are physician-led organizations that serve fewer than 10,000 beneficiaries. About 20 percent of ACOs include community health centers, rural health clinics, and critical access hospitals that serve low-income and rural communities.

Physician-led ACOs continue to grow

"If physicians want to play a role in delivery reform, ACO participation will be a necessity," Dr. Curnow says. "A passive ACO philosophy will allow hospitals and payers to dictate the future to physicians."

Another force pushing physicians to form ACOs comes from Medicare, which offers ways to participate that have all the upsides of being in an ACO with no financial risk if they don't achieve savings, says Thomas Merrill, a senior analyst at Leavitt Partners. This lack of risk appeals to physicians wanting to enter the market cautiously, he says. However, he calls the resulting growth of physician-led ACOs a tricky proposition. "Their numbers seem to be equal to hospital-led groups but Medicare is distorting this. The groups are not equal on a commercial-contract basis," he says. Many are slowly adding commercial contracts, having used Medicare as a "safe way to get started," he says.

Another factor driving physicians to form ACOs, Dr. Kirschner says, is that physician-led groups achieve savings differently than ones owned by hospitals. Physician groups work to save money by keeping patients out of the hospital by taking better care of them upfront. Hospital-led ACOs focus on better managing patients once they are admitted.

"Physician groups may have more freedom to work out how to succeed in a shared savings plan than a hospital," Dr. Kirschner says.

As some physician groups have experienced success in a patient-centered medical home model, they have learned the skills that are necessary to succeed as an ACO, he adds.

In fact, the National Committee for Quality Assurance (NCQA) recently launched a program to acknowledge specialty practices that work well with primary care physicians (PCPs). The Patient-Centered Specialty Practice Recognition recognizes specialty practices that successfully coordinate care with PCPs and each other and that meet the goals of providing timely access to care and continuous quality improvement, according to the NCQA website.

The site says the program also

ACOS see page 54

Quotable

"It shouldn't be a novel. A handbook should state the policies that apply to the employees, and that's it."

Kristin Erenburg, J.D.
Cleveland

On employee handbook best practices

See story, page 50

Physicians use tablets to access EHRs

DT Extra

The mobile revolution has reached a tipping point, according to a recent survey conducted by AmericanEHR Partners. About 51 percent of the 1,400 physician respondents are using tablets to access electronic health records (EHRs). This is in contrast to 7 percent who report using smartphones. Rather, most of the doctors report using smartphones at least once weekly to communicate with other physicians (75 percent) and to research medications (70 percent).

Source: *Medical Economics*

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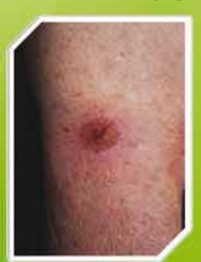

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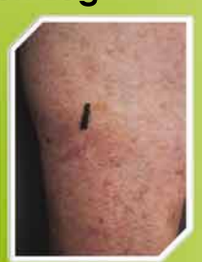

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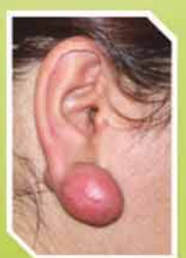
Earlobe Keloid



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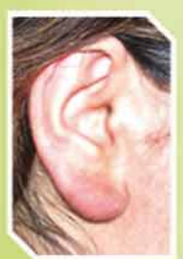

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Best practices for EMPLOYEE HANDBOOKS

By Rachael Zimlich
Staff Correspondent

Employee handbooks should be simple and to-the-point. Outline the practice's most salient expectations and legal obligations when creating them, experts say.

"Some people treat a handbook like 'The Grapes of Wrath.' It shouldn't be a novel," says labor relations attorney Kristin Erenburg, J.D., of Walter Haverfield in Cleveland. "A handbook should state the policies that apply to the employees, and that's it."

A handbook should offer a simple overview of an employer's expectations and legal obligations, an employees' rights, and it also should describe what an employee can expect from his or her employment with the company. The more detail included, she says, the more changes and addendums will be required as benefits change. This could mean trouble if an employer does not make those updates, Ms. Erenburg says.

What to include

Lori Christenson, P.H.R., human resources coordinator for Clayton L. Scroggins Associates, a management consulting agency for doctors, says she generally suggests including:

- a general disclaimer;
- a statement of the business' goals and missions;
- appropriate employee definitions;
- a description of the company work week;
- sexual harassment, disability, and medical leave policies;
- a statement of employee benefits; and
- an outline of the company's discipline policies.

Ms. Erenburg adds these suggestions:

- an at-will statement explaining the nature of the employment relationship and how it could be changed;
- a statement that the handbook is general guidance and that it can be changed at the discretion of the employer and without prior written notice; and,
- statements about equal employment and non-discrimination policies;
- family medical, jury duty, and military leave policies; and,
- vacation, holiday, bereavement, sick leave, or other paid time-off policies.
- workplace conduct standards, including policies on workplace violence, anti-harassment, and dress codes;
- employment classifications;
- employee benefits;
- payment schedules and information on timesheets or timekeeping requirements;
- work hours;
- attendance;
- absences;
- reporting late or leaving early;
- policies on information security and personal safety;
- guidelines on the appropriate use of technology; and
- standards for employee breaks.

What to exclude

Omit verbiage related to salaries or payment rates, because this kind of information could be misconstrued as a contract and could cancel out any at-will disclaimers, Ms. Erenburg says.

In litigation, any statements made in a handbook — even ones made with the best intentions — could come back to haunt them, Ms. Erenburg says.

Putting it together

Although guidelines are helpful, Ms. Erenburg advises that employers consult an attorney who specializes in staying up-to-date on labor laws before drafting a handbook. Admitting that this advice sounds self-serving, she says that this step is critical because handbooks are not a "one-size-fits-all" product.

Local governments and states also may have laws that apply to handbooks, so check with them as well before starting the process, she adds.

Once it is created, a handbook should be distributed to employees at the time of hire, Ms. Erenburg says, and the employer should have each employee sign a paper document acknowledging receipt. That goes for updates, too. All but three states have laws on the books that permit electronic signatures on documents, but Ms. Erenburg says that a hard-copy document is still the best bet.

"Some courts really scrutinize whether these people really opened that email," she cautions.

Match policies, actions

In addition to the dos and don'ts of handbook-writing, Mark D. Scroggins, M.S.B.A., C.P.A., C.H.B.C., a management consultant with Clayton L. Scroggins Associates, says physician practices need to remember that although an accurate handbook helps, what happens in a practice is what really matters.

Mr. Scroggins, a *Medical Economics* editorial consultant, says he has witnessed doctors passing out a handbook that says one thing, then adopting a completely different way of handling various benefits.

"What's frustrating for the employees is, they have a 6-year-old signed handbook, but the doctor changed procedures since then," he says. Often, the employees will ask which practice they are supposed to follow.

The handbook is not a legal document, Mr. Scroggins adds. Sometimes a doctor's actions may not match the handbook, but the practice's leaders must be consistent for all employees, regardless of what the handbook states. For example, if one nurse receives a particular benefit — even if it is not specified in the handbook — then all the nurses should receive the same benefit.

"Try to keep the handbook as general as possible and as flexible in the language as possible," he adds. "That way, the doctor can operate in a greater realm." DT

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Richard J. Quadrino, J.D. The author is a founding partner of Quadrino Schwartz. His practice includes consulting, litigation, trials, and appeals in the areas of insurance litigation and claims, class actions, and business and complex litigation. The law firm has offices in Garden City and New York, New York. Send your legal questions to medec@advanstar.com.

How to challenge and collect on insurance claims denials

ERISA regulations open up new ways for physicians to collect

There are many approaches that can be implemented by doctors and hospitals to maximize their revenue stream by challenging a health insurer's denials of claims in the commercial insurance area. This article focuses on the tools available in the federal law called ERISA that can be used by these medical providers to increase collections.

Using these methods will not only help with collections on current and future claims, but can provide the basis for dusting off piles of older, denied claims that medical providers have forgotten about or written off.

The first task is to get an understanding of how to use Employee Retirement Income Security Act's (ERISA) many rules. Rather than adhering to an insurer or claims administrator's "bulletins," "payment guidelines," or "manual," the focus should be placed on the use of ERISA rules. This accomplishes two things. First, ERISA can actually make the medical provider's in-network provider agreement legally non-binding as to some of the billing or coding rules that are used to deny claims. And second, when ERISA's claims regulations are violated, the provider can argue that the claim decisions are not legally valid and that the claims are immediately payable. When playing on this turf, medical providers will discover new and more effective avenues for getting paid.

In the world of commercial health insurance, nearly all of the insurance polices purchased today are obtained by employers for their employees and families. These group insurance benefits are "employee welfare benefit plans" governed by ERISA. Therefore, no matter what state you practice in, these rules apply to your patients' employer-sponsored health insurance plans. And under the new federal healthcare law, the ERISA claims regulations even apply to claims under plans sponsored by federal, state, and local employees that are typically not governed by ERISA.

1. Preemption of portions of the provider agreement

ERISA provides that once it governs an area, it "preempts"; i.e., it takes over and wipes out all other law that could apply. Thus, on questions of whether a particular claim or service is "covered," it is not the provider agreement, provider manual, or other health insurer created internal rules that apply.

Instead, as the U.S. Supreme Court makes clear, the claims are governed by the employee's health plan document. The health plan documents, adopted by employers and distributed to employees, typically do not address billing or coding issues. Therefore, claims cannot be denied on such grounds because the language of the health plan does not authorize it. And since the health plan is the only document that can define coverage, any internal insurance company rule, guideline, or manual provision that the insurer attempts to use to deny claims is both irrelevant and preempted by ERISA. This concept alone is a "game-changer" that medical providers should employ to challenge improper claim denials.

2. Using ERISA's claims regulations

There are three basic sets of ERISA rules that medical providers need to become familiar with: (1) the timing rules regarding an insurer's response to a claim, (2) the specificity rules as to an insurer's denial in an explanation of benefits (EOB), and (3) the rules that excuse a medical provider's obligation to appeal a claim denial.

Timing: ERISA's regulations provide that a health insurer must respond to a claim within 30 days of receiving it. If the insurance company wants more time to consider the claim, it must notify the medical provider that it needs additional time. If the notification for more time is sent before the 30 days expires, then the insurer gets an additional 15 days. If the health insurer blows either the initial 30-day deadline or an extended deadline, the late-arriving EOB is legally not valid. If a late EOB alleges that a service was not medically necessary, for example, the health insurer can be precluded from asserting that defense to the claim because it was asserted too late. Thus, instead of arguing about medical necessity, how the claim was coded, or whether too many services were allegedly performed in a given visit, the medical provider can simply demonstrate the lateness and demand payment in full.

While there are court decisions that confirm this point, health insurers will likely be reluctant to admit their obligations in this regard, for fear of opening the floodgates. A well armed medical provider, however, who either learns and implements the rules or hires qualified legal counsel, is likely to get the insurer to come to a settlement based on these rule violations.

Specifics required: The ERISA regulations require health insurers to explain the reasons for a claim denial, with specificity. Most EOBs fail this test, and thus they are not legally valid. In addition, if the denial is for an alleged lack of medical necessity, the regulations further require the insurer to provide either "... an explanation of the scientific or clinical judgment for the determination, applying the terms of the plan to the claimant's medical circumstances, or a statement that such explanation will be provided free of charge upon request." Have you ever seen an EOB

INSURANCE CLAIMS see page 58

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ACOS

Whether organizations will lower healthcare costs is up for debate from page 48

addresses reducing the duplication of tests, measuring performance, and improving communication with patients.

Impact on healthcare costs

Mr. Merrill says the question of whether ACOs, particularly physician-led ones, will lower healthcare costs overall is one that is often debated at Leavitt Partners.

"We don't know if the ACO model represents a silver bullet, but they are leading to substantive changes," he says. "We have our doubts that they will lower costs overall but they may slow the growth rates."

One of the greatest changes ACOs represent is a paradigm shift, as providers realize they must provide population-based care, he says.

"They can't just work in silos anymore," Mr. Merrill says. "They need to collaborate with other parts of the healthcare system and physician-led ACOs may have an advantage as doctors listen best to other doctors. They don't like hospitals telling them what to do."

Does ownership matter?

While physician-led groups have some attributes on their side, at least one expert says that ownership of an ACO is not the key that will decide if efficiency goals are realized.

"Physician leadership is not necessarily good or bad. Leadership alone does not dictate the success of an ACO," says Bruce Bagley, M.D., interim president and chief executive officer of TransforMED, a subsidiary of the American Academy of Family Physicians (AAFP).

"If an ACO takes a global payment and does not change how resources are distributed internally, it doesn't matter," he says. "There must be internal incentives to achieve cost effectiveness, quality, and service."

Dr. Bagley says that the ideal structure may be community-led ACOs. Having representation from the community, hospitals, physicians, and business leaders may lead to the most transparent solutions.

"We need resources to be used wisely overall, not just in one group's interest," he says.

Physicians also need to get away from thinking that health plans and providers must have an adversarial relationship, Dr. Bagley adds.

"Some day they will be partners for cost-effective and efficient care that gets the best results for patients. The basic method of payment must change so that there is a shared sense of responsibility for cost, quality, and service," he says. ACOs must be set up for the right reasons, Dr. Bagley adds. They must have strong organizational integrity, optimize outcomes, and be patient-centered.

Unique challenges

Starting any ACO requires a large base of PCPs, solid information technology, and the administrative infrastructure to manage patients more robustly than ever, Dr. Curnow says.

Physician-led ACOs may have the access to PCPs, but the other two can be problematic, he says. These groups may lack the financial means and the historical experience with managing patients in a population-based manner that are required to succeed.

The start-up costs will vary greatly for each group, Mr. Merrill says, but it can be millions of dollars for larger ones. Less will be spent, and it will be spent differently, for smaller ones, he says.

Other obstacles faced by physicians looking to form an ACO include having to create higher levels of collaboration, with both PCPs and specialists, than they are used to. Having professional administration in place to support such necessary functions is a key first step, Dr. Curnow says, as is becoming a patient-centered medical home.

A question of autonomy?

No doubt at least some physicians are seeking to form ACOs out of a desire to have greater autonomy in their work. However, Dr. Bagley believes that many of them will find that autonomy is an impediment to success.

"Physicians should have clear decision-making authority over diagnostic and therapeutic matters (but) that does not mean that everyone just does what they want. Physicians have to agree on best practices, using systems like the electronic health record registries, e-prescribing, and generic drug use. They must standardize treatment to the degree that it is possible," he says.

Dr. Kirschner also sees physician autonomy as a difficult concept.

"Depending on the contractual relationship with the payer, the physician may be freed from various prior authorization and similar administrative hassles. On the other hand, the ACO environment encourages the development of shared treatment protocols that generally must be followed by the participating providers," he says. "These protocols are typically developed by the participating providers and aim to improve efficiency and increase quality and patient safety." It is unclear if physician-led ACOs have more or less leverage in negotiating with third-party payers and hospitals. Variables such as existing competition will matter more than ACO ownership, experts say.

How this differs from capitation

Some physicians are wary of forming or joining ACOs because they remember the failed efforts at capitation that occurred two decades ago. Dr. Curnow stresses, however, that ACOs are different beasts.

"We have so much more technology and resources available to us today to pursue population management," he says. "Also, ACOs emphasize the importance of quality standards. Access to shared savings only comes through the creation of quality metrics, and patient satisfaction is part of that. This is not just about trimming costs."

With capitation, patients were often stuck in a plan. With ACOs, if they are unhappy with the care they receive, they can go elsewhere. This makes ACOs more sustainable and valuable, he says.

Financial models

Many models of funding are being tried for physician-led ACOs, Dr. Curnow says. Some are physician-owned, some are joint ventures with capital partners, and others are integrated systems with primary care as well as specialist ownership. The typical economic model will have patients assigned to an ACO based on their PCP. A benchmark budget will be established, most likely based

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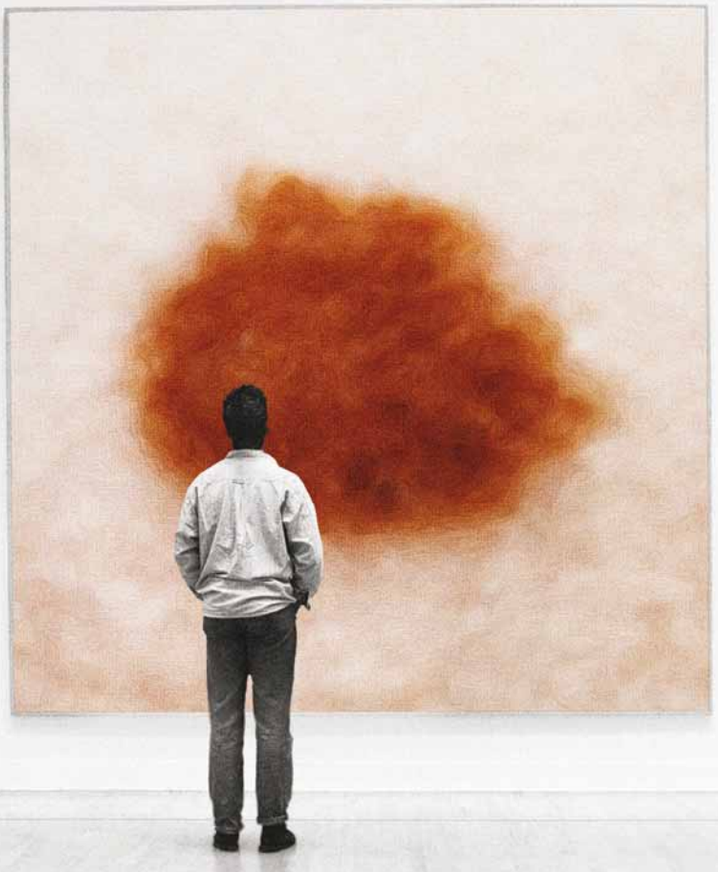

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ACOS

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on recent years' expenditures, and the ACO will need to provide the resources to generate value.

"Fee-for-service is not going anywhere anytime soon. There will always be room for it," he says. "But more and more money will begin to be tied to performance."

Dr. Kirschner says financial arrangements will vary, depending on the model that is being used by the ACO.

"One relatively common sharing arrangement consists of a combination of a portion of the shared revenue shared equally, a second portion based on the productivity of the provider (for example, relative value units produced), and a third portion based on quality measures," he says.

Dr. Bagley agrees there are no fixed rules yet, but says that generally the global payment received by the ACO will be distributed in proportion to the value contributed by each component.

"Each component (such as primary care, specialty care, hospital, imaging, lab, etc.) would have to demonstrate its contribution to the effectiveness and efficiency of the overall enterprise. If they are distributed in the same way they are now, then nothing will happen regarding the cost escalation," he says.

With commercial payers, ACO contracts generally still resemble fee-for-service arrangements but offer incentives for achieving savings, Mr. Merrill adds.

"Most ACOs are built on a fee-for-service chassis," he says. "At the end of the year, they reconcile how much has been saved and bonuses are paid accordingly."

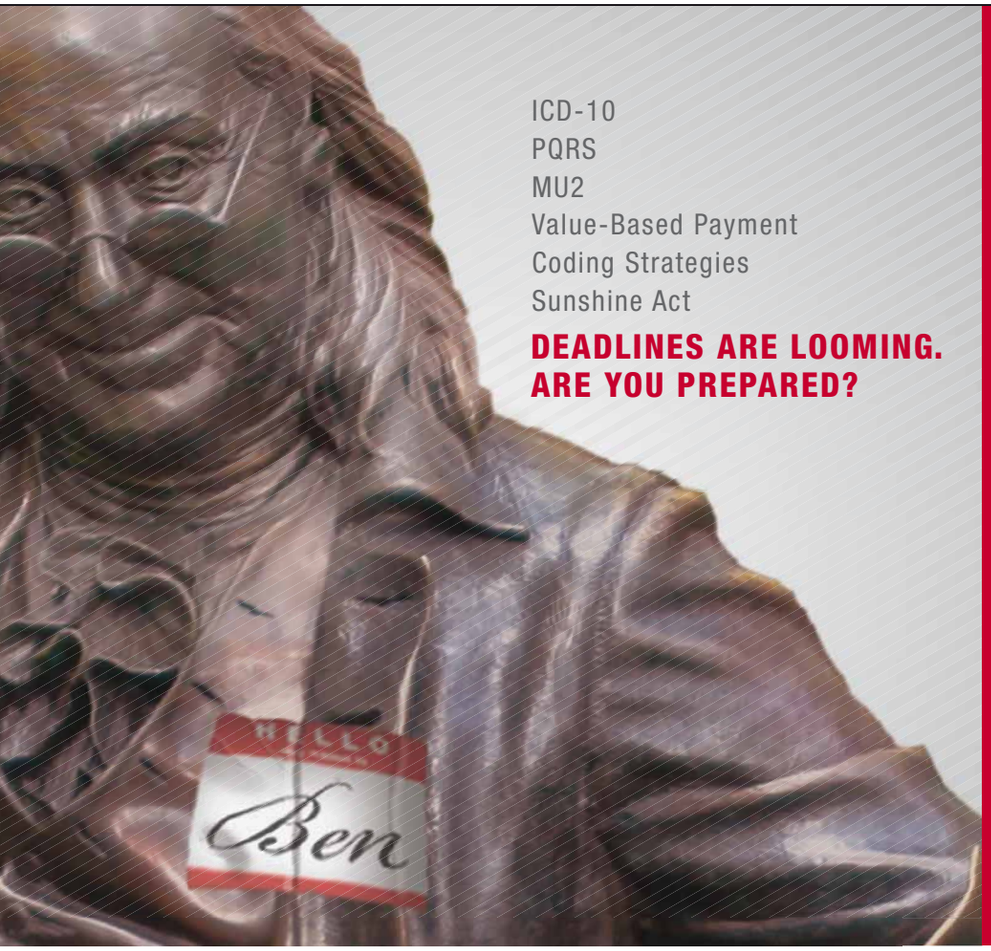
Will physician-led ACOs last?

As for the question of whether physician-led ACOs are sustainable, Dr. Curnow says they show promise.

"They let physicians advocate for the needs of patients, especially if the reimbursement model changes to diminish volume-based payments," he says. "Physician-led groups can be strong, effective advocates for their patients in a way that creates satisfaction, quality, and access. They can yield higher satisfaction for physicians and patients while lowering costs."

Mr. Merrill says, however, that the system of no-risk ACOs is probably not sustainable in the long term. "It is more of a transition and will likely lead to a more shared model of risk in the future," he says.

"The path may not be easy," Curnow says. "A lot of the things we need, such as better EHR technology, are hard to come by," he says. But he encourages physicians not to be dissuaded. "We all need to come to terms with the fact that things are changing and remember why we are doing it. Develop a concrete, transparent plan to get there. It may be a messy transition getting off the hamster wheel of fee for service, but it is worth it, for doctors, for patients, and for society." **DT**



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Cyber insurance now a must for MEDICAL PRACTICES

Large HIPAA violation fines could spell the end

Even if you don't yet use an electronic health record system, the reality is that paper records, portable devices such as smartphones, and employee error all put you and your practice at risk. In the healthcare setting, cases involving medical identity theft are escalating. According to the Ponemon Institute, a leading independent research organization, more than 1.5 million Americans have been affected by medical identity theft at a cost more than $30.9 billion. Ponemon also found in its annual benchmarking report that 52% of healthcare organizations say they experienced one or more incidents of medical identity theft.

Loss prevention

As with most other areas of risk management, an organization's ability to prevent adverse events is based on its people, processes, and technology. Organizations with dedicated information security personnel and those that screen prospective employees will have an edge in preventing unauthorized access to and accidental releases of PHI. Performing background security checks and drug screenings on prospective employees who will have access to health information technology (HIT) systems and infrastructure will help find applicants with criminal records and substance abuse issues. Equally important, these actions will set the tone for the rest of the organization and help create a culture of safety and accountability.

Insurance and liability

Even with the most technologically advanced systems and the most robust risk management program, it is impossible to achieve 100% prevention. Therefore, a growing number of organizations are purchasing "cyber liability" coverage. Towers Watson reports in its 2013 survey of risk and finance managers that the number of organizations purchasing this coverage increased by 11% compared with the previous year.

Insurers such as Axis Insurance, ACE Group, AIG, Beazley, Chubb Group, C.N.A., Ironshore, OneBeacon Insurance Group, and Travelers offer these policies. All of these insurers offer highly customizable policies that can be tailored to focus on those key risks identified in the assessment process. Key coverage considerations:

- Investigation expenses;
- notification and credit monitoring;
- legal liability;
- public relations expenses;
- cyber extortion; and
- regulatory actions (these typically carry a sublimit for covering defense of fines and penalties associated with regulatory actions such as the Health Insurance Portability and Accountability Act (HIPAA).

Most insurers offer a sublimit of coverage to their physician customers. Key national insurers such as the Doctors Company, Medical Protective, Medicus, ProAssurance, and others routinely provide coverage extension, but all practices should investigate the costs and benefits of purchasing a standalone policy to address their unique organization and risk profile.

Under the recently adopted update to HIPAA rules, the fines for PHI violations are high enough to potentially put a small medical practice out of business. That fact alone should make it worthwhile for you to investigate purchasing a cyber insurance policy for your practice. **DT**

INSURANCE CLAIMS:

ERISA regulations open up new ways for physicians to collect from page 52

that complies with this regulation? Probably not. And again, there are consequences for a violation. If the EOB is insufficient, it can be argued that it is the equivalent of no response at all. And no response equals a late response; i.e., a violation of the above 30-day rule. Thus, claims that fail to meet this test are also candidates for a demand for immediate payment, regardless of the true merits of the claim, the patient's condition, or how the billing was coded.

Getting around the appeal requirement: There are many ways in which a medical provider can be excused from the appeal requirement. If the appeal requirement can be excused, then older claim denials that were never appealed are still "alive" and can be pursued for collection. In addition, the provider can also save precious time and resources by avoiding the frustrating process of faxing dozens of pages that get ignored or rejected.

The ERISA claims regulations state that if the claims administrator violates the regulations, then an appeal is not necessary. And that makes sense. For example, if an EOB is vague — and thus violates the regulations — how can a medical provider tender a proper appeal if the true reason for a denial is unknown? Thus, appealing under these circumstances is excused. This rule applies to any type of regulatory violation and can be relied upon to press forward with collection on many of the medical provider's older claims denials that were never appealed.

Medical providers should pursue the use of these rules against the health insurers. Armed with the right tools and represented by qualified ERISA health insurance counsel, medical providers can put together large groups of denied claims and pursue payment in a cost effective manner. **DT**

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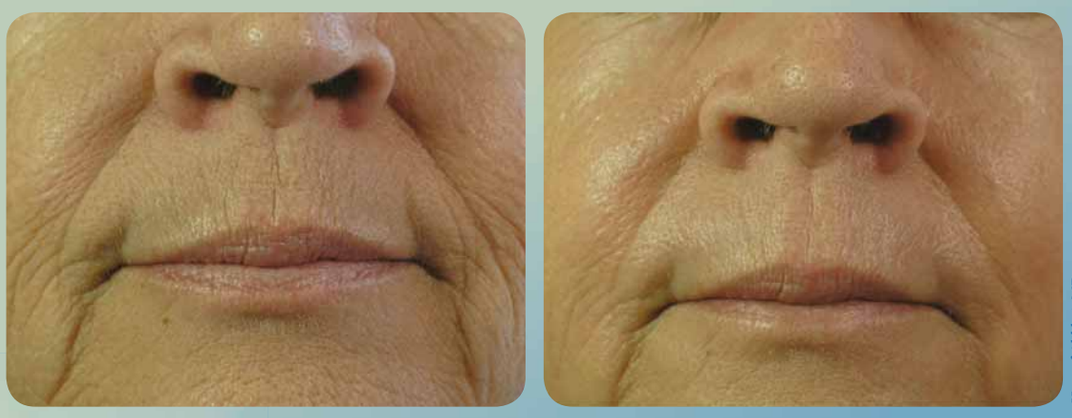

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The financial *contract you should have*

A medical practice owner should spend some of his/her time working *on* the practice, not just *in* the practice. We know this because we have our own practice ourselves. Even if the owner works "on" the practice, however, if they ignore one fundamental legal contract, all of his/her work may be in jeopardy — as a single bad event could wipe out everything they have worked so hard to build.

When a physician dies, his or her family members will only get that doctor's share of the outstanding accounts receivable, if that. The family members will get nothing from a physician's hard work in building the practice — as they typically can't even own the medical practice shares and thus have no way to negotiate any buyout at all.

What about the practice itself? Consider what would happen if a key partner became disabled: Suddenly, the practice is a lot less profitable, as it has the same expenses but less income because one partner alone can't treat patients. Unless these issues are addressed in advance, financial havoc can ensue any time a partner dies, becomes disabled or even retires. The way to address these issues is through a properly-funded buy-sell agreement.

Buy-sell basics

There are various types of buy-sell agreements, which will be discussed below. Nonetheless, there are some basics regarding all buy-sell agreements that can apply to any type of business — specifically the benefit that different stakeholders can gain when one is in place. Buy-sells can be used for corporations (both S and C corporations), partnerships, limited partnerships, limited liability companies (LLC) and other forms as well. For these discussions, we will use the words "business owner" generically to mean any type of business owner.

■ A. **Benefits to the business and remaining owners**. From the standpoint of the business and remaining partners, a properly planned buy-sell agreement will provide the orderly continuation of the ownership and control of the business upon the happening of certain events, including:

- A death or disability of any owner;
- The desire of any owner to sell his/her ownership share;
- Divorce of any owner;
- Bankruptcy of any owner, or other situation where creditors may have rights to ownership.

The buy-sell agreement can prevent unwanted outsiders from becoming owners and eliminate the need for negotiation with surviving spouses and/or children. The agreement may also perform the role of a succession plan, providing for continuity or orderly succession of business management. Furthermore, as discussed below, the buy-sell agreement is often used in conjunction with life and disability insurance policies to effectively provide liquidity for the business to purchase outstanding ownership interests.

This in effect guarantees that the remaining owners will continue to control the business and be able to participate in the future growth of the business while also preventing a competitor from purchasing ownership interests from a retired, disabled or deceased owner, or their families. This guarantees continuity of management in the business.

■ B. **Benefits to each owner**. From the standpoint of a living business owner, the agreement can provide the individual partner with an opportunity to negotiate and obtain the fairest and best price for his or her share of the business. Furthermore, in the case of retirement or disability, the agreement can be a source of additional funds for each owner.

■ C. **Benefits to family members**. For a deceased owner's family, the existence of the buy-sell can assure the family or estate a liquid asset rather than an interest in a private business. In a medical practice, physicians cannot leave it to their families unless they, too, are physicians, essentially not leaving their family any interest in the business. This is the only business that has this consequence. This is why a practice owner *must* have a buy-sell agreement in place clearly stating what each partner's family will receive from the surviving partner upon time of death or disability.

Funding the agreement

Where the agreement contemplates a buy-sell transaction at the time of an owner's death or disability, insurance policies are generally recommended to fund the transaction. There are many reasons for this, including the following:

- Insurance policies pay a pre-determined amount, with proceeds available at exactly the time when they are needed as a funding source;
- Proceeds will be available regardless of the financial state of the practice at that point (so long as premiums have been paid);
- The business "leverages" the cost of premiums to create the proceeds — thus, it costs the business less to buy

insurance than to save money in a special buy-out fund;
- The economic risks of early death or premature disability of any owner are shifted to the insurer;
- Insurance proceeds are paid to the family income tax-free;
- If retirement is also a contemplated buy-out event, whole-life or universal-life policies can allow large cash values to accumulate, providing the retiring owner with a cash-out.

If the payment contemplated under the agreement is not a lump sum cash payment at closing or is a periodic payment other than through a disability insurance policy, it is important to consider some type of security arrangement for the departing owner. The key is what is negotiated up front between the various owners before there is an idea of who may die, be disabled, retire, or divorce first. This way, each owner will be unprejudiced in determining a fair buy-out.

Disability: Reason for the buy-sell

Buy-sell agreements receive a lot of attention when used to deal with the death of a business owner. However, something equally important and much more likely is that before any owner dies, he or she will become permanently disabled.

Business owners may need two-way protection in the event of disability. First, they have to consider providing for adequate income to meet routine personal expenses including increased medical expenses through a disability income program. Then, they must protect the value of their ownership interests, which can most easily be accomplished by expanding a buy-sell agreement to cover the risk of total disability.

An owner's disability may jeopardize the continued existence of the business. Similar to a death or retirement that has not been adequately provided for, the loss of a business owner due to total disability can create the following hardships:
- Impair credit standing and cause forced sale at a distressed price;
- Necessitate sale to parties not compatible with the interests or philosophies of remaining management;
- Reduce employee morale because the future of the business may be in doubt;
- Cause economic hardships to the business if a totally and permanently disabled owner continues as an employee;
- Create future problems if a totally disabled owner retains a decision-making position;
- Impose adverse tax consequences.
- The need for a coordinated team

Creating a buy-sell arrangement that fits a particular business requires expertise and experience. Expertise in areas of corporate and business law, tax law, insurance products, healthcare law and valuation are all absolute requirements.

Plan early

As with any legal or insurance planning, the early bird is richly rewarded. No place is this more true than in buy-sell planning. The reason is not economic, but political. If this planning is done before an owner is close to disability, divorce, retirement or death, then all owners are in the same position relative to each other. That makes the negotiation of a standard deal for all owners a much easier and smoother process.

On the other hand, if owners wait until one wants to retire, is very sick, or is about to get divorced, then these negotiations can be acrimonious. To avoid these problems, consider a buy-sell arrangement as soon as possible and begin the process with an experienced advisory team. Physicians and their practice will be much better off for your efforts. **DT**

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The D-Fine product line contains shampoos, conditioners and vitamin supplements to help volumize, strengthen and thicken hair while also promoting hair growth.

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For more information:
www.rxsystemspf.com

EDERM SYSTEMS

EHR system for iPad tailored to specialty

New iPad electronic health record (EHR) software released by eDerm Systems was developed with the dermatology specialty in mind, to help derm practices run more efficiently, according to the company.

The EHR iPad solution eliminates certain repetitive tasks using Smart Learning, allowing the clinician to document with one touch the anatomic location of a patient's skin condition, as well as the plan of care, e-prescription and patient instructions. The system does not have to be connected to the Internet to work and syncs to the system's cloud when Internet is connected.

A built-in Smart Coder system uses billing expertise to avoid undercoding and overcoding, the company states. Documentation automatically supports billing and is set up for future ICD10 codes.

For more information:
877-877-4500
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GLYTONE

Lotion reduces dark spots

Glytone's new Fading Lotion includes hydroquinone (2 percent) and kojic acid (1 percent) to address brownish, discolored areas and dark spots on the skin. The lightening ingredients help to inhibit tyrosinase activity, which is the enzyme needed to produce melanin, the company states.

The formula also includes glycolic (5 percent) to exfoliate the skin while enhancing the lotion's skin-brightening benefits. The product contains a convenient applicator to target hyperpigmentation on the arms, chest and face.

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SENSUS HEALTHCARE

FDA clears SRT-100 for keloid treatment

The Food and Drug Administration has cleared Sensus' SRT-100 for the treatment of keloid scars, providing an alternative therapeutic option to surgery.

SRT-100, already approved for the treatment of nonmelanoma skin cancer, uses SharpBeam technology that focuses only on the targeted lesion, sparing surrounding and underlying healthy tissue, the company states. The superficial radiation therapy (SRT) is a low-energy radiotherapy. The mobile, compact system requires no anesthesia, results in little to no scarring and procedures are quick, as is the healing process, according to the company.

For more information:
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SCITON

Laser system clears cellulite

A laser module using proprietary M3 technology provides a minimally invasive process for treating cellulite. The CelluSmooth system is designed to cut fibrous septae, emulsify fat and tighten the dermis, the company states.

Using M3 technology, CelluSmooth delivers a 1,319 nm wavelength in three modes. The device can be used on the buttocks, thighs and other parts of the body to treat cellulite. The system is available on the JOULE platform, which offers multiple modules for treating a variety of indications. The company claims the device works to clear cellulite in half or a third of the time that it takes for other minimally invasive procedures on the market to work.

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The UV Smart Daily SPF 40 works to protect skin from sun damage and photoaging. Containing transparent zinc oxide, vitamins C and E, hyaluronic acid and an antioxidant complex, the sunscreen is free of parabens and oil, according to the company.

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Skin Clinical healing lotion improves microcirculation and boosts oxygenation, helping to combat skin conditions such as those associated with eczema, diabetes and psoriasis. In phase 1 and phase 2 scientific studies, the lotion demonstrated the ability to improve skin thickness, elasticity and overall structure, according to the company.

Developed with a grant from the National Institutes of Health, Skin Clinical has patented ingredients that work to decrease transdermal water loss, improve skin hydration and boost collagen formation. The product absorbs quickly, sooths on contact and provides dramatic moisturization, the company states.

For more information:
www.skinclinicallabs.com

AMERICAN COLLEGE OF PHYSICIAN EXECUTIVES

Book highlights challenges of leadership

Lessons Learned: Stories from Women in Medical Management offers the perspective of 24 women who have leadership positions in the fields of academic medicine, hospitals, government and pharmaceutical companies. It highlights some of the challenges women in leadership may face specifically in the healthcare field.

Some of the takeaways from the book include ways to stay true to your values, the importance

of networking, how to find a work-life balance and how to be a lifelong learner.

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NEOVA

Serum diminishes discolorations

The Serious Clarity 4X serum contains four brighteners that help to reverse the appearance of dark spots, leaving an even skin tone and improved moisture, without irritating side effects, the company states.

The serum is effective on discolorations brought on by photodamage, postblemish scarring and hormonal changes. It is recommended for all skin types and can be used on the arms, face, hands, shoulders and chest. Serious Clarity 4X contains Sepiwhite MSH, a brightening agent; manganese tripeptide-1 complex, which inhibits melanin; licorice root extract to slow hyperpigmentation and smooth skin; and tetrahexyldecyl ascorbate, a brightener that has improved skin penetration with less irritation.

For more information:
www.neova.com

CLARK/FERNDALE

Formula ameliorates bruises

The DerMend Moisturizing Bruise Formula uses ceramides, arnica oil, glycolic acid and retinol to help improve the appearance of bruises while also improving skin texture. The product helps to restore the skin's natural barrier, reduce mottled pigmentation, maintain collagen and elastin production and boost moisture, according to the company.

The formula is appropriate for use on the arms, hands, chest and legs. It absorbs easily and won't stain fabric. It does contain alpha hydroxy acid, which may increase user's susceptibility to sunburn.

For more information:
www.dermend.com

VISION USA

Clip-on lenses ease eye strain

The Task Vision e-z clip-on computer filter tackles eye strain caused by "computer vision syndrome." The lenses can be attached to any prescription eyeglasses or safety glasses, the company states. They help to reduce eye strain, a problem for many who work in front of a computer for prolonged periods. The product enhances true color perception and allows for sharper details. It is available in magnification powers +1.00, +1.50, +2.00, +2.50, +3.00, +3.50, +4.00 and +5.00.

For more information:
800-257-5782
www.visionusasupplies.com

NERIUM INTERNATIONAL

Night cream addresses various concerns

The NeriumAD Age-Defying Treatment uses a patent-pending extract from the *Nerium oleander* plant, which uses antioxidant properties to help reduce the signs of aging, according to the company.

The night cream is designed to address fine lines, wrinkles, enlarged pores, uneven skin texture and discoloration. The product underwent five years of clinical trials by a third-party research firm, which found a 30 percent average reduction of the appearance of fine lines, wrinkles and discoloration over a period of 30 days, the company states.

NeriumAD is noncomedogenic, gluten-free, paraben-free and cruelty-free..

For more information:
www.mynerium.com

PRECISIONMD

Formulation has whipped foam delivery

The Vivatia Active Complex is a retinol cream that uses a whipped foam delivery system to provide full facial coverage, and is available in three different strengths.

Consumers can select the 0.5, 0.75 or 1 percent formulation to allow users to become adjusted to the active vitamin A ingredients, according to the company. The whipped foam delivery gives full coverage of the face with only half a pump. The product addresses fine lines and wrinkles, and provides even greater rejuvenation when used in combination with other PrecisionMD skincare system products, the company states. Vivatia Active Complex is distributed in physician offices and medical spas.

For more information:
www.precisionmdskin.com/vivatia

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upcoming events

Dermatology Times lists meeting announcements for the following three months in our print issue.

Controversies & Conversations in Laser and Cosmetic Surgery
www.skincarephysicians.net
Aug. 9-11, 2013
St. Regis Monarch Beach Resort,
Dana Point, Calif.

Pacific Dermatologic Association 65th Annual Meeting
www.pacificderm.org
Aug. 14-18, 2013
The Palace Hotel
San Francisco

American Dermoscopy Meeting
www.americandermoscopy.com
Aug. 15-17, 2013
The Lodge at Whitefish Lake
Whitefish, Mont.

International Society for Dermatologic Surgery 34th Annual Meeting
www.isdsworld.com
Aug. 29-31, 2013
Valamar Hotel Lacroma Dubrovnik
Dubrovnik, Croatia

American Academy of Dermatology Association 2013 Legislative Conference
www.aad.org
Sept. 8-10, 2013
Willard Intercontinental Hotel
Washington

Alabama Dermatology Society Seminar at Sea
www.alabamaderm.org
Sept. 11-19, 2013
Crystal Cruise Line - Crystal Serenity
Barcelona, Spain

9th Annual Coastal Derm Symposium
www.coastalderm.org
Sept. 25-29, 2013
Willows Lodge
Woodinville, Wash.

American Society for Dermatologic Surgery Annual Meeting
www.asds.net
Oct. 3-6, 2013
Hyatt Regency
Chicago

European Academy of Dermatology and Venereology - 22nd EADV Congress
www.eadv.org
Oct. 2-6, 2013
ICC Istanbul Congress Center Taskisla
Istanbul, Turkey

American Society of Dermatopathology 50th annual meeting
www.asdp.org/AM13
Oct. 10-13, 2013
Washington Marriott Wardman Park
Washington

Montagna Symposium on the Biology of Skin
www.montagnasymposium.org
Oct. 10-14, 2013
Skamania Lodge
Stevenson, Wash.

Foundation for Research and Education in Dermatology - 32nd Anniversary Fall Clinical Dermatology Conference
www.clinicaldermconf.org
Oct. 17-20, 2013
Encore at the Wynn
Las Vegas

Florida Society of Dermatologic Surgeons 32nd Annual Meeting
www.fsds.org
Oct. 18-20, 2013
The Breakers
Palm Beach, Fla.

International Society of Hair Restoration Surgery Annual Scientific Meeting
www.ishrs.org
Oct. 23-26, 2013
Hyatt Regency
San Francisco

Hampton University Skin of Color Research Institute - 2013 Skin of Color Symposium
www.huscri.org
Oct. 25-27, 2013
Royal Sonesta Harbor Court Hotel
Baltimore

Ohio Dermatological Association 30th Annual Meeting
www.ohioderm.org
Oct. 25-27, 2013
Hilton Columbus at Easton
Columbus, Ohio

For a full listing of events, go to *www.dermatologytimes.com*

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[1] On file, n=72, Fitzpatrick skin types II-VI, Repeat open application test, no incidence of irritant contact dermatitis

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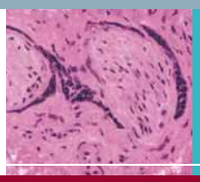

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UPCOMING CME ACTIVITIES

Closure Course, Fundamentals of Mohs Pathology, and Fundamentals of Mohs Surgery

**Fundamentals of Mohs Pathology is new this year!*

DoubleTree Hotel San Diego, Mission Valley, San Diego, California

October 28-30, 2013 – Closure Course
This intense learning experience will feature practical reconstruction techniques, site specific discussions, and numerous closure pearls, designed to take dermatologists to the next level of derm surgery practice.

October 29, 2013 – Fundamentals of Mohs Pathology
Tailored to clinicians returning to dermatopathology after a period of years or whose training did not include significant exposure to skin pathology. Will familiarize attendees with most common entities treated by Mohs surgery: BCC and SCC. Discussion of variations of these cancers, as well as common mimics often found in tissue excised during Mohs. Combined microscope study and didactic lectures by Board-certified dermatopathologists.

October 31 – November 3, 2013 – Fundamentals of Mohs Surgery
Physicians will build and improve their skills in Mohs surgery and related histopathologic interpretation. Course includes valuable information concerning Mohs practice set-up, CLIA-OSHA requirements, and other practice management tips. Mohs technicians will receive individualized instruction in tissue processing and other technical duties, stressing a teamwork approach to patient care.

Annual Clinical Symposium – Dermatologic Surgery: Focus on Skin Cancer

Hyatt Regency Tamaya Resort & Spa, Santa Ana Pueblo, New Mexico

Memorial Day Weekend, May 22-25, 2014
Top experts in the field will provide updates on a wide range of dermatologic surgery and Mohs surgery topics. Interactive forums and panels will discuss appropriate repair strategies for a variety of surgical wounds and innovative approaches to melanoma treatment. Both Mohs and non-Mohs cases will be featured in the microscope laboratory. Mohs support personnel accompanying physicians to the meeting will participate in a standalone session dedicated to important technical topics and updates, discussion of special advanced Mohs laboratory techniques, and sharing of patient care concerns encountered on a regular basis in their work.

AMA PRA Category 1 Credit Available

For additional information regarding ASMS educational activities, membership opportunities, and patient resources, please contact:

Novella Rodgers, Executive Director
American Society for Mohs Surgery
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  - Core curriculum in lasers, peels, fillers, neuromodulators and veins
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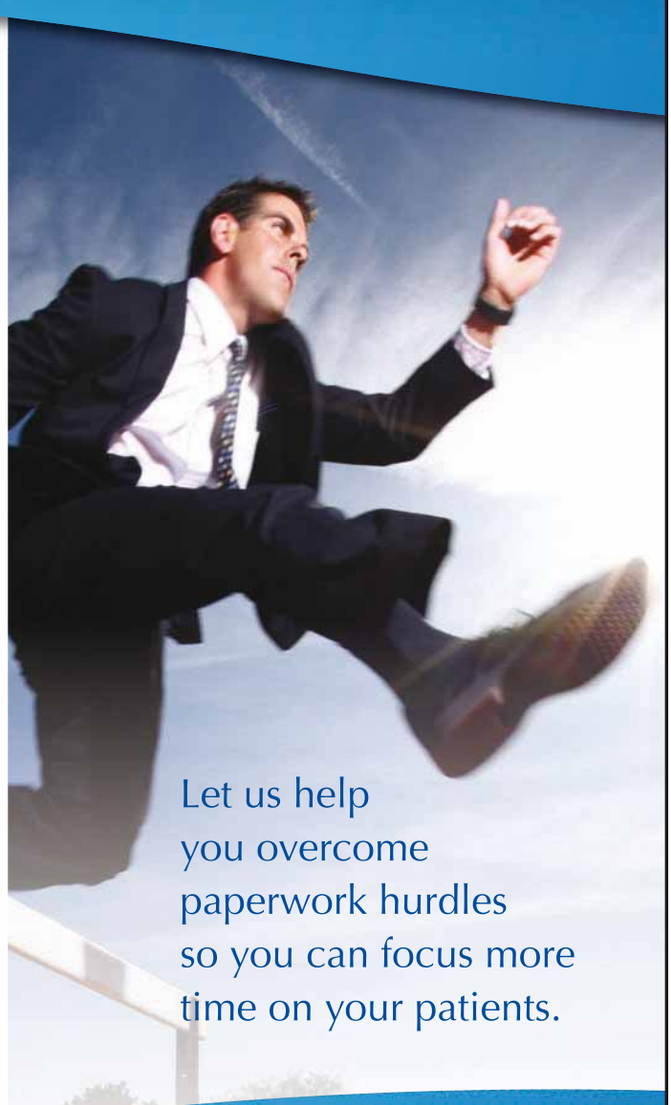

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4 PHYSICIAN TRENDS HAPPENING NOW

Shared by MedCityNews

Some experts have proposed solutions to factors contributing to frustration among physicians and an impending shortage, which include an unseen benefit from participation in accountable care organizations and the impact of healthcare reform on solo practice.

READ MORE: MEDCITYNEWS.COM/2013/07/PESSIMISM-ON-THE-FRONT-LINES-4-PHYSICIAN-TRENDS-THE-NEXT-GENERATION-OF-DOCTORS-SHOULD-KNOW

SHOULD DERMATOLOGY STUDENT SELECTION BE CHANGED?

Shared by KevinMD

Little has changed in the requirements for entering medical school since 1910. Now, students are more diverse, technology and medicine have exploded. Science GPAs and MCAT scores may predict academic capability, but they do not predict how good a physician will be in practice. Should more schools approach a more "holistic review" of prospective medical students?

READ MORE: KEVINMD.COM/BLOG/2013/06/CHANGE-SELECT-MEDICAL-STUDENTS.HTML

COLLAGEN VII PLAYS A DUAL ROLE IN WOUND HEALING

Shared by @ducrest

The basement membrane protein collagen VII (COL7A1), which secures the epidermis to the dermis, is a critical factor in cutaneous wound closure, a new study reveals. This may be a therapeutic target for chronic wounds, as well as the skin fragility disorder recessive dystrophic epidermolysis bullosa.

READ MORE: JCI.ORG/ARTICLES/VIEW/68127

INTERFERON ASSOCIATED WITH HYPERPIGMENTATION

Shared by @Lexi_Comp

Secondary hyperpigmentation is a potential adverse effect associated with interferon treatment, researchers say. In a recent study examining 77 patients treated with pegylated interferon alfa-2b and ribavirin for chronic hepatitis C virus (HCV) infection, nearly a quarter (21 percent) experienced secondary hyperpigmentation, according to a study published in *JAMA Dermatology*. Patients, especially those with darker skin types, should be advised to use sun protection.

READ MORE: ARCHDERM.JAMANETWORK.COM/ARTICLE.ASPX?ARTICLEID=1670410&UTM_

WHITE HOUSE DELAYS ACA EMPLOYER MANDATE

Shared by The Doctor's Channel

The Obama Administration announced that the Affordable Care Act's mandate that larger employers provide coverage for their workers or face penalties has been delayed until 2015.

READ MORE: NYTIMES.COM/2013/07/03/US/POLITICS/OBAMA-ADMINISTRATION-TO-DELAY-HEALTH-LAW-REQUIREMENT-UNTIL-2015.HTML

NEW LABELS DON'T CHANGE OLD PROBLEMS

Shared by @kevinwangdermMD

Although new sunscreen labeling requirements have been phasing into effect since June 2012, some dermatologists warn that the same problems exist, including not wearing enough product and not reapplying with frequency.

READ MORE: MEDPAGETODAY.COM/DERMATOLOGY/GENERALDERMATOLOGY/40292?UTM

6 TIPS TO MANAGE ONLINE REPUTATION

Shared by MDLinx

A positive online reputation is important to maintain; because bad reviews or an unprofessional presence may turn potential patients away, an expert says. A few bad reviews can decrease the value of your practice or support legal action. He offers these proactive tips to manage your digital profile.

READ MORE: MEDPAGETODAY.COM/DERMATOLOGY/GENERALDERMATOLOGY/40292?UTM

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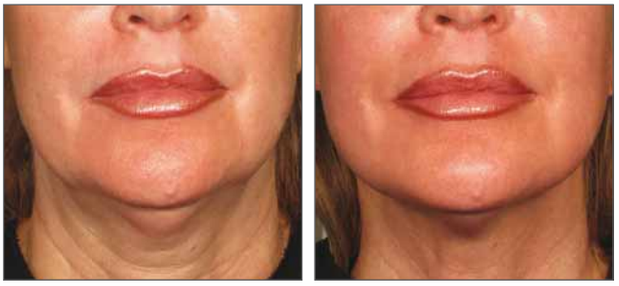
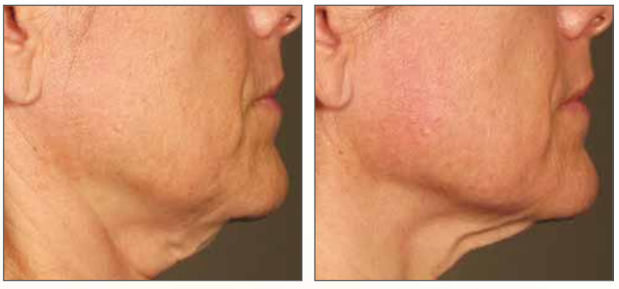
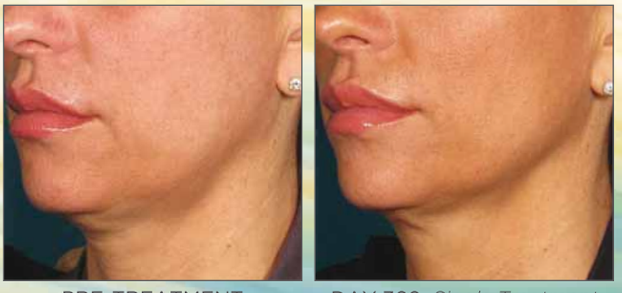


PRE-TREATMENT | DAY 90, *Single Treatment*



PRE-TREATMENT | DAY 180, *Single Treatment*



PRE-TREATMENT | DAY 360, *Single Treatment*

WHY CHOOSE ULTHERAPY?

- Supported by rigorous science and clinical evidence
- Treats deeper than Lasers and RF to lift the skin's support structure
- A single 60-90 minute procedure with NO downtime
- Noticeable results that last 1 year or more
- One of the best ROIs in the aesthetics industry

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Ultherapy®

SEE THE BEAUTY OF SOUND™

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Invisible protection. Visible results.

INTRODUCING CeraVe® SPF 50 sunscreens with InVisibleZinc™

Advanced sun protection with ceramides for barrier repair[1,2]

- Broad-spectrum UVA/UVB SPF 50
- 100% physical sunscreen
- Features Invisible Zinc™
- Lightweight and oil-free
- Very water-resistant (80 minutes)
- Sun protection for all skin types

Other CeraVe® Sunscreen Formulations:

- Wet skin spray
- SPF 30

CeraVe® is not intended to treat underlying skin conditions.

References. 1. Berardesca E, Barbareschi M, Veraldi S, Pimpinelli N. Evaluation of efficacy of a skin lipid mixture in patients with irritant contact dermatitis, allergic contact dermatitis or atopic dermatitis: a multicenter study. *Contact Dermatitis.* 2001;45(5):280-285. **2.** Kao JS, Fluhr JW, Man M-Q, et al. Short-term glucocorticoid treatment compromises both permeability barrier homeostasis and stratum corneum integrity: inhibition of epidermal lipid synthesis accounts for functional abnormalities. *J Invest Dermatol.* 2003;120(3):456-464.

CeraVe® DEVELOPED WITH DERMATOLOGISTS

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