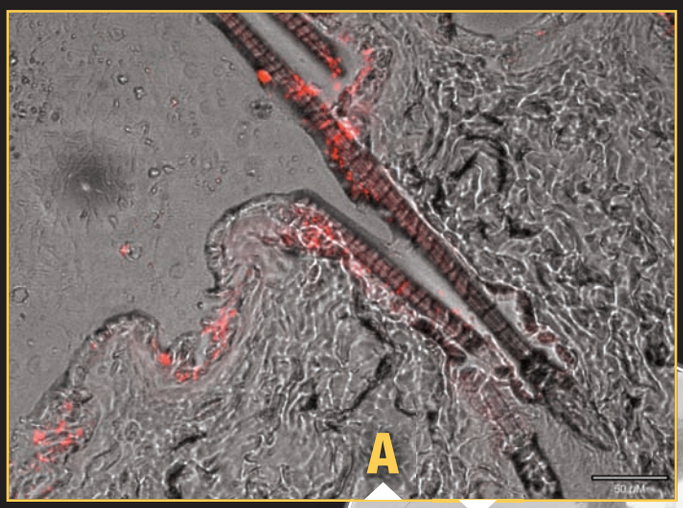
Dermatology Times®
Clinical Analysis for Today's Skincare Specialists
January 2015 | VOL. 36, NO. 01 |

Advancing Research 2015

Dr. Friedman's research is an example of the importance of drug delivery options. He has spent a decade studying a way to utilize nanotechnology to generate nitric oxide, which has the potential to effectively heal wounds, fight skin infections, stimulate pigment production, enhance blood flow and more.



A penetration of fluorescent nanoparticles into rat epidermis and follicular unit; and **B** transmission elec-

Oncology

Opportunities and challenges with new treatments for advanced cancer

Cheryl Guttman Krader
Senior Staff Correspondent

ADVANCES IN SYSTEMIC therapy, including targeted approaches and immunotherapy options, are changing the landscape of management for patients with metastatic and advanced skin cancer. Although current use of the available agents falls predominantly under the purview of medical oncologists, a multidisciplinary team approach represents the best model for

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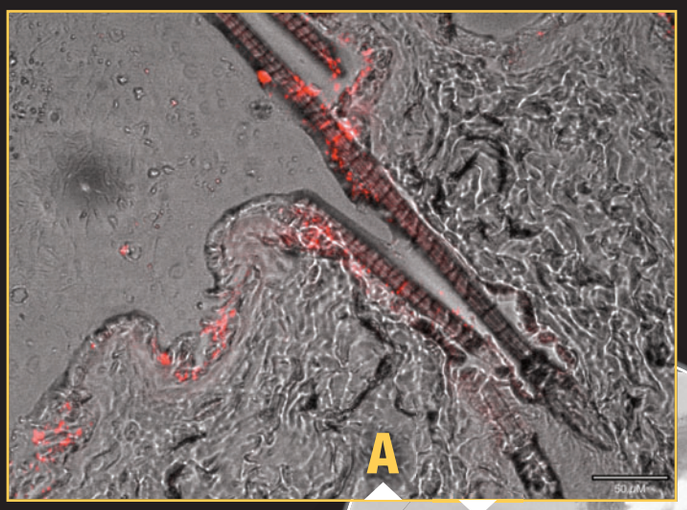

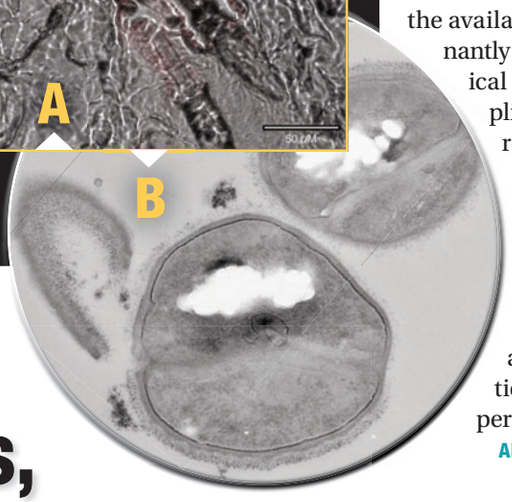

A penetration of fluorescent nanoparticles into rat epidermis and follicular unit; and **B** transmission electron microscopy showing the bactericidal effect of nitrogen oxide nanoparticles against MRSA.

Photos: Adam Friedman, M.D.

Sophisticated research capabilities, big data accelerate discoveries of mechanisms, drug targets

Lisette Hilton | Senior Staff Correspondent

DERMATOLOGY RESEARCH is in high gear in high-tech areas but gaps remain in the understanding of how to treat common problems, like warts, researchers say.

Research has become much more sophisticated in recent decades, says Kevin D. Cooper, M.D., a dermatology researcher since the late 1970s. He is professor and chair of dermatology at Case Western Reserve University and University Hospitals Case Medical Center, Cleveland, Ohio.

"The ability to answer questions in a definitive way and in a way that results in treatment advances or diagnostic advances is much better now," he says.

What does that mean to dermatology? Dr. Cooper says it means accelerated discoveries of new mechanisms, drug targets, drugs and repurposed drugs. It means an explosion of available data and what we can do with it.

"... the breadth of research that dermatologists and cutaneous biologists do is much greater," Dr. Cooper says. "You can start from a very small genetic mutation and one molecule or comb through giant data sets to figure out novel comorbidities and linkages that skin diseases may have that we didn't recognize before."

STARTING AT THE MOLECULE

Genetic research is advancing in dermatology, uncovering not only the source of disease but

ADVANCING RESEARCH *see page* **22**

Oncology

Opportunities and challenges with new treatments for advanced cancer

Cheryl Guttman Krader
Senior Staff Correspondent

ADVANCES IN SYSTEMIC therapy, including targeted approaches and immunotherapy options, are changing the landscape of management for patients with metastatic and advanced skin cancer. Although current use of the available agents falls predominantly under the purview of medical oncologists, a multidisciplinary team approach represents the best model for optimizing patient care, say experts in this area.

Familiarity with the new treatments for advanced skin cancer helps dermatologists to make appropriate referrals for their patients. Dermatologists' expertise also is invaluable con-

ADVANCED CANCER *see page* **47**

In This Issue

January 2015
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UBM ADVANSTAR
UBM

Q&A | THE TAKEAWAY | **CARRIE KOVARIK, M.D.,** discusses the future of teledermatology & how to get involved. SEE PAGE 52

IMPORTANT SAFETY INFORMATION (cont'd)

Warnings and Precautions (cont'd)

for patients with a history of depression and/or suicidal thoughts/behavior, or in patients who develop such symptoms while on Otezla. Patients, caregivers, and families should be advised of the need to be alert for the emergence or worsening of depression, suicidal thoughts or other mood changes, and they should contact their healthcare provider if such changes occur

- Weight Decrease: Body weight loss of 5-10% occurred in 12% (96/784) of patients treated with Otezla and in 5% (19/382) of patients treated with placebo. Body weight loss of ≥10% occurred in 2% (16/784) of patients treated with Otezla compared to 1% (3/382) of patients treated with placebo. Monitor body weight regularly; evaluate unexplained or clinically significant weight loss, and consider discontinuation of Otezla
- Drug Interactions: Apremilast exposure was decreased when Otezla was co-administered with rifampin, a strong CYP450 enzyme inducer; loss of Otezla efficacy may occur. Concomitant use of Otezla with CYP450 enzyme inducers (eg, rifampin, phenobarbital, carbamazepine, phenytoin) is not recommended

Adverse Reactions

- Adverse reactions reported in ≥5% of patients were (Otezla%, placebo%): diarrhea (17, 6), nausea (17, 7), upper respiratory tract infection (9, 6), tension headache (8, 4), and headache (6, 4).

Use in Specific Populations

- Pregnancy and Nursing Mothers: Otezla is Pregnancy Category C; it has not been studied in pregnant women. Use during pregnancy only if the potential benefit justifies the potential risk to the fetus. It is not known whether apremilast or its metabolites are present in human milk. Caution should be exercised when Otezla is administered to a nursing woman
- Renal Impairment: Otezla dosage should be reduced in patients with severe renal impairment (creatinine clearance less than 30 mL/min); for details, see Dosage and Administration, Section 2, in the Full Prescribing Information

Please turn the next page for Brief Summary of Full Prescribing Information.

References: 1. Schafer PH, Parton A, Capone L, et al. *Cell Signal*. 2014;26:2016-2029. **2.** Otezla [package insert]. Summit, NJ: Celgene Corporation; 2014. **3.** Data on file, Celgene Corporation.

- Otezla® (apremilast) was evaluated in 2 multicenter, double-blind, placebo-controlled trials of similar design. Patients with moderate to severe plaque psoriasis (N = 1257) were randomized 2:1 to Otezla 30 mg or placebo twice daily for 16 weeks, after a 5-day titration[2,3]
- Inclusion criteria: Age ≥18 years, BSA involvement ≥10%, sPGA ≥3, PASI score ≥12, candidates for phototherapy or systemic therapy[2]
- PASI-75 response at week 16 (primary endpoint)[2,3]
  - Study 1: Otezla 33% vs placebo 5% ($P < 0.0001$)
  - Similar PASI-75 response was achieved in Study 2

BSA, body surface area; PASI, Psoriasis Area and Severity Index; sPGA, static Physician Global Assessment.

IMPORTANT SAFETY INFORMATION

Contraindications

- Otezla® is contraindicated in patients with a known hypersensitivity to apremilast or to any of the excipients in the formulation

Warnings and Precautions

- Depression: Treatment with Otezla is associated with an increase in adverse reactions of depression

During clinical trials, 1.3% (12/920) of patients treated with Otezla reported depression compared to 0.4% (2/506) on placebo; 0.1% (1/1308) of Otezla patients discontinued treatment due to depression compared with none on placebo (0/506). Depression was reported as serious in 0.1% (1/1308) of patients exposed to Otezla, compared to none in placebo-treated patients (0/506). Suicidal behavior was observed in 0.1% (1/1308) of patients on Otezla, compared to 0.2% (1/506) on placebo. One patient treated with Otezla attempted suicide; one patient on placebo committed suicide

Carefully weigh the risks and benefits of treatment with Otezla

Continued to the left

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Otezla®
(apremilast) 30mg tablets

Rx Only

OTEZLA® (apremilast) tablets, for oral use
The following is a Brief Summary; refer to Full Prescribing Information for complete product information.

INDICATIONS AND USAGE

OTEZLA® (apremilast) is indicated for the treatment of patients with moderate to severe plaque psoriasis who are candidates for phototherapy or systemic therapy.

CONTRAINDICATIONS

OTEZLA is contraindicated in patients with a known hypersensitivity to apremilast or to any of the excipients in the formulation [*see Adverse Reactions (6.1)*].

WARNINGS AND PRECAUTIONS

Depression: Treatment with OTEZLA is associated with an increase in adverse reactions of depression. Before using OTEZLA in patients with a history of depression and/or suicidal thoughts or behavior prescribers should carefully weigh the risks and benefits of treatment with OTEZLA in such patients. Patients, their caregivers, and families should be advised of the need to be alert for the emergence or worsening of depression, suicidal thoughts or other mood changes, and if such changes occur to contact their healthcare provider. Prescribers should carefully evaluate the risks and benefits of continuing treatment with OTEZLA if such events occur. During the 0 to 16 week placebo-controlled period of the 3 controlled clinical trials, 1.3% (12/920) of patients treated with OTEZLA reported depression compared to 0.4% (2/506) treated with placebo. During the clinical trials, 0.1% (1/1308) of patients treated with OTEZLA discontinued treatment due to depression compared with none in placebo-treated patients (0/506). Depression was reported as serious in 0.1% (1/1308) of patients exposed to OTEZLA, compared to none in placebo-treated patients (0/506). Instances of suicidal behavior have been observed in 0.1% (1/1308) of patients while receiving OTEZLA, compared to 0.2% (1/506) in placebo-treated patients. In the clinical trials, one patient treated with OTEZLA attempted suicide while one who received placebo committed suicide.

Weight Decrease: During the controlled period of the trials in psoriasis, weight decrease between 5%-10% of body weight occurred in 12% (96/784) of patients treated with OTEZLA compared to 5% (19/382) treated with placebo. Weight decrease of ≥10% of body weight occurred in 2% (16/784) of patients treated with OTEZLA 30 mg twice daily compared to 1% (3/382) patients treated with placebo. Patients treated with OTEZLA should have their weight monitored regularly. If unexplained or clinically significant weight loss occurs, weight loss should be evaluated, and discontinuation of OTEZLA should be considered.

Drug Interactions: Co-administration of strong cytochrome P450 enzyme inducer, rifampin, resulted in a reduction of systemic exposure of apremilast, which may result in a loss of efficacy of OTEZLA. Therefore, the use of cytochrome P450 enzyme inducers (e.g., rifampin, phenobarbital, carbamazepine, phenytoin) with OTEZLA is not recommended [see *Drug Interactions (7.1)* and *Clinical Pharmacology (12.3)*].

ADVERSE REACTIONS

Clinical Trials Experience in Psoriasis: Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trial 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. Diarrhea, nausea, and upper respiratory tract infection were the most commonly reported adverse reactions. The most common adverse reactions leading to discontinuation for patients taking OTEZLA were nausea (1.6%), diarrhea (1.0%), and headache (0.8%). The proportion of patients with psoriasis who discontinued treatment due to any adverse reaction was 6.1% for patients treated with OTEZLA 30 mg twice daily and 4.1% for placebo-treated patients.

Table 3: Adverse Reactions Reported in ≥1% of Patients on OTEZLA and With Greater Frequency Than in Patients on Placebo; up to Day 112 (Week 16)

Preferred Term	Placebo (N=506) n (%)	OTEZLA 30 mg BID (N=920) n (%)
Diarrhea	32 (6)	160 (17)
Nausea	35 (7)	155 (17)
Upper respiratory tract infection	31 (6)	84 (9)
Tension headache	21 (4)	75 (8)
Headache	19 (4)	55 (6)
Abdominal pain*	11 (2)	39 (4)
Vomiting	8 (2)	35 (4)
Fatigue	9 (2)	29 (3)

(continued)

Table 3: Adverse Reactions Reported in ≥1% of Patients on OTEZLA and With Greater Frequency Than in Patients on Placebo; up to Day 112 (Week 16)

Preferred Term	Placebo (N=506) n (%)	OTEZLA 30 mg BID (N=920) n (%)
Dyspepsia	6 (1)	29 (3)
Decrease appetite	5 (1)	26 (3)
Insomnia	4 (1)	21 (2)
Back pain	4 (1)	20 (2)
Migraine	5 (1)	19 (2)
Frequent bowel movements	1 (0)	17 (2)
Depression	2 (0)	12 (1)
Bronchitis	2 (0)	12 (1)
Tooth abscess	0 (0)	10 (1)
Folliculitis	0 (0)	9 (1)
Sinus headache	0 (0)	9 (1)

*Two subjects treated with OTEZLA experienced serious adverse reaction of abdominal pain.

Severe worsening of psoriasis (rebound) occurred in 0.3% (4/1184) patients following discontinuation of treatment with OTEZLA (apremilast).

DRUG INTERACTIONS

Strong CYP 450 Inducers: Apremilast exposure is decreased when OTEZLA is co-administered with strong CYP450 inducers (such as rifampin) and may result in loss of efficacy [see *Warnings and Precautions (5.3)* and *Clinical Pharmacology (12.3)*].

USE IN SPECIFIC POPULATIONS

Pregnancy: *Pregnancy Category C*: OTEZLA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Pregnancy Exposure Registry: There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to OTEZLA during pregnancy. Information about the registry can be obtained by calling 1-877-311-8972. **Nursing Mothers:** It is not known whether OTEZLA or its metabolites are present in human milk. Because many drugs are present in human milk, caution should be exercised when OTEZLA is administered to a nursing woman. **Pediatric use:** The safety and effectiveness of OTEZLA in pediatric patients less than 18 years of age have not been established. **Geriatric use:** Of the 1257 patients who enrolled in two placebo-controlled psoriasis trials (PSOR 1 and PSOR 2), a total of 108 psoriasis patients were 65 years of age and older, including 9 patients who were 75 years of age and older. No overall differences were observed in the efficacy and safety in elderly patients ≥65 years of age and younger adult patients <65 years of age in the clinical trials. **Renal Impairment:** OTEZLA pharmacokinetics were not characterized in patients with mild (creatinine clearance of 60-89 mL per minute estimated by the Cockcroft–Gault equation) or moderate (creatinine clearance of 30-59 mL per minute estimated by the Cockroft–Gault equation) renal impairment. The dose of OTEZLA should be reduced to 30 mg once daily in patients with severe renal impairment (creatinine clearance of less than 30 mL per minute estimated by the Cockroft–Gault equation) [see *Dosage and Administration (2.2)* and *Clinical Pharmacology (12.3)*]. **Hepatic Impairment:** Apremilast pharmacokinetics were characterized in patients with moderate (Child Pugh B) and severe (Child Pugh C) hepatic impairment. No dose adjustment is necessary in these patients.

OVERDOSAGE

In case of overdose, patients should seek immediate medical help. Patients should be managed by symptomatic and supportive care should there be an overdose.

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Pat. http://www.celgene.com/therapies

Based on APRPI.003 OTZ_PsO_HCP_BSv.003 09_2014

Norman Levine, M.D.,
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Minimize State Medical Board complaint difficulties

A physician in our community recently received a letter from the State Medical Board informing her that a complaint had been filed by one of her patients and that she would have to respond to the grievance in writing. The substance of the complaint was that when the patient first registered at the office front desk, a face photograph was taken which was placed in her medical record. The receptionist explained that this was the policy of the office to help prevent identity theft. The person was not mollified and claimed that this made her "feel like a terrorist". Therein was the sum and substance of the complaint, which was filed with the State Medical Board.

Although this sounds pretty frivolous, the physician needed to prepare a written response and to inform her malpractice carrier when re-applying for insurance coverage. The "case" is still pending. The office continues to use photo identification as a means of preventing identity theft.

Last year, I received one of these fear-provoking documents from the Board asking that I respond to a complaint by a 26-year-old weight lifter with uniform acneiform papules on the trunk. He was insulted that I inquired whether he had taken anabolic steroids in the recent past. After a fair amount of angst and letter writing on my part, the case was dismissed.

These anecdotes have a few things in common and help to explain why oversight by an administrative board is not necessarily the most efficient means of identifying those practicing below the community standard of care. In both instances, unhappy patients could bypass any dialogue with the treating physician and appeal directly to a governing body that automatically begins an investigation of the alleged offending practitioner.

In our state, the statute requires that all complaints must be answered by the physician regardless of the merits of the issue. These illustrative cases also demonstrate what all of us know — there is a general lack of trust between the patient and the care giver. The pressure of caring for too many people per day makes it difficult to take the time to allow a patient to vent his anger and disappointment in the office rather than at the level of the State Board. In the two cases cited here, the patients were new to the practices and there was no opportunity to form any type of rapport in the few minutes allocated to the appointments.

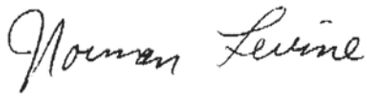
One might ask what real difference it makes if an irate patient complains to the Board. In fact, it can become a very big deal. Unlike a malpractice suit, an adverse outcome could lead to a suspension of one's license to practice medicine and an end to one's professional career.

COMMUNICATION IS KEY

It is quite clear that we cannot please all patients all of the time. Unrealistic expectations, errors in judgment, bad luck and just plain "bad days" are all a part of the complex nature of medical practice. With that in mind, here are some tips for what one can do to minimize the problems associated with a complaint to the Board:

- Try to recognize an adverse interaction while the patient is in the office and attempt to defuse it before he has a chance to fume at home and decide to ruin your day with a Board complaint. When I see an obviously annoyed patient I will often say something like, "It appears that you are not happy with the care that you are receiving today. What seems to be the problem and what can I do to make things right?" This sometimes produces a pretty vicious rant about what a bad and incompetent person I am. I do not try to defend myself (it usually does not do much good anyway); but rather, I apologize for the bad experience that the person has endured. I have never had such an encounter result in a complaint against me to the State Board. Most patients just wish to be heard and to express their feelings. Once this is done, the situation seems to rapidly dissipate.
- Don't take it personally if and when you receive the accusatory letter from the Board. The vast majority of these are completely without merit and have little or nothing to do with your skills as a physician. When responding to the allegations, avoid becoming emotional or defensive and simply present the facts as you see them, including the rationale for the specific care that you delivered.
- In the event that the complaint is of a serious nature where real harm befell the patient and there is some question as to your culpability, by all means you should consult an attorney experienced in interactions with regulatory agencies. That individual can help you prepare rebuttal documents and can accompany you to any hearings that may ensue.

Occasional irate patients are a fact of life in the modern medical practice. We must all attempt to satisfy our patient's needs as much as possible. Sometimes it simply does not work. Try not to let the dreaded communication from the Board annoy you too much (although I must admit that it ruined my day). When called upon to defend your actions, do so in a professional manner. It will almost always conclude in your favor. **DT**



Norman Levine, M.D.

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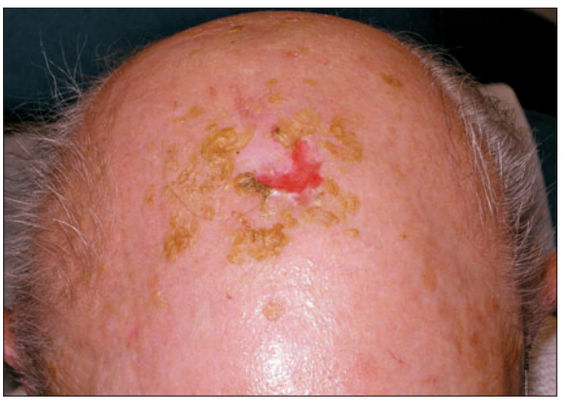

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VIDEOS

E-mazing Medical Marketing Minute

Reza Sadrian, M.D. of Sadrian Plastic Surgery in San Diego, Calif., discusses the power of a patient's story as a a marketing tool and how his practice is sharing these stories online in a very effective and practical way.

bit.ly/e-mazingmarketingtestimonials

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Blog Cosmetic Conundrums

Zoe Diana Draelos, M.D.

Earring dermatitis at the site of a pierced earring can be due to many different factors. It is important to rule out nickel dermatitis and recommend the use of high quality yellow gold earrings.

bit.ly/earlobedermatitis

Blog Is banding in the neck normal after liposuction?

Jason Emer, M.D.

In a recent realself.com post, a patient experienced neck banding shortly after a neck liposuction procedure. She wanted to know if this was a result of the procedure itself and what could be done for improvement. I suggested this patient seek out immediate evaluation. Here's why.

bit.ly/januarycosmeticconsiderations

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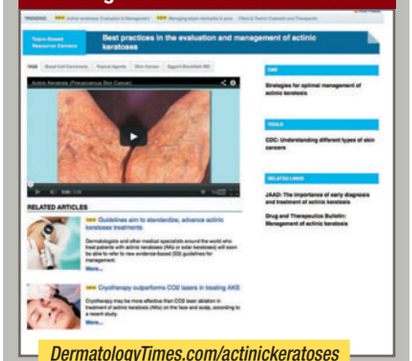
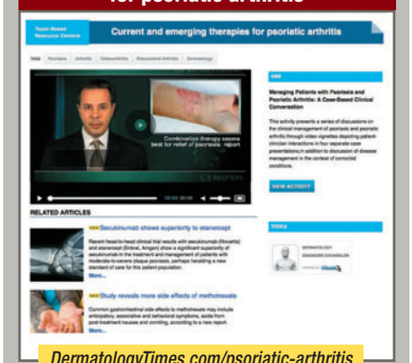
Best practices in the evaluation and management of actinic keratoses



DermatologyTimes.com/actinickeratoses

Current and emerging therapies for psoriatic arthritis



DermatologyTimes.com/psoriatic-arthritis

Fillers and toxins: Cosmetic and therapeutic options

DermatologyTimes.com/injectables

Insights into managing atopic dermatitis and acne

DermatologyTimes.com/atopicdermatitis

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

Can I be sued for asking a patient if he owns a gun?

Dr. Skin has become increasingly concerned about the number of school shootings in the United States. He has established an office policy that has his staff asking patients if they own a gun. If they do, they are not allowed to bring the weapon to the office. He has recently been sued by a patient for simply asking the question, "Do you own a gun?". He seeks legal advice. Is Dr. Skin not allowed to ask such a simple question?

Such a question recently arose in Florida. In Wollschlaeger v. Governor of Florida, physicians and physician interest groups brought an action against the governor of Florida alleging that the Florida Firearm Owners' Privacy Act (the Act) (which prohibited asking patients if they owned guns) violated the physicians' constitutional right of freedom of free speech. The Act, as written, restricts irrelevant inquiry and record-keeping by physicians about patients' use and possession of firearms.

The Act instructs healthcare providers to refrain from inquiring about whether the patient owns firearms unless the provider believes in good faith that the information is relevant to the patient's medical care, safety or the safety of others. Similarly, the Act states that healthcare providers may not intentionally enter information about a patient's ownership of firearms into the patient's medical record that the practitioner knows is not "relevant" to the patient's medical care, safety or the safety of others.

The Act also states that a physician shall not discriminate against a patient on the basis of the patient's ownership of firearms and that providers must "refrain from unnecessarily harassing a patient about firearm ownership." Violations of the Act could lead to disciplinary action including fines, restriction of practice, probation and suspension or revocation of a medical license.

VIOLATION OR VALID REGULATION?

Four days after the Florida governor signed the Act into law, physicians filed an action alleging that the inquiry, record-keeping, discrimination and harassment provision of the Act violated among other things their First amendment right to free speech. The Florida Eleventh Circuit ruled against the physicians. In its ruling, the Court noted that the Act was "a legitimate regulation of professional conduct" which the state has the authority to regulate.

> In the end the issue at hand was whether the regulation was designed to regulate professional conduct of physicians or to regulate their free speech.

The Court first noted that the essence of the Act was that medical practitioners should not record information or inquire about a patient's firearm ownership status when doing so is not necessary to providing the patient with good medical care. The Court said that the Florida state legislature's motivation for passing the Act was that it had received complaints from patients who claimed they were afraid that their doctors may be sharing their medical information, including information about firearm ownership with third parties, including "government bureaucrats." The Act, it noted, was meant to protect a patient's ability to withhold information from his or her doctor, which would ordinarily be stymied by the power imbalance between doctor and patient.

The Court deemed gun ownership information that is not relevant to patient health and safety to be a "private" issue into which a doctor should not transgress, stating that "the practice of good medicine should not require inquiry into private matters unless such inquiry is necessary for the practice of good medicine."

In regard to the claim that the Act impacted physicians' right of free speech, the Court stated that the Act was "a valid regulation of professional conduct that has only an incidental effect on physician free speech – it was not a regulation designed to regulate speech."

In the end, the issue at hand was whether the regulation was designed to regulate professional conduct of physicians or to regulate their free speech. The Court ruled the Act's primary purpose was to regulate conduct and therefore was perfectly legal.

If Dr. Skin practices in Florida, the Court would agree that he could council patients on safety, but cannot mention guns. What would happen if Dr. Skin practices in other states is not clear. **DT**

Questions? Comments?
Give **Dermatology Times** your feedback by contacting us at **editor@dermatologytimes.com**

NOW APPROVED

for adolescents ages 12 and older with scalp plaque psoriasis[1]

Taclonex®
(calcipotriene and betamethasone dipropionate) Topical Suspension
0.005% / 0.064%

Corticosteroid
DUAL ACTION
Vitamin D_3 analog

Experience the combined efficacy and safety of 2 active ingredients with Taclonex® Topical Suspension[1,2]

Learn more about dual action at www.taclonex.com

INDICATION AND USAGE

Taclonex® Topical Suspension is indicated for the topical treatment of plaque psoriasis of the scalp and body in patients 18 years and older and for plaque psoriasis of the scalp in patients 12 to 17 years. Patients 18 years and older should not use more than 100 g per week and patients 12 to 17 years should not use more than 60 g per week.

IMPORTANT SAFETY INFORMATION

Taclonex® Topical Suspension is not for oral, ophthalmic, or intravaginal use and should not be applied to the face, axillae, or groin. Do not use if atrophy is present at the treatment site. Do not use with occlusive dressings unless directed by a physician.

If hypercalcemia or hypercalciuria develop, discontinue until parameters of calcium metabolism normalize. Taclonex® can cause reversible hypothalamic-pituitary-adrenal (HPA) axis suppression with the potential for clinical glucocorticosteroid insufficiency. If HPA axis suppression is documented, gradually withdraw the drug, reduce the frequency of application, or substitute with a less potent steroid. Cushing's syndrome and hyperglycemia may also occur in adults. Pediatric patients are at a greater risk than adults of systemic toxicity, HPA axis suppression and adrenal insufficiency.

The most common adverse reactions (≥1%) are folliculitis and burning sensation of skin.

Patients who apply Taclonex® to exposed skin should avoid excessive exposure to either natural or artificial sunlight. There are no adequate and well-controlled studies of Taclonex® Topical Suspension in pregnant women. Safety and effectiveness of the use of Taclonex® Topical Suspension in pediatric patients under the age of 12 years have not been established.

Please see Brief Summary of Prescribing Information on the following page.

References: 1. Taclonex® Topical Suspension [package insert]. Parsippany, NJ: LEO Pharma Inc.; August 2014. **2.** Segaert S, Ropke M. The biological rationale for use of vitamin D analogs in combination with corticosteroids for the topical treatment of plaque psoriasis. *J Drugs Dermatol.* 2013;12(8):e129-e137.

LEO®

Taclonex®

(calcipotriene and betamethasone dipropionate)
Topical Suspension, 0.005%/0.064%

Rx Only

BRIEF SUMMARY (See Package Insert for full Prescribing Information).

INDICATIONS AND USAGE: Taclonex® Topical Suspension is indicated for the topical treatment of:

- Plaque psoriasis of the scalp and body in patients 18 years and older
- Plaque psoriasis of the scalp in patients 12 to 17 years

WARNINGS AND PRECAUTIONS: Hypercalcemia and Hypercalciuria: Hypercalcemia and hypercalciuria have been observed with use of Taclonex® Topical Suspension. If hypercalcemia or hypercalciuria develop, discontinue treatment until parameters of calcium metabolism have normalized. The incidence of hypercalcemia and hypercalciuria following Taclonex® Topical Suspension treatment of more than 8 weeks has not been evaluated. **Effects on Endocrine System:** Taclonex® Topical Suspension can cause reversible hypothalamic-pituitary-adrenal (HPA) axis suppression with the potential for clinical glucocorticosteroid insufficiency. This may occur during treatment or upon withdrawal of treatment. Factors that predispose a patient to HPA axis suppression include the use of high-potency steroids, large treatment surface areas, prolonged use, use of occlusive dressings, altered skin barrier, liver failure, and young age. Evaluation for HPA axis suppression may be done by using the adrenocorticotropic hormone (ACTH) stimulation test. In a trial evaluating the effects of Taclonex® Topical Suspension and Taclonex® Ointment on the HPA axis, 32 adult subjects were treated with both Taclonex® Topical Suspension on the scalp and Taclonex® Ointment on the body. Adrenal suppression was identified in 5 of 32 subjects (16%) after 4 weeks of treatment and in 2 of 11 subjects (18%) who continued treatment for 8 weeks. In another trial of 43 subjects treated with Taclonex® Topical Suspension on body (including the scalp in 36 out of 43 subjects) adrenal suppression was identified in 3 out of 43 subjects (7%) after 4 weeks of treatment and in none of the 36 subjects who continued treatment for 8 weeks. In a trial evaluating the effects of Taclonex® Topical Suspension on the HPA axis, 31 subjects aged 12 to 17 years were treated with Taclonex® Topical Suspension on the scalp. Adrenal suppression was identified in 1 of 30 evaluable subjects (3.3%) after 4 weeks of treatment. If HPA axis suppression is documented, gradually withdraw the drug, reduce the frequency of application, or substitute with a less potent corticosteroid. Cushing's syndrome and hyperglycemia may also occur due to the systemic effects of the topical corticosteroid. These complications are rare and generally occur after prolonged exposure to excessively large doses, especially of high-potency topical corticosteroids. Pediatric patients may be more susceptible to systemic toxicity due to their larger skin surface to body mass ratios. Use of more than one corticosteroid-containing product at the same time may increase the total systemic corticosteroid exposure. **Allergic Contact Dermatitis with Topical Corticosteroids:** Allergic contact dermatitis to a topical corticosteroid is usually diagnosed by observing a failure to heal rather than a clinical exacerbation. Such an observation should be corroborated with appropriate diagnostic patch testing. **Allergic Contact Dermatitis with Topical Calcipotriene:** Allergic contact dermatitis has been observed with use of topical calcipotriene. Such an observation should be corroborated with appropriate diagnostic patch testing. **Eye Irritation:** Avoid eye exposures. Taclonex® Topical Suspension may cause eye irritation. **Risks of Ultraviolet Light Exposures:** Patients who apply Taclonex® Topical Suspension to exposed skin should avoid excessive exposure to either natural or artificial sunlight, including tanning booths, sun lamps, etc. Physicians may wish to limit or avoid use of phototherapy in patients who use Taclonex® Topical Suspension.

CONTRAINDICATIONS: None.

ADVERSE REACTIONS: 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 directed compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. *Clinical Trials Conducted in Subjects 18 years and older with Scalp Psoriasis:* The rates of adverse reactions given below were derived from randomized, multicenter, prospective vehicle- and/or active controlled clinical trials in adult subjects with scalp psoriasis. Subjects applied study product once daily for 8 weeks, and the median weekly dose was 12.6 g.
Adverse reactions that occurred in ≥1% of subjects treated with Taclonex® Topical Suspension and at a rate higher than in subjects treated with vehicle are presented in Table 1:

Table 1

Number and Percentage with Adverse Reactions in Scalp Psoriasis Trials (Events Reported by ≥1% of Subjects and for Which a Relationship is Possible)				
	Taclonex® Topical Suspension N=1,953	**Betamethasone dipropionate in vehicle N=1,214**	**Calcipotriene in vehicle N=979**	**Vehicle N=173**
Event	# of subjects (%)			
Folliculitis	16 (1%)	12 (1%)	5 (1%)	0 (0%)
Burning sensation of skin	13 (1%)	10 (1%)	29 (3%)	0 (0%)

Other less common adverse reactions (<1% but >0.1%) were, in decreasing order of incidence: acne, exacerbation of psoriasis, eye irritation, and pustular rash. In a 52-week trial, adverse reactions that were reported by >1% of subjects treated with Taclonex® Topical Suspension were pruritus (3.6%), psoriasis (2.4%), erythema (2.1%), skin irritation (1.4%), and folliculitis (1.2%). *Clinical Trials Conducted in Subjects 18 years and older with Psoriasis on the Body:* In randomized, multicenter, prospective vehicle- and/or active controlled clinical trials in adult subjects with plaque psoriasis on non-scalp areas, subjects applied study product once daily for 8 weeks. A total of 824 subjects were treated with Taclonex® Topical Suspension and the median weekly dose was 22.6 g.
There were no adverse reactions that occurred in ≥1% of subjects treated with Taclonex® Topical Suspension and at a rate higher than in subjects treated with vehicle. Other less common adverse reactions (<1% but >0.1%) were, in decreasing order of incidence: rash and folliculitis. *Clinical Trials Conducted in Subjects 12 to 17 years with Scalp Psoriasis:* In two uncontrolled prospective clinical trials, a total of 109 subjects aged 12-17 years with plaque psoriasis of the scalp were treated with Taclonex® Topical Suspension once daily for up to 8 weeks. The median weekly dose was 40 g. Adverse reactions included acne, acneiform dermatitis and application site pruritus (0.9% each).

USE IN SPECIFIC POPULATIONS: Pregnancy: *Teratogenic Effects: Pregnancy Category C:* Animal reproduction studies have not been conducted with Taclonex® Topical Suspension. Taclonex® Topical Suspension contains calcipotriene that has been shown to be fetotoxic and betamethasone dipropionate that has been shown to be teratogenic in animals when given systemically. There are no adequate and well-controlled studies in pregnant women. Taclonex® Topical Suspension should be used during pregnancy only if the potential benefit to the patient justifies the potential risk to the fetus. **Nursing Mothers:** Systemically administered corticosteroids appear in human milk and can suppress growth, interfere with endogenous corticosteroid production, or cause other untoward effects. It is not known whether topically administered calcipotriene or 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 Taclonex® Topical Suspension is administered to a nursing woman. The patient should be instructed not to use Taclonex® Topical Suspension on the breast when nursing. **Pediatric use:** Safety and effectiveness of the use of Taclonex® Topical Suspension in pediatric patients under the age of 12 years have not been established. The safety and effectiveness of Taclonex® Topical Suspension for the treatment of plaque psoriasis of the scalp have been established in the age group 12 to 17 years. Two prospective, uncontrolled trials (N=109) were conducted in pediatric subjects age 12 to 17 years with scalp psoriasis, including assessment of HPA axis suppression in 30 subjects. Because of a higher ratio of skin surface area to body mass, pediatric patients are at a greater risk than adults of systemic toxicity when treated with topical drugs. They are, therefore, also at greater risk of HPA axis suppression and adrenal insufficiency upon the use of topical corticosteroids. Rare systemic toxicities such as Cushing's syndrome, linear growth retardation, delayed weight gain, and intracranial hypertension have been reported in pediatric patients, especially those with prolonged exposure to large doses of high potency topical corticosteroids. Local adverse reactions including striae have also been reported with use of topical corticosteroids in pediatric patients. **Geriatric use:** Clinical studies of Taclonex® Topical Suspension in plaque psoriasis on non-scalp areas included 124 subjects who were 65 years of age or over, and 36 were 75 years of age or over. Clinical studies of Taclonex® Topical Suspension in scalp psoriasis included 334 subjects who were 65 years or over and 84 subjects who were 75 years or over. No overall differences in safety or effectiveness of Taclonex® Topical Suspension were observed between these subjects and younger subjects, and other reported clinical experience has not identified any differences in response between elderly and younger patients. However, greater sensitivity of some older individuals cannot be ruled out.

DOSAGE AND ADMINISTRATION: Instruct patients to shake bottle prior to using Taclonex® Topical Suspension and to wash their hands after applying the product. Apply Taclonex® Topical Suspension to affected areas once daily for up to 8 weeks. Therapy should be discontinued when control is achieved. Patients 18 years and older should not use more than 100 g per week and patients 12 to 17 years should not use more than 60 g per week. Taclonex® Topical Suspension should not be used with occlusive dressings unless directed by a physician. Taclonex® Topical Suspension is not for oral, ophthalmic, or intravaginal use. Avoid use on the face, groin, or axillae, or if skin atrophy is present at the treatment site.

NONCLINICAL TOXICOLOGY: Calcipotriene may enhance the effect of UVR to induce skin tumors. Long-term animal studies have not been performed to evaluate the carcinogenic potential of betamethasone dipropionate.

PATIENT COUNSELING INFORMATION: See FDA-approved patient labeling (Patient Information and Instructions for Use)
Inform patients of the following:

- Instruct adult patients (18 years and older) not to use more than 100 g per week.
- Instruct pediatric patients (12 to 17 years) not to use more than 60 g per week.
- Discontinue therapy when control is achieved unless directed otherwise by the physician.
- Do not apply Taclonex® Topical Suspension to the scalp in the 12 hours before or after any chemical treatments to the hair. Since hair treatments may involve strong chemicals, talk with physician first.
- If applied to the scalp, do not wash hair or take a bath or shower right after application.
- Avoid use of Taclonex® Topical Suspension on the face, underarms, groin or eyes. If this medicine gets on face or in eyes, wash area right away.
- Do not occlude the treatment area with a bandage or other covering unless directed by the physician.
- Note that local reactions and skin atrophy are more likely to occur with occlusive use, prolonged use or use of higher potency corticosteroids.
- Wash hands after application.
- Instruct patients not to use other products containing calcipotriene or a corticosteroid with Taclonex® Topical Suspension without first talking to the physician.
- Instruct patients who use Taclonex® Topical Suspension to avoid excessive exposure to either natural or artificial sunlight (including tanning booths, sun lamps, etc.).

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LEO®

LONGER-WAVE LASER FOUND EFFECTIVE IN TREATING CERTAIN KP SYMPTOMS

JAMA Dermatology
November 2014

Treatment of keratosis pilaris (KP) with a longer wavelength laser is effective for improving skin roughness and textural irregularities, but does little for the erythema associated with KP, a recent study suggests. Northwestern University researchers examined whether the longer-wavelength 810-nm diode laser would be more effective overall. The researchers enrolled 23 patients with KP on both arms and Fitzpatrick skin types I through III from March 1 to October 1, 2011. Eighteen of the patients completed the study, three were unavailable for follow-up, and two withdrew due to inflammatory hyperpigmentation following laser treatment.

3.0 THE MEDIAN OVERALL SCORE COMBINING ERYTHEMA AND ROUGHNESS/BUMPINESS FOR THE TREATMENT SIDES

Patients randomly received treatment with the 810-nm pulsed diode laser on either the right or left arm. Treatments were repeated twice for a total of three treatments administered four to five weeks apart. Two blinded dermatologists rated the sites at 12 weeks after the first visit.

At follow-up, the blinded raters assigned a 2.0 median redness score for both the treatment and control sides. The median roughness/bumpiness score was a 1.0 for the treatment sides and a 2.0 for the control sides. The median overall score combining erythema and roughness/bumpiness was 3.0 for the treatment sides and 4.0 for the control sides.

"Three treatments with the 810-nm diode laser may induce significant improvements in skin texture and roughness/bumpiness in KP patients with Fitzpatrick skin types I through III, but baseline erythema is not improved," the authors conclude. "Complete treatment of erythema and texture in KP may require diode laser treatment combined with other laser or medical modalities that address redness." **DT**

—Bill Gillette

Read the study
bit.ly/KPlasertreatment

Nail stem cell discovery could lead to tissue regeneration of severe skin injuries and more

Proceedings of the National Academy of Sciences
October 2014

Researchers at the University of Southern California have identified a new nail stem cell population, which can self-renew or undergo specialization into different tissues.

Scientists found these stem cells by attaching visible labels, including fluorescent proteins, to mouse nail cells. In doing so, they detected a yet unreported population of quiescent cells within the basal layer of the nail proximal fold. The cells appear in a ring-like configuration around the nail root, according to the study's abstract.

While many of the cells divided repeatedly, a few in the nail base's soft tissue either did not divide or divided slowly. The slow-dividing stem cells, the researchers learned, can perform dual roles. The stem cells normally contribute to the growth of the nails and adjacent skin. But, if the nail is injured or lost, the bone morphogenic protein, or BMP, signals a shift in stem cell function and focus to nail repair, according to a USC press release.

"That was a very surprising discovery, since the dual characteristic of these nail stem cells to regenerate both the nail and skin under certain physiological conditions is quite unique and different from other skin stem cells, such as those of the hair follicle or sweat gland," Krzysztof Kobielak, M.D., Ph.D., the study's principal investigator and assistant professor of pathology at USC, says in a press release.

The question remains about whether or not the right signals or environmental cues could induce these nail stem cells to generate other tissue types.

"Collectively, we demonstrate the plasticity of these stem cells: bifunctional under normal homeostasis, but adaptive in response to wounding. Such principles may exist in the interface between other ectodermal organs and skin," the authors write. **DT**

—Lisette Hilton

Read the study
bit.ly/nailstemcelldiscovery

ACQUISITION BREATHES NEW LIFE INTO ALLERGAN'S R&D EFFORTS

The recently announced acquisition of Allergan Inc., by Actavis means the Irvine, Calif.-based maker of Botox will no longer be the target of a hostile takeover by Canadian firm Valeant Pharmaceuticals—which, in turn, means Allergan's research-and-development programs will continue unabated.

Actavis' bid for Allergan
$66 BILLION

The Valeant cash-and-stock deal was reportedly worth about $54 billion and included a proposal to cut R&D by $900 million. According to Reuters, Actavis proposed a relatively modest $400 million in R&D cuts in its more generous $66 billion bid.

"We were shocked that Valeant wanted to reduce our R&D by 90 percent—thank God that's past tense now," Allergan Chairman and CEO David E. I. Pyott told *Dermatology Times*. "Both companies—Allergan and Actavis—have matching values in terms of R&D and service to customers."

Actavis President and CEO Brent Saunders said any R&D cuts will come from both companies, not just Allergan, and that they will be to functions, not programs.

"We're fully committed to R&D, especially in the medical dermatology and cosmetic areas," he said. "R&D is an essential part of our commitment to our customers."

Pyott said now that the Valeant cloud has passed, the company will focus on getting FDA approval for Volift, a nasolabial filler already approved in Canada and Europe, and on further development with a South Korean firm of a liquid neuromodulator. Both are about two years away, he said.

Saunders added that Aczone X, for acne, and an oxymetazoline treatment for rosacea are also in the development pipeline.

Saunders said the deal should be finalized by the second quarter of 2015. **DT**

—Bill Gillette

STUDY: MULTI-POLAR RF FOR STRETCH MARKS

Journal of Clinical and Aesthetic Dermatology **September 2014**

Striae can be treated safely and effectively with a radiofrequency (RF) energy-generating system featuring a multi-polar (MP2) pulsed electromagnetic field (PEMF), results of a recent study suggest.

Dermatologists Jeffrey S. Dover, M.D., Chestnut Hill, Mass.; Kenneth Rothaus, M.D., New York; and Michael H. Gold, M.D., Nashville, conducted a two-center, single-arm pilot study involving 16 women between the ages of 30 and 72 (mean age, just over 46) with varying degrees of stretch marks. Each patient received six treatments using RF and PEMF. Treatment visits included measurements of striae bands and photos of the treated areas. Pre- and post-treatment photographs were compared by two independent physicians. Treatment parameters, such as time (10 minutes for a 4-by-5-inch area) and output energy (60 to 80 percent, with the goal of reaching therapeutic in the first minute of treatment), were determined based on patient skin type and area of treatment. Immediately after treatment, treated areas were visually assessed for side effects such as edema, erythema, burn, localized infection and skin pigmentation. Patients were asked to assess their willingness to continue with the treatment and to rate observed improvements.

All 16 patients completed treatment. Following are some of the study results:

- **No side effects or undesirable safety events were recorded for any patient throughout the study;**
- **Fourteen patients reported visible improvement; one was not sure; and one saw no improvement;**
- **All patients said treatment was comfortable;**
- **After evaluating the pre- and post-treatment photographs, the two physicians agreed that there was reduction in the visibility of stretch marks after treatment in some of the photos.**

"Although results are promising, the long-term sustainability of the reduced visibility of the striae is not known, and further investigation is required. Patients may achieve a noticeable improvement; however, the complete elimination of the striae is not achieved using this method." **DT**

—Bill Gillette

Read the study
bit.ly/RFforstretchmarks

RESEARCHERS REFINE DEFINITION OF FAT NECROSIS

Plastic and Reconstructive Surgery **December 2014**

DESPITE THE fact that fat necrosis is an increasingly common complication of free tissue transfer and fat grafting, there has been no clear consensus on how to define and classify it in the plastic surgery literature.

In an effort to correct this, a research team led by New York plastic surgeon Pierre B. Saadeh, M.D., undertook a systematic review of the literature. Using keywords such as "fat necrosis" and "plastic surgery," the team searched the PubMed database of the National Library of Medicine and National Institutes of Health and Google Scholar for the period covering Jan. 1, 2003, to Nov. 1, 2013.

The researchers chose 69 articles that met their criteria for analysis. They found there was a wide variety of size requirements and postoperative timing among the definitions of fat necrosis. Moreover, they found that work-ups sought after clinical examination to confirm a diagnosis of fat necrosis varied widely, ranging from radiographic studies to histopathologic examination or a series of studies.

Based on their analysis, the authors suggest defining fat necrosis as "a palpable, discrete and persistent subcutaneous firmness found postoperatively that measures at least 1 cm during physical examination." They write that necrosis can be identified and confirmed by imaging and histopathology or through intraoperative findings.

The authors provide a classification system for fat necrosis that can be used by clinicians to describe fat necrosis in varying grades of severity that ultimately could help guide clinical decision-making. **DT**

—Bill Gillette

Read the study
bit.ly/fatnecrosis

ANTIPSYCHOTIC DRUG LINKED TO RARE BUT POTENTIALLY FATAL SKIN REACTIONS

The antipsychotic drug ziprasidone is associated with rare but potentially fatal skin reactions, the FDA announced December 11, 2014.

Ziprasidone (Geodon, Pfizer and generics) can decrease psychotic symptoms, such as hallucinations and delusions, as well as mania, in people suffering from schizophrenia and bipolar I disorder. This is a commonly prescribed drug. About 2.5 million prescriptions for oral formulations of ziprasidone were dispensed in 2013.

Number of prescriptions for oral formulations of ziprasidone dispensed in 2013

2.5 MILLION

FDA issued the warning after reviewing information about six patients taking ziprasidone who presented with Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) between 11 and 30 days after starting the drug. DRESS reoccurred in three of those patients, soon after they re-started the drug (after having stopped it).

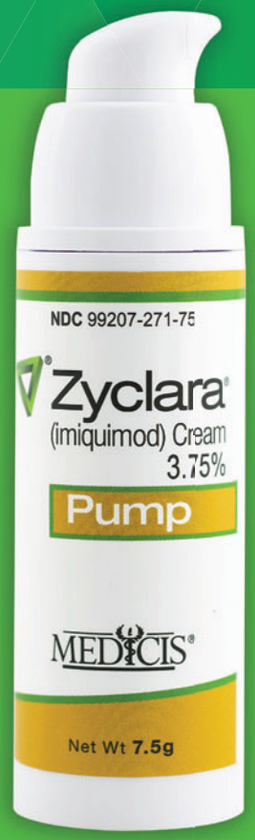
Dermatologists should note that DRESS includes not only cutaneous reactions, such as a rash or exfoliative dermatitis, but might also involve eosinophilia, fever, lymphadenopathy and one or more systemic complications, such as hepatitis, nephritis, pneumonitis, myocarditis, pericarditis and pancreatitis. Because of DRESS, patients might have a high number of eosinophils in their blood. And while none of the six patients reviewed by the FDA have died, DRESS results in serious outcomes, including hospitalization. It can be fatal in up to 10 percent of cases, according to the government.

The exact cause of DRESS is unknown and there is no specific DRESS treatment. For now, health providers are told to focus on recognizing symptoms early, discontinuing the offending agent as quickly as possible and managing symptoms—possibly with systemic corticosteroids, if patients have extensive organ involvement.

Dermatologists who suspect DRESS from ziprasidone should report cases to the FDA's MedWatch program. **DT**

—Lisette Hilton

ZYCLARA®:
Efficacy for the Full Field Treatment of Actinic Keratosis



TREATS THE FULL FACE OR BALDING SCALP WITH A METERED DOSE PUMP.

Indication
ZYCLARA (imiquimod) Cream 3.75% is indicated for the topical treatment of clinically typical, visible or palpable actinic keratoses (AK) of the full face or balding scalp in immunocompetent adults.[1]

Important Safety Information for ZYCLARA Cream

- Intense local skin reactions including skin weeping or erosion can occur after a few applications of ZYCLARA Cream and may require an interruption of dosing. ZYCLARA Cream has the potential to exacerbate inflammatory conditions of the skin, including chronic graft versus host disease.[1]
- Administration of ZYCLARA Cream is not recommended until the skin is healed from any previous drug or surgical treatment.[1]
- ZYCLARA Cream should be used with caution in patients with pre-existing autoimmune conditions because imiquimod activates immune cells.[1]
- Exposure to sunlight (including sunlamps) should be avoided or minimized during use of ZYCLARA Cream. Patients should be warned to use protective clothing (e.g., hat) when using ZYCLARA Cream. Patients with sunburn should be advised not to use ZYCLARA Cream until fully recovered. Patients who may have considerable sun exposure, e.g. due to their occupation, and those patients with inherent sensitivity to sunlight should exercise caution when using ZYCLARA Cream.[1]
- Avoid concomitant use of ZYCLARA Cream and any other imiquimod cream because of increased risk for adverse reactions.[1]
- In clinical studies for actinic keratosis, the most common adverse events involved skin reactions in the application area including erythema, scabbing/crusting, flaking/scaling/dryness, edema, erosion/ulceration, and exudate. Most local skin reactions were rated as mild to moderate.[1]

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

References: 1. ZYCLARA Cream Package Insert. Scottsdale, AZ: Medicis, the Dermatology Company; February 2012.

DM/ZCL/13/0004

VALEANT® Dermatology

Zyclara® (imiquimod) Cream 3.75%

Zyclara Brief Summary

CONTRAINDICATIONS None

WARNINGS AND PRECAUTIONS

Local Skin Reactions

Intense local skin reactions including skin weeping or erosion can occur after a few applications of ZYCLARA Cream and may require an interruption of dosing [see Dosage and Administration (2) and Adverse Reactions (6)]. ZYCLARA Cream has the potential to exacerbate inflammatory conditions of the skin, including chronic graft versus host disease.

Severe local inflammatory reactions of the female external genitalia can lead to severe vulvar swelling. Severe vulvar swelling can lead to urinary retention. Dosing should be interrupted or discontinued for severe vulvar swelling.

Administration of ZYCLARA Cream is not recommended until the skin is healed from any previous drug or surgical treatment.

Systemic Reactions

Flu-like signs and symptoms may accompany, or even precede, local skin reactions and may include fatigue, nausea, fever, myalgias, arthralgias, malaise and chills. An interruption of dosing and an assessment of the patient should be considered [see Adverse Reactions (6)]

Lymphadenopathy occurred in 2% of subjects with actinic keratosis treated with ZYCLARA Cream, 3.75% and in 3% of subjects treated with ZYCLARA Cream, 2.5% [see Adverse Reactions (6)]. This reaction resolved in all subjects by 4 weeks after completion of treatment.

Ultraviolet Light Exposure Risks

Exposure to sunlight (including sunlamps) should be avoided or minimized during use of ZYCLARA Cream. Patients should be warned to use protective clothing (e.g., a hat) when using ZYCLARA Cream. Patients with sunburn should be advised not to use ZYCLARA Cream until fully recovered. Patients who may have considerable sun exposure, e.g. due to their occupation, and those patients with inherent sensitivity to sunlight should exercise caution when using ZYCLARA Cream.

In an animal photo-carcinogenicity study, imiquimod cream shortened the time to skin tumor formation [see Nonclinical Toxicology (13.1)]. The enhancement of ultraviolet carcinogenicity is not necessarily dependent on phototoxic mechanisms. Therefore, patients should minimize or avoid natural or artificial sunlight exposure.

Increased Risk of Adverse Reactions with Concomitant Imiquimod Use

Concomitant use of ZYCLARA Cream and any other imiquimod products, in the same treatment area, should be avoided since they contain the same active ingredient (imiquimod) and may increase the risk for and severity of local skin reactions.

The safety of concomitant use of ZYCLARA Cream and any other imiquimod products has not been established and should be avoided since they contain the same active ingredient (imiquimod) and may increase the risk for and severity of systemic reactions.

Immune Cell Activation in Autoimmune Disease

ZYCLARA Cream should be used with caution in patients with pre-existing autoimmune conditions because imiquimod activates immune cells [see Clinical Pharmacology (12.2)].

ADVERSE REACTIONS

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.

Clinical Trials Experience: Actinic Keratosis

The data described below reflect exposure to ZYCLARA Cream or vehicle in 479 subjects enrolled in two double-blind, vehicle-controlled trials. Subjects applied up to two packets of ZYCLARA Cream or vehicle daily to the skin of the affected area (either entire face or balding scalp) for two 2-week treatment cycles separated by a 2-week no treatment period.

Table 1: Selected Adverse Reactions Occurring in ≥ 2% of ZYCLARA-Treated Subjects and at a Greater Frequency than with Vehicle in the Combined Studies (AK)

Adverse Reactions	ZYCLARA Cream, 3.75% (N=160)	ZYCLARA Cream, 2.5% (N=160)	Vehicle (N=159)
Headache	10 (6%)	3 (2%)	5 (3%)
Application site pruritus	7 (4%)	6 (4%)	1 (<1%)
Fatigue	7 (4%)	2 (1%)	0
Nausea	6 (4%)	1 (1%)	2 (1%)
Influenza like illness	1 (<1%)	6 (4%)	0
Application site irritation	5 (3%)	4 (3%)	0
Pyrexia	5 (3%)	0	0
Anorexia	4 (3%)	0	0
Dizziness	4 (3%)	1 (<1%)	0
Herpes simplex	4 (3%)	0	1 (<1%)
Application site pain	5 (3%)	2 (1%)	0
Lymphadenothapy	3 (2%)	4 (3%)	0
Oral herpes	0	4 (3%)	0
Arthralgia	2 (1%)	4 (3%)	0
Cheilitis	0	3 (2%)	0
Diarrhea	3 (2%)	2 (1%)	0

Local skin reactions were recorded as adverse reactions only if they extended beyond the treatment area, if they required any medical intervention, or they resulted in patient discontinuation from the study. The incidence and severity of selected local skin reactions are shown in Table 2.

Table 2: Local Skin Reactions in the Treatment Area in ZYCLARA-Treated Subjects as Assessed by the Investigator (AK)

All Grades* (%) Severe	ZYCLARA Cream, 3.75% (N=160)	ZYCLARA Cream, 2.5% (N=160)	Vehicle (N=159)
Erythema Severe Erythema	96% 25%	96% 14%	78% 0%
Scabbing/Crusting Severe Scabbing/ Crusting	93% 14%	84% 9%	45% 0%
Edema Severe Edema	75% 6%	63% 4%	19% 0%
Erosion/Ulceration Severe Erosion/ Ulceration	62% 11%	52% 9%	9% 0%
Exudate Severe Exudate	51% 6%	39% 1%	4% 0%
Flaking/Scaling/ Dryness Severe Flaking/ Scaling/Dryness	91% 8%	88% 4%	77% 1%

* All Grades: mild, moderate or severe

Overall, in the clinical trials, 11% (17/160) of subjects in the ZYCLARA Cream, 3.75% arm, 7% (11/160) of subjects in the ZYCLARA Cream, 2.5% arm, and 0% in the vehicle cream arm required rest periods due to adverse local skin reactions.

Other adverse reactions observed in subjects treated with ZYCLARA Cream include: application site bleeding, application site swelling, chills, dermatitis, herpes zoster, insomnia, lethargy, myalgia, pancytopenia, pruritus, squamous cell carcinoma, and vomiting.

Postmarketing Experience

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

Application Site Disorders: tingling at the application site
Body as a Whole: angioedema
Cardiovascular: capillary leak syndrome, cardiac failure, cardiomyopathy, pulmonary edema, arrhythmias (tachycardia, supraventricular tachycardia, atrial fibrillation, palpitations), chest pain, ischemia, myocardial infarction, syncope
Endocrine: thyroiditis
Gastro-Intestinal System Disorders: abdominal pain
Hematological: decreases in red cell, white cell and platelet counts (including idiopathic thrombocytopenic purpura), lymphoma
Hepatic: abnormal liver function
Infections and Infestations: herpes simplex
Musculo-Skeletal System Disorders: arthralgia
Neuropsychiatric: agitation, cerebrovascular accident, convulsions (including febrile convulsions), depression, insomnia, multiple sclerosis aggravation, paresis, suicide
Respiratory: dyspnea
Urinary System Disorders: proteinuria, urinary retention, dysuria
Skin and Appendages: exfoliative dermatitis, erythema multiforme, hyperpigmentation, hypertrophic scar, hypopigmentation
Vascular: Henoch-Schonlein purpura syndrome

USE IN SPECIFIC POPULATIONS

Pregnancy

Pregnancy Category C:

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

The animal multiples of human exposure calculations were based on daily dose comparisons for the reproductive toxicology studies described in this section and in Section 13.1. The animal multiples of human exposure were based on weekly dose comparisons for the carcinogenicity studies described in Section 13.1. For the animal multiple of human exposure ratios presented in this section and Section 13.1, the Maximum Recommended Human Dose (MRHD) was set at 2 packets (500 mg cream) per treatment of actinic keratosis with ZYCLARA Cream (imiquimod 3.75%, 18.75 mg imiquimod) for BSA comparison. The maximum human AUC value obtained in the treatment of external genital and perianal warts was higher than that obtained in the treatment of actinic keratosis and was used in the calculation of animal multiples of MRHD that were based on AUC comparison.

Systemic embryofetal development studies were conducted in rats and rabbits. Oral doses of 1, 5 and 20 mg/kg/day imiquimod were administered during the period of organogenesis (gestational days 6–15) to pregnant female rats. In the presence of maternal toxicity, fetal effects noted at 20 mg/kg/day (163X MRHD based on AUC comparisons) included increased resorptions, decreased fetal body weights, delays in skeletal ossification, bent limb bones, and two fetuses in one litter (2 of 1567 fetuses) demonstrated exencephaly, protruding tongues and low-set ears. No treatment related effects on embryofetal toxicity or teratogenicity were noted at 5 mg/kg/day (28X MRHD based on AUC comparisons).

Intravenous doses of 0.5, 1 and 2 mg/kg/day imiquimod were administered during the period of organogenesis (gestational days 6–18) to pregnant female rabbits. No treatment related effects on embryofetal toxicity or teratogenicity were noted at 2 mg/kg/day (2.1X MRHD based on BSA comparisons), the highest dose evaluated in this study, or 1 mg/kg/day (115X MRHD based on AUC comparisons).

A combined fertility and peri- and post-natal development study was conducted in rats. Oral doses of 1, 1.5, 3 and 6 mg/kg/day imiquimod were administered to male rats from 70 days prior to mating through the mating period and to female rats from 14 days prior to mating through parturition and lactation. No effects on growth, fertility, reproduction or post-natal development were noted at doses up to 6 mg/kg/day (25X MRHD based on AUC comparisons), the highest dose evaluated in this study. In the absence of maternal toxicity, bent limb bones were noted in the F1 fetuses at a dose of 6 mg/kg/day (25X MRHD based on AUC comparisons). This fetal effect was also noted in the oral rat embryofetal development study conducted with imiquimod. No treatment related effects on teratogenicity were noted at 3 mg/kg/day (12X MRHD based on AUC comparisons).

Nursing Mothers

It is not known whether imiquimod is excreted in human milk following use of ZYCLARA Cream. Because many drugs are excreted in human milk, caution should be exercised when ZYCLARA Cream is administered to nursing women.

Pediatric Use

AK is a condition not generally seen within the pediatric population. The safety and effectiveness of ZYCLARA Cream for AK in patients less than 18 years of age have not been established.

Safety and effectiveness in patients with external genital/perianal warts below the age of 12 years have not been established.

Imiquimod 5% cream was evaluated in two randomized, vehicle-controlled,double-blind trials involving 702 pediatric subjects with molluscum contagiosum (MC) (470 exposed to imiquimod; median age 5 years, range 2–12 years). Subjects applied imiquimod cream or vehicle 3 times weekly for up to 16 weeks. Complete clearance (no MC lesions) was assessed at Week 18. In Study 1, the complete clearance rate was 24% (52/217) in theimiquimod cream group compared with 26% (28/106) in the vehicle group.

In Study 2, the clearance rates were 24% (60/253) in the imiquimod cream group compared with 28% (35/126) in the vehicle group. These studies failed to demonstrate efficacy.

Similar to the studies conducted in adults, the most frequently reported adverse reaction from 2 studies in children with molluscum contagiosum was application site reaction. Adverse events which occurred more frequently in imiquimod-treated subjects compared with vehicle-treated subjects generally resembled those seen in studies in indications approved for adults and also included otitis media (5% imiquimod vs. 3% vehicle) and conjunctivitis (3% imiquimod vs. 2% vehicle).

Erythema was the most frequently reported local skin reaction. Severe local skin reactions reported by imiquimod-treated subjects in the pediatric studies included erythema (28%), edema (8%), scabbing/ crusting (5%), flaking/scaling (5%), erosion (2%) and weeping/ exudate (2%).

Systemic absorption of imiquimod across the affected skin of 22 subjects aged 2 to 12 years with extensive MC involving at least 10% of the total body surface area was observed after single and multiple doses at a dosing frequency of 3 applications per week for 4 weeks. The investigator determined the dose applied, either 1, 2 or 3 packets per dose, based on the size of the treatment area and the subject's weight. The overall median peak serum drug concentrations at the end of week 4 was between 0.26 and 1.06 ng/mL except in a 2-year old female who was administered 2 packets of study drug per dose, had a Cmax of 9.66 ng/ mL after multiple dosing. Children aged 2–5 years received doses of 12.5 mg (one packet) or 25 mg (two packets) of imiquimod and had median multiple-dose peak serum drug levels of approximately 0.2 or 0.5 ng/ mL, respectively. Children aged 6–12 years received doses of 12.5 mg, 25 mg, or 37.5 mg (three packets) and had median multiple dose serum drug levels of approximately 0.1, 0.15, or 0.3 ng/mL, respectively. Among the 20 subjects with evaluable laboratory assessments, the median WBC count decreased by $1.4*10^9$/L and the median absolute neutrophil count decreased by $1.42*10^9$/L.

Geriatric Use

Of the 320 subjects treated with ZYCLARA Cream in the AK clinical studies, 150 subjects (47%) were 65 years or older. No overall differences in safety or effectiveness were observed between these subjects and younger subjects.

Clinical studies of ZYCLARA Cream for EGW did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Of the 400 subjects treated with ZYCLARA Cream, 3.75% in the EGW clinical studies, 5 subjects (1%) were 65 years or older.

OVERDOSAGE

Topical overdosing of ZYCLARA Cream could result in an increased incidence of severe local skin reactions and may increase the risk for systemic reactions.

Hypotension was reported in a clinical trial following multiple oral imiquimod doses of >200 mg (equivalent to ingestion of the imiquimod content of more than 21 packets or pump actuations of ZYCLARA Cream, 3.75% or more than 32 packets or pump actuations of ZYCLARA Cream, 2.5%). The hypotension resolved following oral or intravenous fluid administration.

PATIENT COUNSELING INFORMATION

"See FDA-approved patient labeling (Patient Information)"

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RESEARCHERS AFFIRM BENEFITS OF FRACTIONAL CO2 LASER SCAR TREATMENT

Lasers in Surgery and Medicine
October 2014

A RECENT STUDY appears to support findings that fractional CO2 laser treatment of hypertrophic and burn scars results in improvement of erythema, a common problem following treatment with vascular lasers.

To describe the mechanism behind reduced erythema following treatment with the fractional CO2 laser, researchers conducted an uncontrolled, prospective study of 10 patients with mature burn scars. They obtained biopsy specimens before and two months after three treatment sessions and performed anti-CD31 immunostaining to highlight vascular patterns.

Post-treatment histological analysis showed an 82.6 percent average increase in vascular density, particularly in small-caliber vessels. This increase correlated with a decrease in clinical erythema and vascularity scores, as measured by the Vancouver Scar Scale.

"What we learned from our research is that persistent long-term scar erythema can be multifactorial," study author David M Ozog, M.D., director of cosmetic dermatology at Henry Ford Hospital in Detroit, tells Dermatology Times. **DT**

—Bill Gillette

Read the study
bit.ly/burnscars

Study looks at pollution's adverse effects on skin

10th Annual Conference of the Chinese Dermatologist Association
November 2014

THE EFFECTS OF AIR POLLUTION on the skin trumps the benefits that can be gained through lifestyle choices such as proper diet and regular exercise.

In a collaborative project, Olay researchers joined with Wei Liu, M.D., head of the dermatology department at the General Hospital of the Air Force, Beijing, to study the relationship between that city's air quality and skin health.

Dr. Liu's team looked at the relationship between air quality and incidence of dermatological skin conditions among patients in Beijing, using data collected from 2013 to 2014. Nearly 15,000 patients were included in the analysis.

"Our initial study showed a positive correlation between PM2.5 values [particulate matter up to 2.5 micrometers] and the numbers of urticaria outpatients in Beijing," Dr. Liu tells Dermatology Times. "When the PM2.5 level is above 200μg/m3, the correlation starts to be stronger than in the lower level. Also, there's a lag effect of PM2.5 on urticarial outpatient number which can last up to 20 days. For us as researchers, this means we could set 200μg/m3 as the reference level in future research to study the impact of PM2.5 in high-level concentrations and the relationship between PM2.5 and other skin diseases.

"Further study is needed, but for dermatologists and their patients, it's becoming more and more important to acknowledge the influence of air pollution on skin diseases and take this influence into consideration while providing treatment suggestions, such as thorough and gentle cleansing and skin barrier repair."

On the Olay side of the project, a research team led by Olay Principal Scientist Frauke Neuser, Ph.D., conducted a year-long clinical study involving more than 200 women in Beijing's least and most polluted districts. The research team measured multiple aspects of skin health and appearance as well as noting participants' lifestyles and skin-care routines. They found that women who lived in highly polluted areas had significantly worse skin hydration and more compromised skin-barrier function than those living in the less-polluted suburbs. This held true even among women from the high-pollution districts who made better lifestyle choices than those in the less-polluted suburbs.

"While common sense suggests that air pollution would have a negative impact on skin health and appearance, very little published research is currently available," Dr. Neuser tells Dermatology Times. "Our finding that something as fundamental to skin's health as hydration and barrier function can be compromised by continued exposure to air pollution is therefore highly significant. Olay is committed to further research in this area, as only a better understanding of the exact biological mechanisms at work will allow us to develop better and more targeted skin care solutions." **DT**

—Bill Gillette

Read the study
bit.ly/pollutioneffects

STUDY HIGHLIGHTS BENEFITS OF INCISIONLESS OTOPLASTY

JAMA Facial Plastic Surgery
November/December 2014

INCISIONLESS OTOPLASTY is a reliable and replicable technique for correcting prominauris, recent study results indicate.

The study, led by Toronto plastic surgeon Andres Gantous, M.D., is based on a review of electronic medical records for 72 patients with prominauris — ranging in age from three to 55 years, with most being adults — who had undergone incisionless otoplasty by a single surgeon from November 2006 to April 2013. The mean follow-up time for outcomes was 31 months and included 70 patients.

The researchers found no significant difference in the number of sutures used in the left ear as compared with the right: a mean of 2.5 sutures in the left, 2.48 in the right. All patients had horizontal mattress sutures placed for correction of prominauris. No serious perioperative complications — such as infection, bleeding, hematoma, perichondritis or cartilage necrosis — were observed. Complications were seen in 10 patients: four were due to suture failure, three to suture exposure, two to granuloma formation and one to a Polysporin reaction. Nine patients needed a revision to achieve a desirable result.

"The most significant finding from this study is that we were able to show that the incisionless otoplasty technique is a good option in treating prominent ears — equal to or better than the more traditional techniques and very safe," Dr. Gantous tells *Cosmetic Surgery Times*. "This surgical approach is easy to learn and master, offers a more comfortable and quicker recovery and has few if any serious complications." **DT**

—Bill Gillette

Read the study
bit.ly/incisionlessotoplasty

Dermatology Times

New topical antifungals provide better penetration

JOHN JESITUS | STAFF CORRESPONDENT

Efinaconozole and tavaborole use non-lacquer vehicles to help them penetrate the nail surface more effectively versus previous topical antifungal agents for onychomycosis, according to David M. Pariser, M.D., professor, Eastern Virginia Medical School department of dermatology and past president, American Academy of Dermatology (AAD).

"Toenail fungus, although not the scourge of the earth, is a very common problem which can produce discomfort and physical and cosmetic disability," Dr. Pariser says. To date, he adds, the primary treatments for onychomycosis have been systemic agents.

Conversely, "The topical agents we've had up to now have not been that effective. And many people either don't want to take systemic drugs for toenail fungus, or they're afraid of side effects."

QUICK READ

New topical antifungal treatments provide better penetration and efficacy than their predecessors, says an expert.

Many patients fear such side effects more than actual adverse event rates warrant, Dr. Pariser emphasizes. Still, "Most doctors don't want to prescribe a drug to somebody who doesn't want to take it for fear of side effects."

Additionally, he says, "The primary challenge in topical treatment is getting the active antifungal ingredient to penetrate through the nail and get under the nail where the infection actually is." The infection does not penetrate from the nail bed into the nail itself until late in the infection's course, he explains. "So if you're just treating the top surface of the nail, you're not getting where the action is."

MORE EFFECTIVE FORMULATIONS

To avoid this problem, Dr. Pariser says, the new topical antifungals have been formulated to penetrate the nail much more effectively than nail lacquers, which essentially remain on the nail surface. In contrast, he says that the water-soluble vehicles for efinaconozole and tavaborole are "clear, runny liquids containing surfactants that allow them to penetrate either through or around the nail to the nail bed. And that's what gives them the higher efficacy" than previous topical agents provide.

In phase 3 studies, subjects used either efinaconozole or tavaborole daily for 48 weeks, with an efficacy assessment at 52 weeks. Efficacy calculations also depend partly on how much of the nail was affected at baseline, Dr. Pariser adds. In this regard, the efinaconozole and tavaborole studies' enrollment criteria

TOPICAL ANTIFUNGAL *see page* **33**

Quotable

"In this case, it is the nanoparticle, the delivery system, that both allows us to now effectively deliver nitric oxide to the skin, and, more importantly, generate the NO in the first place."

Adam Friedman, M.D.
Bronx, N.Y.

on drug delivery technologies

See story page 21

DTExtra

Researchers in the Netherlands evaluated an argon gas-based system for the treatment of keloids in 25 patients of all Fitzpatrick skin types with a total of 30 keloid scars. Scar quality and possible scar recurrence were assessed before treatment and at six and 12 months post-treatment. The 12-month follow-up revealed an overall volume reduction of 62 percent. Scar pigmentation recovered in 62 percent of all keloid scars within 12 months. Five of 30 scars (17 percent) recurred within 12 months — three of those five had previously been treated with liquid nitrogen-based IL cryotherapy.

MORE ON THE FINDINGS: BIT.LY/KELOIDSCARTX

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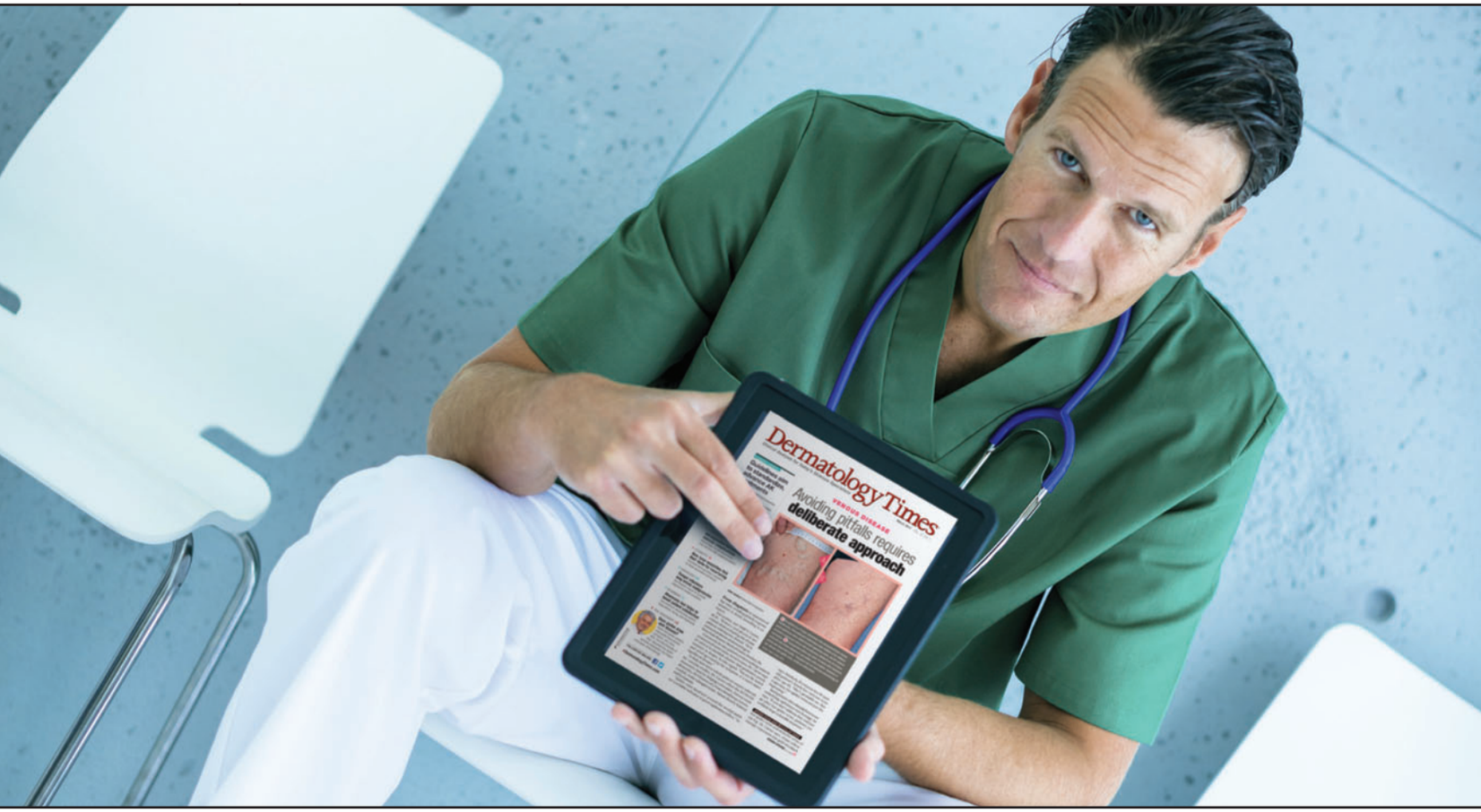

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Biofilm presents challenge in wound care

LOUISE GAGNON | STAFF CORRESPONDENT

EMERGING DRESSINGS used in wound care will have to address biofilm in order to achieve effective wound healing.

"It's very hard to treat the biofilm component of a wound," says Randall Wolcott, M.D., founder and medical director, Regional Wound Care Center in Lubbock, Texas. Biofilm behaves differently than planktonic bacteria, which is associated with acute infection, Dr. Wolcott explains.

"They are different phenotypes," Dr. Wolcott says. "When you treat, you should treat both (planktonic bacteria and biofilm). Biofilm attaches and inflames the tissue in the host environment, and it uses plasma to nourish itself."

Addressing biofilm improves health and reduces health-care costs in medical practice, Dr. Wolcott says. In the United States, chronic wounds affect 6.5 million patients. More than US$25 billion is estimated to be dedicated to the treatment of chronic wounds, and that cost is growing with increasing health care costs, an aging population, and a steep climb in the incidence of diabetes and obesity worldwide. *Wound Repair and Regeneration*. 2009;17(6):763-771.

A dressing needs to contain components to allow the physical disruption of biofilm, Dr. Wolcott explains.

The formulation of wound care dressings that tackle biofilm are based on principles of allowing the antimicrobial agent to more effectively penetrate through the biofilm to kill cells, Dr. Wolcott explains, noting in some designs that includes a chelating agent.

The efficacy of a dressing can make the difference between a patient losing or salvaging a limb, according to Dr. Wolcott. "If we save a limb, we can save a life," Dr. Wolcott says.

A RETROSPECTIVE, COHORT STUDY

A retrospective, cohort study that looked at mortality rate after a first lower limb amputation found nearly one quarter of people died within 30 days after a first lower limb amputation and almost half at one year. *European Journal of Vascular and Endovascular Surgery*. 2013 Jul;46(1):124-31.

Speaking about research into new antimicrobial dressings, Phil Bowler, vice-president, science & technology, ConvaTec, agrees that biofilm is not going away and is a serious threat to medicine.

"It's a major problem in medicine that is not limited to wound care," Mr. Bowler says. "It is not new, but the recognition of biofilm involvement in infectious diseases is fairly new. It is involved, for example, in urinary tract infections, periodontal disease, and otitis media. Biofilm is so difficult to manage because it is tolerant to antimicrobial agents and leads to chronicity."

To address biofilm, wound bed preparation is vital to successful wound healing, Mr. Bowler says.

"Wound bed preparation is important through debridement and cleansing, giving the wound the best chance to heal," Mr. Bowler says. "That preparation can involve physical techniques like sharp debridement and appropriate antimicrobial strategies. These are wounds that are 'stuck' and are not healing."

Future strategies may involve combination technologies where anti-biofilm agents help to maximize the efficacy of antimicrobial agents such as antibiotics and antiseptics.

ConvaTec has recently developed a dressing designed to manage the local wound environment and also break down wound biofilm, which is approved for use in the European Union and in Canada. ConvaTec is seeking clearance of such a dressing by the U.S. Food and Drug Administration for use in the United States. **DT**

Study measures social impact of facial lesions

BILL GILLETTE | STAFF CORRESPONDENT

RESEARCHERS AT Johns Hopkins School of Medicine have released the results of a study that measures the social impact of facial lesions before and after surgical reconstruction — a topic not investigated heretofore.

In a prospective, randomized setting, 120 people were asked to view images of faces with lesions of varying sizes and locations before and after reconstruction. For comparison, they also viewed lesion-less faces. The observers were instructed to rate faces using a battery of metrics, including how comfortable they would be having a conversation with the participant in each facial image. The conversation questions were answered on a scale of zero to 100, with higher numbers indicating a higher level of comfort the observer would feel talking with the face viewed.

RESEARCHERS FOUND:

- The mean conversation score for subjects with lesion-less faces was 85.02
- Facial lesions had a negative effect, or penalty, on conversation (61.63)
- Penalties varied with lesion size and location, with large and central lesions generating the greatest penalty
- Reconstructive surgery increased observers' comfort and willingness to converse with individuals with facial lesion by an average of 19.83 points, an improvement that also varied with preoperative lesion size and location
- Reconstructive surgery seemed to normalize observer comfort in communicating with people with small peripheral, small central and large peripheral lesions
- Even after surgery, substantial discomfort communicating with patients with large central lesions remained

"Facial lesions induce a significant social penalty as rated by the casual observer," the authors write. "Specifically, observers are less comfortable communicating with people who have facial lesions. Surgical reconstruction of facial lesions increased observers' comfort in conversing with people with facial lesions, an impact that varied with lesion size and location."

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

Advancing Research 2015

Drug delivery an important research focus

Lisette Hilton | Senior Staff Correspondent

THERAPEUTIC DELIVERY is an important research focus, according to Dr. Friedman, who has won several awards for his research, including the American Dermatologic Association Young Leadership Award, for a decade of research identifying a way to utilize nanotechnology to generate nitric oxide.

Dr. Friedman's research is an example of the importance of drug delivery options. While NO is not new, its use has been limited because NO is short-lived, according to Dr. Friedman. It has the potential, however, to effectively heal wounds, fight skin infections, stimulate pigment production, enhance blood flow and more.

"[To date] I have to be nine publications showing that the technology can accelerate wound healing as well as clear up infection in MRSA-infected incision wounds. NO is also very good at clearing burn infections infected with candida albicans, a very common yeast in the environment that's well known for wreaking havoc on burn victims," he says.

But too much NO is not good. Too much NO will kill everything, Dr. Friedman says.

The focus of drug development research has long been on the drug, Dr. Friedman says. The transition in recent years has been to include an emphasis on how active agents are being delivered.

"If you look up what drugs have come out recently, you see acne drugs, for example, Epiduo [adapalene and benzoyl peroxide gel, Galderma]. They're unique in how they're being delivered. The active agents have been around."

The development of drug delivery technologies have the potential, he says, to enhance topical drugs' penetration through the skin, make drugs more tolerable and increase compliance.

"Hence, we have nitric oxide, a seemingly simple gaseous molecule which has escaped us for God knows how long in terms of our ability to use it in the clinical space due to its high reactivity and short half-life," he says. "In this case, it is the nanoparticle, the delivery system, that both allows us to now effectively deliver nitric oxide to the skin, and, even importantly, generate it the NO in the first place. The nanoparticle, itself, is the key to creating the active agent—a 'smart' delivery vehicle if you will." **DT**

Advancing Research 2015

Experts highlight areas laying groundwork for better understanding, treatments *from page* 1

ways in which to correct it at the genetic level.

"Now there are studies that show we can replace a protein or put cells into a child who has a genetic defect, let's say a blistering disease defect," Dr. Cooper says. "Clinical trials are in process, and those therapies are being studied now to determine practicality. If they are efficacious and safe, they'll help kids and may lay the groundwork for other cell-based or protein therapies for other diseases."

Research analyzing the entire human genome is phenomenal, according to researcher and dermatologist Steven R. Feldman, M.D., Ph.D., professor of dermatology, Wake Forest University School of Medicine, Winston-Salem, NC.

"I anticipate that [researchers] are going to keep finding, through genetics, a better understanding of diseases like psoriasis and alopecia areata that will transform our understanding, if not the treatment, of those conditions," Dr. Feldman says.

Today's dermatology researchers are not only coding for certain genes and alterations of RNA molecules that code for proteins, but they're also looking at how non-coding RNAs regulate how cells work. It's more akin to epigenetics—changes brought on by the cellular environment that causes genes to be turned on or off over time, according to Dr. Cooper. This area of study, according to Dr. Cooper, is likely to affect inflammatory diseases, including psoriasis and eczema, as well as diseases acquired with age, such as photoaging and skin cancers.

"I don't think we'll see any such new therapeutics next year but it's an area that's being studied pretty intensively because it offers new opportunities with intellectual property and the ability to target disease processes in a different way," Dr. Cooper says.

"I anticipate that [researchers] are going to keep finding, through genetics, a better understanding of diseases like psoriasis and alopecia areata..."

Steven Feldman, M.D., Ph.D.
Winston-Salem, N.C.

Tips for junior investigators

This is a challenging time for researchers—especially younger, less established investigators, says Adam Friedman, M.D., assistant professor of medicine (dermatology)/physiology and biophysics and director of dermatologic research at Montefiore - Albert Einstein College of Medicine, Bronx, NY. Money is short, so researchers have to work extra hard to secure funding.

TIPS TO FELLOW JUNIOR INVESTIGATORS:

- ☑ The theme in federal funding, foundational funding and industry funding is there has to be a clinical endpoint or translatability to the work. That's not always the case, but often it is.
- ☑ Especially with NIH funding, a lot of it is who you know. Put the time in on committees, meeting people and submitting multiple grants.
- ☑ Consider nontraditional routes. There are ways to find synergy between your interests and those of industry. The turnaround with and accessibility to industry partners is often faster and easier then when dealing with federal sources.
- ☑ There are plenty of foundations looking to support junior faculty. "I would not be where I am today without the Dermatology Foundation – let them be there for you," he says.

Finally, don't give up."It's not easy, but it's worth it because one small finding can have a ripple effect. And one day that single data point could change the lives of millions of people," he says. DT

IMMUNE SYSTEM MODIFICATION

Melanoma research is among the areas setting the stage for a series of medications that modify the immune system or modify signaling that melanoma cells need.

"That area continues to evolve, where people are combining immunologic therapy with cell signaling therapy or boosting the immune system in another way in order to optimize combination therapies for melanoma patients," Dr. Cooper says.

Trying to suppress or modify the immune system is another exciting area in research.

Dr. Feldman says there's a lot of work going on in psoriasis and inflammatory diseases, looking at comorbidities of inflammatory disease and new treatments based on a growing understanding of the immune system. Then, comes research on the marriage of those two: what the effects of those treatments are on the comorbidities of inflammatory disease, Dr. Feldman says.

"With psoriasis, we've seen a lot of new drugs, and we're going to see more drugs in the IL23, IL17 pathways. Those are very exciting in the sense that they're very specifically targeted. They're antibodies. They don't have the toxicity of small molecules. They can reverse an altered balance, without knocking down the entire immune system," Dr. Cooper says.

Topical and systemic agents are being developed thanks to research looking at signaling pathways required for T-cell activation, and small molecule inhibitors for what are called the JAK-STAT pathways. These drugs allow a more nimble wash-out, if desired. While researchers don't yet know the full implications to dermatology, there's evidence to suggest these agents will benefit psoriasis, as well as auto-inflammatory diseases, such as alopecia areata, Dr. Cooper says.

ADVANCING RESEARCH *see page* 25

Desonate®
(desonide) Gel 0.05%

INDICATION & USAGE

Desonate® (desonide) Gel 0.05% is indicated for the treatment of mild to moderate atopic dermatitis in patients 3 months of age and older.

Patients should be instructed to use Desonate® for the minimum amount of time as necessary to achieve the desired results because of the potential for Desonate® to suppress the hypothalamicpituitary-adrenal (HPA) axis. Treatment should not exceed 4 consecutive weeks.

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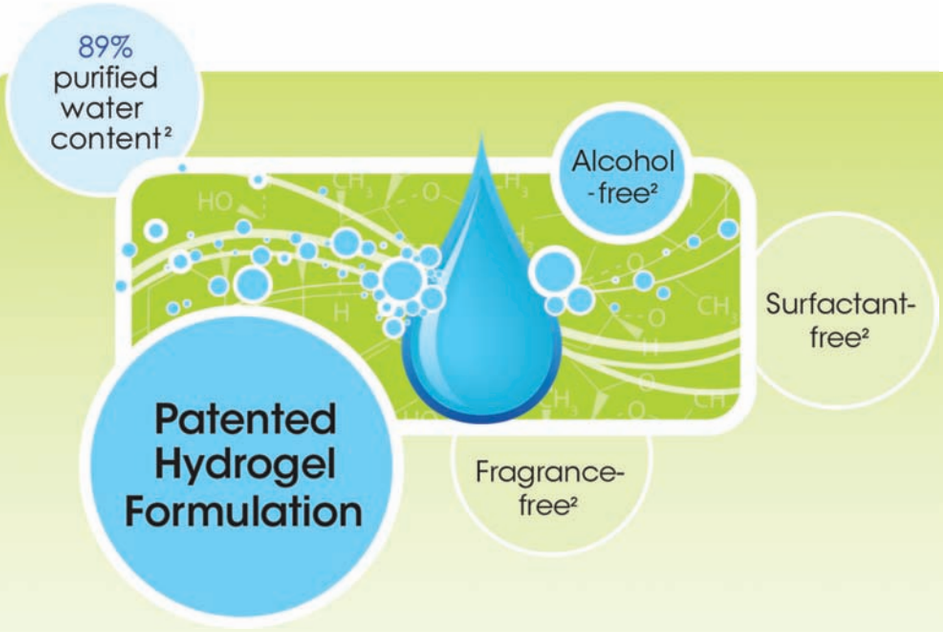

About Desonate®

- Approved for use in patients 3 months of age and older.
- Pediatric patients may be more susceptible to systemic toxicity due to their larger skin surface-to-body mass ratios. Unless directed by a physician, do not use on the underarm or groin area of children. Do not use to treat diaper dermatitis. Use in children less than 3 months of age is not recommended.
- No AB rated generic equivalent[1]

IMPORTANT SAFETY INFORMATION

Desonate® is contraindicated in those patients with a history of hypersensitivity to any of the components of the preparation.

Topical corticosteroids can produce reversible hypothalamic pituitary adrenal (HPA) axis suppression with the potential for clinical glucocorticosteroid insufficiency, Cushing's syndrome, hyperglycemia and unmasking of latent diabetes. Systemic absorption may require periodic evaluation 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. 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 due to their larger skin surface-to-body mass ratios. Unless directed by a physician, do not use on the underarm or groin area of children. Do not use to treat diaper dermatitis. Use in children less than 3 months of age is not recommended.

Local adverse reactions may be more likely to occur with occlusive use, prolonged use or use of higher potency corticosteroids. Reactions may include skin 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.

If concomitant skin infections are present or develop during treatment, an appropriate antifungal or antibacterial agent should be used. If a favorable response does not occur promptly, use of Desonate® should be discontinued until the infection is adequately controlled.

If irritation develops, Desonate® should be discontinued and appropriate therapy instituted.

The most common adverse reactions (incidence ≥ 1%) are headache, application site burning and rash.

Desonate® is for topical use only. Not for ophthalmic, oral or intravaginal use. As with other corticosteroids, therapy should be discontinued when control is achieved.

See adjacent page for Brief Summary of full Prescribing Information.

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

References: **1**. US Food and Drug Administration. Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations. Active ingredient search results from "OB_Rx" table for query on "desonide." http://www.accessdata.fda.gov/scripts/cder/ob/docs/tempai.cfm. Accessed July 2014. **2**. Kircik L, Del Rosso J. A novel hydrogel vehicle formulated for the treatment of atopic dermatitis. J Drugs Dermatol. 2007;6(7):718-722. Drugs Dermatol. 2007;6(7):718-722.

DESONATE® (desonide) Gel 0.05%

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BRIEF SUMMARY
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1 INDICATIONS AND USAGE

Desonate is indicated for the treatment of mild to moderate atopic dermatitis in patients 3 months of age and older.

Patients should be instructed to use Desonate for the minimum amount of time as necessary to achieve the desired results because of the potential for Desonate to suppress the hypothalamic-pituitary-adrenal (HPA) axis *[see Warnings and Precautions (5.1)]*. Treatment should not exceed 4 consecutive weeks *[see Dosage and Administration (2)]*.

4 CONTRAINDICATIONS

Desonate is contraindicated in those patients with a history of hypersensitivity to any of the components of the preparation.

5 WARNINGS AND PRECAUTIONS

5.1 Effects on Endocrine System

Systemic absorption of topical corticosteroids can produce reversible hypothalamic-pituitary-adrenal (HPA) axis suppression with the potential for clinical glucocorticosteroid insufficiency. This may occur during treatment or upon withdrawal of the topical corticosteroid.

The effect of Desonate on HPA axis function was investigated in pediatric subjects, 6 months to 6 years old, with atopic dermatitis covering at least 35% of their body, who were treated with Desonate twice daily for 4 weeks. One of 37 subjects (3%) displayed adrenal suppression after 4 weeks of use, based on the cosyntropin stimulation test. As follow-up evaluation of the subject's adrenal axis was not performed, it is unknown whether the suppression was reversible *[see Use In Specific Populations (8.4) and Clinical Pharmacology (12.2)]*.

Pediatric patients may be more susceptible than adults to systemic toxicity from equivalent doses of Desonate due to their larger skin surface-to-body mass ratios *[see Use In Specific Populations (8.4)]*.

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 more potent steroids, use over large surface areas, use over prolonged periods, use under occlusion, use on an altered skin barrier, and use in patients with liver failure.

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.

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 skin 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 Concomitant Skin Infections

If concomitant skin infections are present or develop during treatment, an appropriate antifungal or antibacterial agent should be used. If a favorable response does not occur promptly, use of Desonate should be discontinued until the infection is adequately controlled.

5.4 Skin Irritation

If irritation develops, Desonate should be discontinued and appropriate therapy instituted. Allergic contact dermatitis with corticosteroids is usually diagnosed by observing failure to heal rather than noting a clinical exacerbation as with most topical products not containing corticosteroids. Such an observation should be corroborated with appropriate diagnostic patch testing.

6 ADVERSE REACTIONS

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 controlled clinical studies of 425 Desonate-treated subjects and 157 Vehicle-treated subjects, adverse events occurred at the application site in 3% of subjects treated with Desonate and the incidence rate was not higher compared with vehicle-treated subjects. The most common local adverse events in Desonate treated subjects were application site burning in 1% (4/425) and rash in 1% (3/425) followed by application site pruritus in <1% (2/425).

Adverse events that resulted in premature discontinuation of study drug in Desonate treated subjects were telangiectasia and worsening of atopic dermatitis in one subject each. Additional adverse events observed during clinical trials for patients treated with Desonate included headache in 2% (8/425) compared with 1% (2/157) in those treated with vehicle.

The following additional local adverse reactions have been reported infrequently with topical corticosteroids. They may occur more frequently with the use of occlusive dressings, especially with higher potency corticosteroids. These reactions are listed in an approximate decreasing order of occurrence: folliculitis, acneiform eruptions, hypopigmentation, perioral dermatitis, secondary infection, skin atrophy, striae, and miliaria.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Teratogenic effects: Pregnancy Category C:

There are no adequate and well-controlled studies in pregnant women. Therefore, Desonate 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. Some corticosteroids have been shown to be teratogenic after dermal application in laboratory animals.

No reproductive studies in animals have been performed with Desonate. Dermal embryofetal development studies were conducted in rats and rabbits with a desonide cream, 0.05% formulation. Topical doses of 0.2, 0.6, and 2.0 g cream/kg/day of a desonide cream, 0.05% formulation or 2.0 g/kg of the cream base were administered topically to pregnant rats (gestational days 6-15) and pregnant rabbits (gestational days 6-18). Maternal body weight loss was noted at all dose levels of the desonide cream, 0.05% formulation in rats and rabbits. Teratogenic effects characteristic of corticosteroids were noted in both species. The desonide cream, 0.05% formulation was teratogenic in rats at topical doses of 0.6 and 2.0 g cream/kg/day and in rabbits at a topical dose of 2.0 g cream/kg/day. No teratogenic effects were noted for the desonide cream, 0.05% formulation at a topical dose of 0.2 g cream/kg/day in rats and 0.6 g cream/kg/day in rabbits. These doses (0.2 g cream/kg/day and 0.6 g cream/kg/day) are similar to the maximum recommended human dose based on body surface area comparisons.

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 Desonate is administered to a nursing woman.

8.4 Pediatric Use

Safety and effectiveness of Desonate in pediatric patients less than 3 months of age have not been evaluated, and therefore its use in this age group is not recommended.

The effect of Desonate on HPA axis function was investigated in pediatric subjects, with atopic dermatitis covering at least 35% of their body, who were treated with Desonate twice daily for 4 weeks. One of 37 subjects (3%) displayed adrenal suppression after 4 weeks of use, based on the cosyntropin stimulation test *[see Warnings and Precautions (5.1)]*.

In controlled clinical studies in subjects 3 months to 18 years of age, 425 subjects were treated with Desonate and 157 subjects were treated with vehicle *[see Adverse Reactions (6) and Clinical Studies (14)]*.

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 when they are treated with topical corticosteroids. They are therefore also at greater risk of glucocorticosteroid insufficiency after withdrawal of treatment and of Cushing's syndrome while on treatment.

Adverse effects, including striae, have been reported with inappropriate use of topical corticosteroids in infants and children. 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.

8.5 Geriatric Use

Clinical studies of Desonate did not include patients aged 65 and older to determine if they respond differently than younger patients. Treatment of this patient population should reflect the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

17 PATIENT COUNSELING INFORMATION

Patients using topical corticosteroids should receive the following information and instructions:

- This medication is to be used as directed by the physician. It is for external use only. Avoid contact with the eyes.
- This medication should not be used for any disorder other than that for which it was prescribed.
- Unless directed by the physician, the treated skin area should not be bandaged or otherwise covered or wrapped so as to be occlusive.
- Unless directed by a physician, this medication should not be used on the underarm or groin areas of pediatric patients.
- Parents of pediatric patients should be advised not to use Desonate in the treatment of diaper dermatitis. Desonate should not be applied in the diaper area, as diapers or plastic pants may constitute occlusive dressing *[see Dosage and Administration (2)]*.
- Patients should report to their physician any signs of local adverse reactions.
- Other corticosteroid-containing products should not be used with Desonate without first consulting with the physician.
- As with other corticosteroids, therapy should be discontinued when control is achieved. If no improvement is seen within 4 weeks, contact the physician.

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Rev. July 2014

Advancing Research 2015

Experts highlight areas laying groundwork for better understanding, treatments *from page* **22**

BASIC SKIN RESEARCH

Today's research might be sophisticated, but it continues to ask the basic question: How does the skin work? Researchers are always looking at basic interactions between cells and the skin, to identify mechanisms of those interactions and how those cells work. That knowledge helps to identify what Dr. Cooper calls "druggable" targets, as well as why it is that treatments work.

One example of this kind of research is dermatology's paradigm shift in atopic dermatitis.

"In atopic dermatitis, we've really evolved our understanding from it being primarily an allergic disease to being a barrier disease with altered microbiome, all intertwined. Now we have new therapies that are coming into atopic dermatitis as a result of that," Dr. Cooper says.

Stem cell researchers in the specialty continue to study stem cells' potential to differentiate into cells needed to replace cells lost with disease or aging. Target areas for stem cell therapy include vitiligo, hair loss and aesthetic dermatology, Dr. Cooper says.

LOOKING BEYOND THE SKIN

The skin-nerve-brain connection is a hot topic in research, Dr. Cooper says. Among the many questions researchers are trying to answer: How does itch occur? Is it always in the skin? In the spine? In the brain? Can you test that? How do skin diseases create anxiety and depression and vice versa? If your nervous system is not working right, does that affect your immunology? Does the inflammation have a role in mood, per se?

BIG DATA

Big data is opening big doors in genetics and other areas of dermatology. Large databases from multiple specialties, full of information about patients' genetics, the diseases they have and the drugs they're on are becoming the Holy Grail, according to Dr. Cooper.

"Knowing the genetics of people and linking that to their healthcare outcomes over time is a very important area. We're sort of that the beginning of that," he says.

With access to big data, researchers should better understand many things at the practice to population levels, including which patients respond to treatments and which don't. The result? Personalized medicine, according to Dr. Cooper.

> "Knowing the genetics of people and linking that to their healthcare outcomes over time is a very important area."
>
> **Kevin Cooper, M.D.**
> Cleveland, OH

GAPS REMAIN

Research and research dollars need to focus on what's common in dermatology, according to Dr. Feldman.

"If I could cure one thing, I would find a cure for warts," Dr. Feldman says.

"Dermatologists have little to offer patients with warts and there isn't much in the pipeline as far as I'm aware," he says. "We tend to put our focus on narrow scientific issues that are totally fascinating, and they highlight a greater understanding of human biology. But the real opportunities lie, I think, in much broader, more common, less 'test-tubey' kinds of research."

ADVANCING RESEARCH *see page* **26**

Closing Gaps in Psoriasis Research

Dr. Feldman and colleagues reported in January 2014 that gaps remain in psoriasis research. Based on their study, the authors recommend:

- *Basic science and clinical research studies to determine the true prevalence and natural history of psoriasis.*
- *Studies to pinpoint disease severity biomarkers and treatment response to improve patient therapy.*
- *Investigations centered on the relationship between cardiometabolic disease and psoriasis.*
- *Studies examining environmental factors' roles in psoriasis development of psoriasis.*
- *Studies focused on the potential impact of adjunctive therapies, including psychological interventions.*
- *Molecular studies in patients with psoriasis and psoriatic arthritis, looking at the function of psoriasis susceptibility genes and to identify new therapeutic targets.*

Source: Ryan C, Korman NJ, Gelfand JM, Lim HW, Elmets CA, Feldman SR, Gottlieb AB, Koo JY, Lebwohl M, Leonardi CL, Van Voorhees AS, Bhushan R, Menter A. Research gaps in psoriasis: opportunities for future studies. J Am Acad Dermatol. 2014 Jan;70(1):146-67. doi: 10.1016/j.jaad.2013.08.042. Epub2013 Oct 11. Review.

Advancing Research 2015

Experts highlight areas laying groundwork for better understanding, treatments *from page* **25**

Seborrheic dermatitis is another example of something that seems so simple but remains elusive, according to Adam Friedman, M.D., assistant professor of medicine (dermatology)/physiology and biophysics and director of dermatologic research at Montefiore - Albert Einstein College of Medicine, Bronx, NY.

"No question, a couple of patients come to the practice with it every day. We still don't 100 percent understand how it really happens. Therefore, the treatments haven't changed that much. I think there needs to be continuing stimulus to encourage investigators to not just evaluate if a drug is effective, but to elucidate the pathophysiologic underpinnings of the disease, itself, to better identify new and more specific drug targets," Dr. Friedman says. **DT**

> **If I could cure one thing, I would find a cure for warts."**
>
> **Stephen R. Feldman, M.D., Ph.D.**
> Winston-Salem, N.C.

Gaps in dermatology research

Kevin D. Cooper, M.D., professor and chair of dermatology at Case Western Reserve University and University Hospitals Case Medical Center, Cleveland, Ohio, and **Steven R. Feldman, M.D., Ph.D.,** professor of dermatology, Wake Forest University School of Medicine, Winston-Salem, N.C., weigh in on important gaps in dermatology research today.

Measuring results Interestingly, one of the gaps in dermatology research is the specialty's lack of outcomes measures, Dr. Cooper says. "Research in outcome measures is needed in dermatology, and it's being done. The American Academy of Dermatology is working on trying to get consensus outcomes measures for a variety of inflammatory and neoplastic skin diseases," Dr. Cooper says.

Understanding adverse events Dr. Cooper says he doesn't think the specialty has a good grasp of adverse events. An example at the practice level is how often do your patients get an adverse reaction when you prescribe antibiotics?

Drug targets transitioning to drugs Derm research doesn't always attract coveted attention from big pharma, according to Dr. Cooper, because skin diseases aren't as financially attractive as cardiology, for example. Because of that, dermatology has many more "druggable" targets than there are drugs being developed, he says.

Engineering a human skin model An area of research that is needed in the specialty and is underway is in developing a three-dimensional human skin equivalent model, Dr. Cooper says. "We have animal models. Those models are really useful for segments of disease, but there is a gap in understanding how well they actually model human skin disease. How well do they model eczema, psoriasis, melanoma?" Dr. Cooper says.

Better imaging techniques Imaging is yet another research area that needs focus in the specialty, Dr. Cooper says. "A lot of other fields have very sophisticated imaging. And we have some imaging devices to try and computerize the features that are being seen by the eyes, but it's still pretty much what we see. Can we image the cells that are moving? Do we know what the cells are doing functionally versus having a static biopsy?" Dr. Cooper says.

Understanding bugs and derm disease Translating our understanding of microbiome to therapeutic interventions remains a mystery. Among those questions, according to Dr. Cooper: How do the bugs that we carry influence diseases that we have or the function of those diseases?

Understanding healthcare disparities Dermatology lacks a solid understanding of where socioeconomic, ethnic and other disparities exist, and how healthcare systems and access to healthcare affect disparity-related health outcomes. "There are people out there with severe acne getting scars. In theory, there's probably no reason why anybody should ever have a scar from acne. It's treatable, we can prevent severe acne, we can cure the disease, but we have people running around who aren't in our offices and we're not getting to provide them the therapy," Dr. Feldman says.

Connecting the skin and brain Research focused on the skin-brain connection in dermatology is not getting the attention it deserves, some say. That includes studies on psychosocial impacts on skin disease and behavioral research. More knowledge about how emotions and behaviors affect compliance, disease and outcomes would be a big boost in dermatology, where many patients struggle psychologically with skin issues. **DT**

TOPICAL ANTIFUNGAL:
Newer formulations offer better penetration, efficacy than predecessors *from page* **18**

stipulated that patients could have up to 50 percent nail involvement and 60 percent nail involvement, respectively.

Comparing cure rates in onychomycosis studies requires caution, Dr. Pariser says. In such studies, the Food and Drug Administration (FDA) mandates that the definition of "complete cure" include complete clinical and mycological cure – a completely normal nail appearance and a total absence of fungus observed in culture and KOH stain.

> "With even the best oral agents available now, complete clearance rates are slightly under 50 percent. That's because of the extremely stringent criteria" set by the FDA."
>
> **David M. Pariser, M.D.**
> Norfolk, Va.

"With even the best oral agents available now, complete clearance rates are slightly under 50 percent. That's because of the extremely stringent criteria" set by the FDA. "Even if you had a treatment that completely and permanently eradicated the fungus, the nail may never look completely normal because the infection may have damaged the nail matrix. Or the nail itself might have experienced some sort of trauma originally, and that's why the patient got the fungal infection in the first place."

Conversely, the new topical agents offer complete cure rates of six percent to 18 percent, depending on the study. Specifically, efinaconozole's complete cure rate was 18.5 percent, versus 4.7 percent for vehicle (P<0.001; Gupta AK, Elewski BE, Sugarman JL et al. J Drugs Dermatol. 2014 Jul;13(7):815-20.). Additionally, in two separate studies, tavaborole achieved complete cure rates of 6.5 percent and 9.1 percent, versus 0.5 percent and 1.5 percent, respectively, for vehicle.[1]

For both products, however, Dr. Pariser says, "The rate of negative cultures – actual obliteration of the fungus, even if the nail isn't completely normal – was above 50 percent." Furthermore, he adds, approximately 30 percent of patients achieved 90 percent clinical clearance, although it was defined differently in the two studies.

"If you look at the mycological cure rate, the number for efinaconozole – around 55 percent – is almost the same as for oral itraconazole, but still a bit less than for oral terbinafine (just under 70 percent). The two new topicals do not have as high an efficacy rate as the oral drugs do, but they're better than any of the topical drugs we've had" in terms of efficacy.

SIDE EFFECT PROFILES

As with previous topical agents, Dr. Pariser says, "The side effect profiles of the new topicals are pretty minimal, including, in some cases, a very small amount of irritation." But the new treatments provide no systemic absorption and therefore cause no systemic side effects, he says. As such, "There's no real or perceived problem with side effects. So patients may be more likely to use them" than existing oral agents.

The most commonly used oral antifungal, terbinafine, requires liver function testing because it has been associated with liver problems in some patients. "Also, a small number of patients on the drug experience alterations in their sense of taste," he says. Additional patient concerns include the fact that oral antifungals can interact negatively with other drugs such as blood pressure and cholesterol medications.

Because some patients indeed experience adverse events with oral antifungals, Dr. Pariser says, "It's good that we've got some new topical alternatives that have better efficacy" than previous topical treatments for this condition.

> "There's no real or perceived problem with side effects. So patients may be more likely to use [the new topicals]" than existing oral agents.
>
> **David M. Pariser, M.D.**
> Norfolk, Va.

From a practical standpoint, he adds, study protocols prohibited the use of nail polish. "In the real world, there are patients who will not go a year without using nail polish." To see what would happen when one applies these drugs over nail polish, Dr. Pariser tried it on a highly anecdotal sample – his own nails.

"I found that efinaconozole, which has the higher efficacy rate, dissolves nail polish." Accordingly, he says that it's more practical to use tavaborole in these circumstances because it doesn't dissolve nail polish. "That may be a factor in why patients would choose one versus the other – the ability to wear nail polish while under treatment." **DT**

Disclosure: Dr. Pariser has been an investigator and consultant for Valeant, maker of efinaconozole, and an investigator for Anacor, maker of tavaborole.

For more information:
www.clinicaldermconf.org
http://www.globalacademycme.com/conferences.html

Reference:
1 http://investor.anacor.com/releasedetail.cfm?ReleaseID=858211

Dermatology Times

39 AT-HOME DEVICES: BOOM OR BUST?
Using these devices as therapy adjuncts — even profit centers.

The medical spa: pros, cons and legalities

LISETTE HILTON | STAFF CORRESPONDENT

QUICK READ

Medspas can be a great add-on business, but experts strongly advise understanding issues of legality, which vary by state, and proper management.

DERMATOLOGISTS AND cosmetic surgeons who direct medical spas — whether these medical practices are extensions of their practices or not — assume responsibility for all procedures performed. And while it can be a financially rewarding career move, getting involved is not always simple, nor is it easy. In fact, many physician and nonphysician medspa owners may be operating these facilities illegally and not know it.

"As a medical director, [physicians are] putting their licenses on the line for basically anything that's going on in that medspa."

Landon Pryor, M.D.
Rockford, Ill.

Alex Thiersch, J.D., sees and hears about cases involving medspas all the time. Thiersch, founder and director of the American Med Spa Association (AmSpa) and partner at Thiersch and Associates, a Chicago-based law firm specializing in medical spa regulation, says medspas loosely encompass any aesthetic practice that offers services like Botox, fillers, laser hair removal, tattoo removal and more.

Dermatologists and cosmetic surgeons who get involved in medspas usually don't intend to do anything wrong. The business model might make perfect sense on the outside, but be a legal mess in reality. Take this scenario, which Thiersch says happens quite often in Illinois (the outcome could vary in other states): A nurse who is experienced at injecting Botox and fillers decides to open a medspa to offer those services. She enters into a contract with a medical director, a dermatologist, who doesn't have Botox experience, and pays that medical director a percentage of the medspa's revenue.

Mr. Thiersch

"I would say over half the medspas in Illinois are set up kind of like this," Mr. Thiersch says. "Once they are open for business and start treating people, they've broken all sorts of laws."

Among those broken laws: The nurse is engaging in the unauthorized practice of medicine. She owns the med-

MEDSPA *see page* **36**

Quotable

"I think the best way to use at-home devices is to incorporate them. I see them as an added benefit, not a threat."

Judith Hellman, M.D.
New York

on how at-home devices can benefit your practice

See story page 39

DTExtra

A European study indicates that laser lipolysis (LAL) is safe and effective for submental and neck remodeling. Researchers, led by Franck Marie Leclère, M.D., of the Department of Plastic and Reconstructive Surgery, Gustave Roussy Institute, Paris, prospectively studied 30 patients treated for Rohrich type I to III aging neck with a 980 nm diode laser (Quanta system, spa model D-plus, Solbate Olona, Italy). With the exception of three patients who developed mild hyperpigmentation — which was gone four months later — there were no complications in the series

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MEDSPA:
Experts advise understanding legal issues before getting involved *from page* **34**

spa, which is illegal in the state. And, while the spa offers Botox, the medical director didn't have Botox experience.

"The state will come in and say, even though we admit it's difficult to determine what these laws are and many people don't know them, you've just broken three laws. We're going to fine you $10,000 for each offense, and we're going to censure your license, not only for the nurse but for the doctor who has no idea this is going on," Mr. Thiersch says.

Landon Pryor, M.D., a plastic surgeon in Rockford, Ill., directs a medspa within his practice. Dr. Pryor joined forces with an existing medspa, called True Laser, which offered predominately hair removal services. True Laser had been operating illegally, unbeknownst to the nonphysician owner and physician medical director. Dr. Pryor stepped in and helped to restructure the business. Now, the medspa is a separate corporate legal entity, but Dr. Pryor technically owns it due to the way the Illinois law is set up.

"In Illinois, a medical practice has to be 100 percent physician-owned," Dr. Pryor says.

While laws vary from state to state, Dr. Pryor says even many attorneys are not familiar with medspa regulations.

"I think a lot of physicians that get involved with these things think it's a nice way to generate ancillary revenue, but there are definitely a lot of potential legal and licensure-related issues that they can run into if they're just doing it arbitrarily and not thinking about the actual logistics.... As a medical director, they're putting their licenses on the line for basically anything that's going on in that medspa," Dr. Pryor says.

IF IT SOUNDS TOO GOOD...

Listening to that little voice inside could help you avoid a bad experience as a medspa director.

Jessica J. Krant, M.D., M.P.H., who practices in New York City, says, she receives phone calls asking whether she'd sign on as medical director for medical spas owned by others. She thought it was shady when she was told the job would be easy because she wouldn't have to physically be at the medspa.

"I did not feel it sounded safe, appropriate or necessarily even legal to have such an arrangement," Dr. Krant says. "I wasn't comfortable having cosmetic medical procedures happening without them being done under my direct supervision, or, at the very least, by staff I had personally trained and supervised myself over time to the point where I trusted their individual expertise and judgment levels. I didn't feel comfortable 'supervising' procedures in name — that I wasn't fully trained on and experienced in myself — since I would have been responsible for damage control."


Ms. Coover

Directing a medspa is a hands-on job in many states. And when it is, it's more than showing up maybe once or twice a month, without having to actually see patients. It's more than seeing patients once a month, then collecting a paycheck in the mail, says Renee Elise Coover, J.D., an associate of Thiersch and Associates.

"In Illinois, it's very important that the physician see each and every patient before they're treated for any type of medical procedure or treatment," Ms. Coover says.


Dr. Langsdon

And that's a good thing, because a lack of a physician's oversight will eventually come back to haunt the doctor, says Phillip Langsdon, M.D., facial plastic surgeon in Germantown, Tenn..

"I personally think that a lot of physicians are taken advantage of by individuals who want to have 'medical spas.' They're using [our] years of education and expertise in order to allow them to have an independent business, and I just think that is a bad formula," Dr. Langsdon says. "If you're going to be involved with a spa, let it be your own spa."

Dr. Langsdon says it's not only important that physicians own their medspas, but also integrate them physically with their practices. He says he attempted to put his medical spa in office space he owns across the street, and that wasn't close enough. So, he moved the medspa into his practice space.

"... not only can you not oversee the treatments being done there, but you can't oversee the business and the people. That's an accident waiting to happen," Dr. Langsdon says.

DONE RIGHT, DIRECTING A MEDSPA IS A GOOD THING

For dermatologists and cosmetic surgeons, directing a medspa can be financially rewarding and a great referral source for their primary practice.

Bruce Katz, M.D., directs and owns an established medspa and laser practice in New York City. He coined and trademarked a term often used to describe medspas: Medispa.

"I think it's a great add-on business. It sort of becomes intertwined with your medical practice, your dermatology-cosmetic practice or your laser practice, because we refer back and forth," Dr. Katz says. "But — and it's a big but — you have to manage it properly. [Running a] medispa is like running a high-end hotel or high-end restaurant. It's very service-oriented. ... your staff has to treat clientele extremely well, and they have to be well trained in what they do. It is a high-intensity service business."

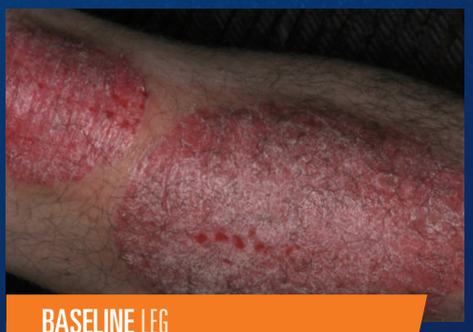
By restructuring an existing medspa, Dr. Pryor gained access to the medspa's patients.

"The medical spa with me now previously had a presence in Rockford... the last 12 years, so they definitely have an ongoing patient base and patient flow.... There is good traffic between the two businesses, where I'm able to send patients to them for their services and vice versa," Dr. Pryor says. "There are definitely up sides [to directing a medspa]. ... if it's geographically in an area where the physician is practicing, there is certainly room for synergy, collaboration, co-marketing and working together to maximize the benefits from patient flow." **DT**

ONE TOUGH SPRAY

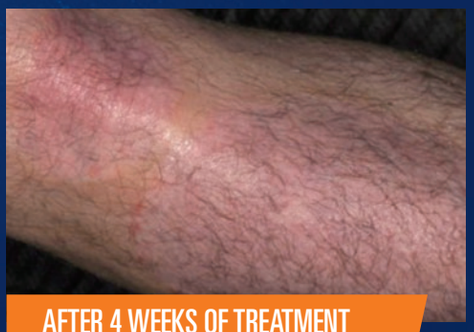
A super-potent spray for moderate to severe plaque psoriasis

Patient pictured was not a participant in the Phase 3 clinical studies for Topicort® Topical Spray. Individual results may vary. Photos and notes provided by J. Bikowski, M.D.[1]



BASELINE LEG

Erythematous, scaling plaques on anterior left leg.



AFTER 4 WEEKS OF TREATMENT

Lesions decreased in thickness and scale.

Topicort®
(desoximetasone)
Topical Spray 0.25%

0.25%
SPRAY

CLASS 1 *STRENGTH*

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

Important Safety Information

- 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.

1. Data on file, Taro Pharmaceuticals U.S.A., Inc.

TaroPharma®

See brief summary of Prescribing Information on reverse side.

AD100-0036 June 2014

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

BRIEF SUMMARY

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

4 CONTRAINDICATIONS
None

5 WARNINGS AND PRECAUTIONS

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

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

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

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

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

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

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

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

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

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

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

ADVERSE REACTIONS

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

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

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

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

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

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

8 USE IN SPECIFIC POPULATIONS

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

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

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

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

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

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

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

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

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

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

Mfd. by: Taro Pharmaceuticals Inc., Brampton, Ontario, Canada L6T 1C1
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Revised: April 2013

AD100-0030

At-home devices: Bottom line bust or boom?

LISETTE HILTON | STAFF CORRESPONDENT

FOR DERMATOLOGISTS, it seems logical to think that the flood of at-home treatment devices — promising everything from hair removal to skin rejuvenation — will hurt business.

But some dermatologists say it doesn't have to be so. Dermatologists can use these devices as therapy }adjuncts — even profit centers. And there's plenty of business to go around, regardless of how big the at-home aesthetic device market gets, according to Michael Gold, M.D., a dermatologist in Nashville, Tenn.

"When home devices first came out, everybody in dermatology, plastic surgery — everybody in the aesthetic community — said, 'Oh my God! We're going to be losing all our patients,'" Dr. Gold tells *Dermatology Times*.

The reality, according to Dr. Gold, is dermatologists and cosmetic surgeons who offer in-office procedures such as hair removal, only capture a fraction of the market. And the home device industry doesn't seem to be shaking up the physician's piece of the pie. Statistics released by the American Society of Plastic Surgeons in 2013, for example, show a slight downward trend in laser hair removal in plastic surgery practices, from 1,118,254 in 2012 to 1,077,158 in 2013. However, during the same time period, in-office offerings such as nonablative resurfacing rose from 361,784 to 365,596.

Charles E. Crutchfield III, M.D., clinical professor of dermatology at the University of Minnesota Medical School, tells *Dermatology Times*, "We really feel absolutely no competition from 'at home' laser[s]. In fact, our laser business has steadily increased over time; and I think that's purely based on the advances in laser technology and increased abilities that we have with newer generation lasers."

Whether the do-it-yourself market will impact dermatologists and cosmetic surgeons depends on how they handle things, says Dr. Gold. If they embrace the option for patients, hair removal, skin rejuvenation and acne therapy and other home devices could help aesthetic practices.

QUICK READ

Experts agree that at-home devices aren't poised to hurt in-office business. In fact, they may also offer added profit to your practice.

DO THEY ACTUALLY WORK?

While some dermatologists say at-home devices for skin care, skin rejuvenation and hair removal work, others believe that today's do-it-yourself devices don't work well enough to recommend to patients.

According to Dr. Crutchfield, he doesn't sell at-home devices in his office because they don't work that well "and I want my patients to be happy."

"Results from at-home devices come slowly and only with continued use."

Michael Gold, M.D.
Nashville, Tenn.

However, Dr. Gold believes that the FDA-cleared devices for hair removal, skin rejuvenation and acne treatment work. "I have some LED-type devices, which are red light that work very nicely for rejuvenating the skin," he says. They're just not as powerful as what dermatologists can offer in the office. Results from at-home devices come slowly and only with continued use.

At the same time, Dr. Gold says he only recommends home devices to people who understand what they can and can't do. Without properly educating patients about the limitations of these devices, dermatologists might indeed be setting themselves up for unhappy customers.

"First and foremost, the people who purchase them must have realistic expectations, otherwise they will think that these all will act just like the professional devices, which is just not the case. I also think that without realistic expectations, people will just not be happy," Dr. Gold says. "For instance — we are getting ready to have some nonablative fractional devices for home use — will they make every wrinkle or scar disappear? People will spend good money for them and think they should, but we know they will not."

Showing efficacy is an FDA requirement, along with proving safety, Dr. Gold points out.

Dr. Crutchfield

"Now we're entering the whole world.... There's a device that we're just starting to use called Newa (EndyMed Medical). It is a radiofrequency device that promotes skin tightening and works very nicely...."

In a study of 69 patients, published November 2014 in the *American Journal of Drugs in Dermatology*, the Newa Skin Rejuvenation System was shown to reduce wrinkles by an average 36 percent after one month of treatment.

In another study of 124 patients, an at-home nonablative fractional laser device for wrinkle reduction was shown to improve most patients' periorbital wrinkles. (Leyden J, Stephens TJ, Herndon JH Jr. Multicenter clinical trial of a home-use nonablative fractional laser device for wrinkle reduction. *J Am Acad Dermatol*. 2012;67:975-984.)

Other new devices that Dr. Gold recommends include the iluminage Skin Smoothing Laser, a take-home nonablative fractional device.

FINDING SYNERGY

As the old adage goes, if you can't beat 'em, join 'em! Rather than try to beat at-home devices, dermatologists and cosmetic surgeons may want to consider joining the industry's momentum.

According to Dr. Gold, results from

AT-HOME DEVICES *see page* 40

AT-HOME DEVICES:

Experts reveal how these devices can benefit your practice *from page* **39**

at-home device use — whether it's for facial rejuvenation, acne treatment, hair removal or hair growth — improve when patients combine in-office and at-home treatments for maintenance.

Dr. Hellman

Judith Hellman, M.D., associate professor of dermatology at Mount Sinai Hospital in New York City, says she recommends at-home devices as adjuncts to in-office treatment, including acne therapy. She says she does not think at-home devices take the place of what dermatologists do in the office.

"In all honesty… the actual at-home devices are really great, but I think they're more used as an adjunct to real treatments.," says Dr. Hellman. "I think any patient will tell you that the result they get with the in-office laser [for example] is much more effective, much more quickly effective, much more long-term…."

At-home devices empower patients to improve upon what dermatologists do in the office to treat acne, remove hair, rejuvenate the skin and more, according to Dr. Hellman. "I think the best way to use at-home devices is to incorporate them. I see them as an added benefit, not a threat."

WHERE THERE ARE BUYERS….

The at-home aesthetic device market is here for the long-term.

A 2011 report by consulting and research firm Kline and Company revealed a booming market for power-operated devices designed for acne elimination, anti-aging treatment and daily cleansing. Kline predicted the retail market for at-home skin care devices would be close to $1 billion that year, with exceptional growth expected for the next five years.

"While sonic cleansing products, led by market leader Clarisonic, top the list as the highest growth segment, acne treatment devices are the fastest growing. Meanwhile, anti-aging devices are expected to grow by a very healthy 50 percent this year alone, benefiting from consumers' demand for products to reduce the appearance of fine lines, wrinkles, and age spots," according to a Kline press release.

What can dermatologists and other aesthetic practitioners do to use home aesthetic devices to their advantage? Dr. Gold offers these tips:

Become aware of what's out there — the different technologies and what they do. Know which are quality products and have been FDA cleared and which have not.

Consider recommending your favorite devices to patients, using them to improve results you achieve with in-office treatments, and, even, selling quality devices.

"If people would sit back and take a deep breath and realize that if you use them as adjuncts to your practice, it's a great idea. If somebody comes in and they've used some of these home devices, they're still most likely going to need you for something. The new devices are actually getting more sophisticated, but there are still enough patients out there, so that it's not going to hurt us," Dr. Gold says. **DT**

Disclosure: Dr. Gold is a consultant to Home Skinnovations, has performed clinical research for Syneron Beauty (now iluminage) and has performed clinical research for Tria.

Study suggests acne patients benefit from Silk'n Blue at-home device

LISETTE HILTON | STAFF CORRESPONDENT

MILD TO severe acne patients experienced an average 41.8 percent reduction in inflammatory acne counts after 12 weeks of using the Silk'n Blue (Home Skinovations Ltd) at-home device, according to a study published in the June 2014 issue of the *Journal of Cosmetics, Dermatological Sciences and Applications*. Silk'n Blue is a 415 nm wavelength blue light emitting diode (LED), FDA-cleared device.

In the study, 15 patients were instructed to use Silk'n Blue daily, holding the applicator on affected areas of the skin for three minutes (or if tolerable, five minutes). While patients didn't have in-office laser or other treatments during the study period, they were able to continue with any prescribed topical medications for their acne, according to study coauthor and New York City dermatologist Judith Hellman, M.D.

Researchers followed up with patients at one and three months. These were their findings:

- Inflammatory acne counts decreased on average from 41.26 to 24.46.
- At three months, 14 of the 15 patients improved with a decrease in acne lesions from baseline. Two patients had reductions of 61 percent and 67 percent.
- Three patients had an increase in lesions after the first month, but finished the study with fewer or the same number of lesions compared to baseline.
- Two patients with darker Fitzpatrick skin type IV reported minor pain and tenderness, which disappeared soon after the first few treatments. This suggests, according to Dr. Hellman, "… that maybe darker skin types are more sensitive to the infrared heat in the device, and maybe they should get used to the device more gradually."
- Eight patients said in a survey they "liked" the device and found it to be effective. Four said they "loved" the treatment system and wanted to continue using the device.
- One patient didn't see improvement and stopped using the device regularly.
- Four patients reported difficulty with maintaining a consistent schedule of use.

The authors concluded the Silk'n Blue device may be a safe and effective at-home treatment for mild, moderate and severe inflammatory acne.

"One way I use this treatment is to accommodate people who, for whatever reason, do not have other options besides a topical. The other way I use the device is when I have patients who do have laser treatment and need something to maintain their skin in between [treatments]." **DT**

Disclosures: Dr. Hellman has no disclosures to report, other than she conducted the research.

Submental Fullness IN FOCUS

No matter the view, **submental fullness** associated with subcutaneous fat can detract from an otherwise balanced and harmonious facial appearance[1] – leading to an older and heavier look.[2]

According to a 2014 survey by the American Society for Dermatologic Surgery, **68% of consumers** are bothered by submental fullness.[3]

Learn more from the experts at **submentalfullness.com**

Tina Alster, MD

Doris Day, MD

Steven Dayan, MD, FACS

Lisa Donofrio, MD

Julius Few, MD, FACS

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2. Dayan S. Neck rejuvenation. In: Hirsch, Aesthetic Rejuvenation: A Regional Approach. 1st ed. New York, NY: McGraw Hill Professional Publishing; 2008: 123-147.
3. American Society for Dermatologic Surgery 2014 Consumer Survey on Cosmetic Dermatologic Procedures (N=8,315); Exact survey language was, "How bothered are you by excess fat under the chin/neck?"

KYTHERA® biopharmaceuticals

Diagnosing, managing aBCC in elderly patients

SNEHAL P. AMIN, M.D., F.A.C.M.S.
STAFF CORRESPONDENT

Basal cell carcinoma (BCC) is the most common type of skin cancer with an estimated 2.8 million cases diagnosed annually in the United States [1]. Close to 40 percent to 50 percent of people who live to age 65 will have at least one non-melanoma skin cancer with BCC being the most common type. BCC more frequently affects older adults and, with an aging U.S. population, the incidence is likely to rise. Advanced basal cell carcinoma (aBCC) is a subset of BCCs that have extensive, invasive or metastatic involvement and are often recalcitrant to standard treatments.

Although aBCC is an unusual variant of BCC, when it does occur, it is often in the elderly population. Later-stage or more complicated lesions in the geriatric population may be caused by both a delay in seeking medical care as well as limited therapeutic options. James Sligh, M.D., Ph.D., associate professor and dermatology division chief at University of Arizona, adds that "locally advanced BCC in older patients tends to have evolved more often from previously treated, recurrent BCC than in younger patients" and presents with a "higher tumor burden".

Seniors, adults aged 65 and older, represent about 13.7 percnet (about 1 in 7 people) of the United States population.[2] Over 90 percent of seniors have at least one chronic medical condition and approximately 75 percent have at least two conditions. Close to 40 percent of seniors will have some type of disability including difficulty in hearing, vision, cognition, ambulation, self-care, or independent living. With many comorbidities, disabilities and a limited life span, treatment of aBCC in the geriatric population can present a difficult challenge.

QUICK READ

Advanced BCC may be more common in elderly patients but many cannot tolerate surgery or radiation. Many elderly patients have comorbidities and limitations that limit therapeutic options for aBCC. Vismodegib and other medications that are under study are novel options to help manage their aBCC.

The benign neglect or watchful waiting approach has often been an option for aBCC patients who are severely-ill. However, even with metastatic BCC, the median overall survival from the time of diagnosis was found to be seven years in a small case series from the Stanford University School of Medicine.[3] In that time period, tumors can begin to ulcerate, bleed and cause significant disability and disfigurement. Therefore, it is reasonable to treat elderly patients with even the most advanced cases, unless a severe comorbidity is likely to lead to death in the very near future. Gary Goldenberg, M.D., assistant clinical professor of dermatology at the Icahn School of Medicine at Mount Sinai, emphasizes that oral medication "can be used just for a few months...to reduce symptoms, especially bleeding or ulceration." There is "no ceiling for treatment," according to Dr. Sligh, adding, "I believe that elderly patients can benefit greatly from medical management of locally advanced BCC and in many cases are ideal for treatment with non-surgical modalities."

ABCC TREATMENT OPTIONS FOR ELDERLY

Treatment options for aBCC in the geriatric population do not differ from other populations but can be more complicated depending on the health status of the patient. Surgery, including Mohs micrographic surgery or wide local excision is still the treatment of choice if the patient could reasonably be expected to tolerate the procedure and as long as it doesn't subsequently cause significant morbidity.

Patients with significant dementia, tremor or Parkinson's disease may not be able to stay sedentary for a procedure under local anesthesia. General anesthesia would lend many more risks in this population as well.[4]

Radiotherapy is a good treatment option for patients with aBCC who are unable to tolerate surgery. Again, like surgery with local anesthesia, patients would need to remain motionless during the radiation sessions. In addition, transportation for the radiation therapy needs to be considered as treatments are often two to three times per week over several weeks.

NEW DRUG OPTIONS

Smoothened inhibitors, such as vismodegib (Erivedge, Genentech) and other drugs under study, present new options for patients who refuse or are unable to tolerate procedures. Studies on the

aBCC IN ELDERLY *see page* **44**

DTExtra

A new methodology may predict whether advanced melanoma patients will or will not respond to pembrolizumab (Keytruda, Merck). UCLA researchers studied 46 patients who had undergone tumor biopsies before and during treatment with the drug. Over two years, they analyzed and classified patients' biopsies according to whether or not patients responded. They then developed an algorithm to predict treatment success or failure. The algorithm was tested by applying it to 15 other tumor samples from different patients, and it correctly predicted outcomes in 13 of those cases.

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David L. Wagener, MBA, CPA
S. Randolph Waldman, MD
Susan H. Weinkle, MD
Robert A. Weiss, MD
Allan S. Wirtzer, MD

Preliminary List – more faculty added soon!

Clinical Dermatology Symposium

February 12, 13 and 15

The Clinical Dermatology Symposium will host the world's top medical and surgical dermatology faculty to cover topics ranging from advances in clinical and therapeutic dermatology, photodynamic therapy, immune response modifiers, biologic therapies for psoriasis, wound care management, acne, rosacea, psoriasis and much more.

Aesthetic Dermatology Symposium

February 12, 14 and 15

The Aesthetic Dermatology Symposium will present new innovations in aesthetic procedures and technologies through multiple live patient demonstration and certification workshops given by world leaders in cosmetic and aesthetic dermatology.

Practice Management Symposium

February 12, 13, 14 and 16

The Practice Management Symposium will include an interactive session on elements to improve both clinical and cosmetic practice, EMR and imaging solutions and risk management strategies. Don't miss an important session on the Affordable Care Act and how the changes in health care reform affect dermatology.

Masters of Pediatric Dermatology Symposium

February 12

This popular one–day program aims to educate physicians about advances in pediatric dermatology and supporting children with dermatological diseases.

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aBCC IN ELDERLY:
Comorbidities may limit treatment options for elderly *from page* **42**

safety of vismodegib included patients up to 101 years old with locally aBCC and 92 years old with metastatic aBCC.[5]

Vismodegib and its metabolites are eliminated primarily via the hepatic route. Unfortunately, the effect of hepatic or renal impairment on the systemic exposure of vismodegib has not been studied. However, population pharmacokinetic analyses have shown that creatinine clearance as low as 30 mL/min, weight up to 140 kg (308lbs), and age up to 89 years did not have a clinically meaningful influence on the systemic effects of vismodegib.[6]

It may prove prudent to assess pretreatment and periodic complete metabolic panels to gather information on electrolytes, hepatic and renal function in the elderly. In clinical trials, although rare, azotemia, hyponatremia and hypokalemia were observed. Dr. Goldenberg recommends that visit to the primary care doctor and a baseline CPK may be appropriate for elderly patients about to start vismodegib therapy.

POLYPHARMACY CONSIDERATIONS

Another consideration in the elderly population is the prevalence of polypharmacy and risk of medication interactions or toxicity. Vismodegib is excreted predominantly as an unaltered drug but has several minor metabolites produced by hepatic CYP enzymes, CYP2C9 and CYP3A4.[6] It does not appear to be altered when coadministered with CYP3A4 inducers or inhibitors.

Medications that inhibit the efflux transporter P-glycoprotein (e.g. clarithromycin, erythromycin, azithromycin) may increase systemic levels of vismodegib leading to more adverse effects and should be monitored closely. Medications that alter the pH of the upper GI tract may alter the absorption and bioavailability of vismodegib.

It is perhaps best to advise patients to avoid proton pump inhibitors, H2 receptor antagonists, and antacids within several hours of taking vismodegib. The only medication with serious interactions is ivacaftor, a medication for cystic fibrosis, which can systemically increase levels of vismodegib.[7] A more complete list of medication interactions can be found using medication interaction tools such as Epocrates or Medscape.[7,8]

TREATMENT SIDE EFFECTS IN THE ELDERLY

Side effects of vismodegib are likely to be similar in the elderly as other populations. However, Dr. Sligh advises that the clinician "watch elderly patients carefully for signs of weight loss or dehydration as they tend tolerate [these] potential side effects less than some younger patients might."

Muscle spasms may be managed with hydration, massage, warm compresses and stretching exercises. Alopecia is more common in the elderly and may be less alarming to this population. Gentle hair care and topical minoxidil may be recommended for patients concerned with alopecia.

Dysgeusia and weight loss may be quite alarming for older adults. Smaller meals with high protein, high caloric content and strong flavors should be eaten more frequently throughout the day. Medications such as megestrol or dronabinol may help relieve anorexia and weight loss in patients on vismodegib. For a list of other helpful tips to combat adverse effects from vismodegib, see the discussion guide for providers and side effects brochure for patients available on the Genentech website.[9]

ALTERNATIVES TO SURGERY

Although less than ideal, some patients are unsuitable for surgery and may prefer a nonradiotherapy or nonchemotherapeutic treatment. Topical and destructive therapies are generally associated with lower clearance rates and higher recurrence rates than surgery or radiotherapy but may be all the patient consents to or can tolerate.

Topical imiquimod is FDA approved for superficial BCCs and provides immunomodulator effects by increasing proinflammatory cytokines. For aBCC, combining therapies such as imiquimod with cryotherapy or curettage and electrodessication may prove better than doing nothing at all.[10,11] Imiquimod plus another destructive or debulking method may be an alternative treatment in elderly patients who have unwillingness or are poor candidates for surgery, vismodegib and/or radiotherapy.

CONCLUSION

Treatment of aBCC in the elderly is challenging. With a rising incidence of BCC and an aging population, cases of aBCC may be expected to rise. As more data on smoothened inhibitors in this population are published, dermatologists will be able to better guide patients on treatment options. Oral medications may allow us to address aBCC symptoms in nonsurgical candidates such as ulceration, bleeding, pain and tumor size. In addition, combination therapy is likely to be a promising option for any patient with advanced BCC. **DT**

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NEW!

JUBLIA®
(efinaconazole)
Topical Solution 10%

FIGHT ONYCHOMYCOSIS*
AT THE SITE OF INFECTION[1]

*For the treatment of onychomycosis of the toenail(s) due to *Trichophyton rubrum* and *Trichophyton mentagrophytes.*

Rx Only

INDICATION

JUBLIA (efinaconazole) topical solution, 10% is indicated for the topical treatment of onychomycosis (tinea unguium) of the toenail(s) due to *Trichophyton rubrum* and *Trichophyton mentagrophytes.*

IMPORTANT SAFETY INFORMATION

- JUBLIA is for topical use only and is not for oral, ophthalmic, or intravaginal use.
- Patients should be instructed to contact their health care professional if a reaction suggesting sensitivity or severe irritation occurs.
- The most common adverse reactions (incidence >1%) were (vs vehicle): ingrown toenail (2.3% vs 0.7%), application-site dermatitis (2.2% vs 0.2%), application-site vesicles (1.6% vs 0%) and application-site pain (1.1% vs 0.2%).
- JUBLIA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus, and should be used with caution in nursing women. The safety and effectiveness in pediatric patients have not been established.

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

Reference: 1. JUBLIA [prescribing information]. Bridgewater, NJ: Valeant Pharmaceuticals North America LLC; 2014.

Find out more by visiting **www.JubliaRx.com.**

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JUBLIA®
(efinaconazole)
Topical Solution 10%

BRIEF SUMMARY OF PRESCRIBING INFORMATION

This Brief Summary does not include all the information needed to use JUBLIA safely and effectively. See full prescribing information for JUBLIA.

JUBLIA® (efinaconazole) topical solution, 10%

For topical use
Initial U.S. Approval: 2014

INDICATIONS AND USAGE

JUBLIA (efinaconazole) topical solution, 10% is an azole antifungal indicated for the topical treatment of onychomycosis of the toenail(s) due to *Trichophyton rubrum* and *Trichophyton mentagrophytes*.

DOSAGE AND ADMINISTRATION

Apply JUBLIA to affected toenails once daily for 48 weeks, using the integrated flow-through brush applicator. When applying JUBLIA, ensure the toenail, the toenail folds, toenail bed, hyponychium, and the undersurface of the toenail plate, are completely covered.

JUBLIA is for topical use only and not for oral, ophthalmic, or intravaginal use.

CONTRAINDICATIONS

None.

ADVERSE REACTIONS

Clinical Trials Experience

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

In two clinical trials, 1227 subjects were treated with JUBLIA, 1161 for at least 24 weeks and 780 for 48 weeks. Adverse reactions reported within 48 weeks of treatment and in at least 1% of subjects treated with JUBLIA and those reported in subjects treated with the vehicle are presented in Table 1.

Table 1: Adverse Reactions Reported by at Least 1% of Subjects Treated for up to 48 Weeks

Adverse Event, n (%)	JUBLIA N = 1227	Vehicle N = 413
Ingrown toenail	28 (2.3%)	3 (0.7%)
Application site dermatitis	27 (2.2%)	1 (0.2%)
Application site vesicles	20 (1.6%)	0 (0.%)
Application site pain	13 (1.1%)	1 (0.2%)

DRUG INTERACTIONS

In vitro studies have shown that JUBLIA, at therapeutic concentrations, neither inhibits nor induces cytochrome P450 (CYP450) enzymes.

USE IN SPECIFIC POPULATIONS

Pregnancy

Pregnancy Category C

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

Systemic embryofetal development studies were conducted in rats and rabbits. Subcutaneous doses of 2, 10 and 50 mg/kg/day efinaconazole were administered during the period of organogenesis (gestational days 6-16) to pregnant female rats. In the presence of maternal toxicity, embryofetal toxicity (increased embryofetal deaths, decreased number of live fetuses, and placental effects) was noted at 50 mg/kg/day [559 times the Maximum Recommended Human Dose (MRHD) based on Area Under the Curve (AUC) comparisons]. No embryofetal toxicity was noted at 10 mg/kg/day (112 times the MRHD based on AUC comparisons). No malformations were observed at 50 mg/kg/day (559 times the MRHD based on AUC comparisons).

Subcutaneous doses of 1, 5, and 10 mg/kg/day efinaconazole were administered during the period of organogenesis (gestational days 6-19) to pregnant female rabbits. In the presence of maternal toxicity, there was no embryofetal toxicity or malformations at 10 mg/kg/day (154 times the MRHD based on AUC comparisons).

In a pre- and post-natal development study in rats, subcutaneous doses of 1, 5 and 25 mg/kg/day efinaconazole were administered from the beginning of organogenesis (gestation day 6) through the end of lactation (lactation day 20). In the presence of maternal toxicity, embryofetal toxicity (increased prenatal pup mortality, reduced live litter sizes and increased postnatal pup mortality) was noted at 25 mg/kg/day. No embryofetal toxicity was noted at 5 mg/kg/day (17 times the MRHD based on AUC comparisons). No effects on postnatal development were noted at 25 mg/kg/day (89 times the MRHD based on AUC comparisons).

Nursing Mothers

It is not known whether efinaconazole is excreted in human milk. After repeated subcutaneous administration, efinaconazole was detected in milk of nursing rats. Because many drugs are excreted in human milk, caution should be exercised when JUBLIA is administered to nursing women.

Pediatric Use

Safety and effectiveness of JUBLIA in pediatric subjects have not been established.

Geriatric Use

Of the total number of subjects in clinical trials of JUBLIA, 11.3% were 65 and over, while none were 75 and over. No overall differences in safety and effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and the younger subjects, but greater sensitivity of some older individuals cannot be ruled out.

NONCLINICAL TOXICOLOGY

Carcinogenesis, Mutagenesis, Impairment of Fertility

A 2-year dermal carcinogenicity study in mice was conducted with daily topical administration of 3%, 10% and 30% efinaconazole solution. Severe irritation was noted at the treatment site in all dose groups, which was attributed to the vehicle and confounded the interpretation of skin effects by efinaconazole. The high dose group was terminated at week 34 due to severe skin reactions. No drug-related neoplasms were noted at doses up to 10% efinaconazole solution (248 times the MRHD based on AUC comparisons).

Efinaconazole revealed no evidence of mutagenic or clastogenic potential based on the results of two in vitro genotoxicity tests (Ames assay and Chinese hamster lung cell chromosome aberration assay) and one in vivo genotoxicity test (mouse peripheral reticulocyte micronucleus assay).

No effects on fertility were observed in male and female rats that were administered subcutaneous doses up to 25 mg/kg/day efinaconazole (279 times the MRHD based on AUC comparisons) prior to and during early pregnancy. Efinaconazole delayed the estrous cycle in females at 25 mg/kg/day but not at 5 mg/kg/day (56 times MRHD based on AUC comparisons).

PATIENT COUNSELING INFORMATION

See FDA-Approved Patient Labeling (Patient Information).

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Valeant Pharmaceuticals North America LLC, Bridgewater, NJ 08807 USA

Manufactured by:
Kaken Pharmaceutical Co. Ltd, Shizuoka, Japan

Product of Japan

U.S. Patents 8,039,494; 7,214,506

Based on 9391901 DM/JUB/14/0030(1)b Issued: 06/2014

ADVANCED CANCER:
Dermatologists play important role in managing patients with advanced skin cancer *from page* 1

sidering that some of the new therapies can cause treatment-limiting cutaneous side effects.

"In our experience, cross-specialty collaboration helps to optimize results with the new therapies for advanced and metastatic skin cancers," says Clara Curiel, M.D., associate professor of dermatology, University of Arizona Medical Center, and director, of the Pigmented Lesion Clinic and Multidisciplinary Cutaneous Oncology Program, The University of Arizona Cancer Center, Tucson.

Dr. Curiel's colleague, Lee D. Cranmer, M.D., Ph.D, associate professor of medicine, University of Arizona and director, Melanoma/Sarcoma program, The University of Arizona Cancer Center, notes that cutaneous toxicities can both limit patients from receiving maximally effective doses of the new therapies and also detract from any quality of life improvements that are achieved through a positive oncologic response.

"While traditionally there has been a flow of skin cancer patients from the dermatologist towards the medical oncologists; with these new medications, there also has to be a reverse order of flow in order for patients to achieve maximum benefit," Dr. Cranmer says.

A NEW SET OF THERAPEUTIC TOOLS

The development of new targeted systemic therapies for skin cancers is based on increasing understanding of the biology of these tumors. In January, 2012, dermatologists saw the approval of the first oral medication for the treatment of basal cell carcinoma (BCC) – vismodegib (Erivedge, Genentech), which is indicated for use in adults with metastatic BCC or with locally advanced BCC that has recurred after surgery or who are not candidates for surgery or radiation. Studies are now ongoing investigating vismodegib for treatment of patients with multiple, surgically resectable BCCs, a population of patients more likely to fall under the umbrella of dermatologist care. Meanwhile, however, dermatologists prescribing of vismodegib for its approved indication may begin to increase as they gain familiarity and comfort with its safety profile.

Dr. Cranmer notes that the safety profile of vismodegib makes it amenable to prescribing by dermatologists.

"From the standpoint of toxicity, I certainly believe vismodegib fits well into the dermatologist's armamentarium. Although it can cause some significant side effects, by comparison, the overall toxicity of vismodegib is of similar magnitude to that of the systemic retinoids, drugs that dermatologists are accustomed to prescribe and manage," he explains.

Dr. Curiel observed that dermatologists are still most likely to refer patients who are candidates for vismodegib to a medical oncologist.

QUICK READ

Optimal patient outcomes using new systemic therapies for advanced basal cell carcinoma and malignant melanoma requires active involvement of the dermatologist in a multidisciplinary care team.

EXPANDING OPTIONS FOR MELANOMA

Targeted therapies for malignant melanoma include two BRAF inhibitors [vemurafenib (Zelboraf, Roche), dabrafenib (Tafinlar, GlaxoSmithKline)], and a mitogen-activated protein kinase enzymes (MEK) inhibitor [trametinib (Mekinist, GlaxoSmithKline)]. Dr. Cranmner notes that the introduction of these agents for patients with unresectable advanced disease and recurrent melanoma harboring a BRAF mutation has been a real breakthrough for medical oncology. However, while these medications can lead to dramatic responses, none is able to provide a cure.

Dr. Cranmer also highlighted the available immunotherapy options for melanoma, ipilimumab (Yervoy, Bristol-Myers Squibb) and pembrolizumab (Keytruda, Merck).

"Approval of these checkpoint inhibitors for melanoma therapy is a major breakthrough. These drugs exploit the immune system to yield durable remissions of melanoma, in some cases lasting years," he says. "Their novel toxicities, including prominent autoimmune skin toxicities, mean that dermatologists will be close collaborators in managing patients being treated with these agents."

SQUAMOUS CELL CARCINOMA (SCC)

Currently, there are no targeted therapies for cutaneous SCC available or on the near horizon. Various epidermal growth factor receptor (EGFR) inhibitors are approved for the treatment of other types of SCCs, but there is only a limited dataset pertaining to their use for cutaneous tumors.

"It seems that researchers are still looking for some link to disease pathogenesis in order to establish a better target that will allow us to do have greater efficacy in treating SCC," Dr. Cramner says.

He adds that because metastatic SCC is so uncommon, there has been little motivation for industry to allocate research resources to that condition. However, the situation may change if a candidate drug with a reasonably favorable side effect profile is found.

MANAGING CUTANEOUS REACTIONS

Treatment-limiting cutaneous adverse events associated with the new skin cancer systemic therapies occur predominantly with the BRAF inhibitors. Development of SCC, primarily of the keratoacanthoma type, is one of the most common side effects, occurring in about 60% of patients. Photosensitivity to ultraviolet A light and rash are also common, both reported to occur at rates ranging from 30 percent to 50 percent. Other cutaneous disorders that occur at a relatively high incidence include alopecia and keratosis pilaris. Less frequently, but importantly, patients treated with the BRAF inhibitors may also develop an increased number of nevi, erythema nodosum, Stevens-Johnson syndrome, toxic epidermal necrolysis, and Grover's disease.

Dr. Curiel notes that drug eruptions are common with the use of immunological therapies (ipilimumab and pembrolizumab). According to the prescribing information, these events occur at a rate of up to 50 percent to 60 percent. However, they are more of a bother than a serious concern, she and Dr. Cranmer agree.

"When counseling patients being treated with these agents about cutaneous toxicities, I describe the drug reactions as being annoying in most cases, rather than dangerous. While severe reactions are possible, they are rare, and the benefits of these agents in melanoma therapy vastly outweigh their risks," Dr. Cranmer says. **DT**

Dr. Cranmer's institution receives research funding from Genentech/Roche, Glaxo SmithKline, Merck, and Bristol Meyers Squibb. He has also served as a compensated speaker for Genentech/Roche and Bristol Meyers Squibb. Dr. Curiel is a consultant for Medical Directions LTD, and is a founder and stock holder for DermSpectra LLC.

Art Gross is co-founder, president and CEO of Entegration. He started a second company, HIPAA Secure Now!, focused on the unique IT requirements of medical practices. Email Mr. Gross at artg@hipaasecurenow.com

What happens if your business associate has a patient data breach?

Here's a cautionary tale: A medical practice comes to us in a panic. It turns out the physician had received a letter from the Office of Civil Rights (OCR) ordering an investigation related to a patient data breach – not his own.

In this instance, the practice's business associate, a web hosting company, had committed the breach and exposed patient information, part of which ended up in a Google search. The web hosting company was investigated and is awaiting a final determination from OCR. However, the medical practice is also being investigated because it had contracted the services of the web hosting provider.

IMPACT TO THE PHYSICIAN

This particular medical practice, an oral surgeon with a staff of six, had 20 days to answer 15 questions all pointing to electronic security measures it should have taken to protect the thousands of patients stored in its systems (the investigation came after the initial 60 days that they had to notify patients).

The workload in response to an OCR investigation could be enough to make a physician want to shutter his practice. Here is just a taste of the OCR's questions:

- Copies of any notes, documents and reports relating to any internal investigation, including any forensic analysis conducted by the covered entity, or its designated contractor or agent of the alleged incident. Please detail any corrective measures taken as a result of this alleged incident.
- Please indicate whether you conducted a breach risk assessment for the alleged incident. If so, please provide a copy of the breach risk assessment.
- If you determined that a breach of patients' PHI occurred as a result of this incident, please indicate, as applicable, whether you notified the affected individuals, the media, and the HHS Secretary.
- If you notified the affected individuals, the media, and the HHS Secretary, please provide OCR with documentation of said notifications.

You can view the remaining 13 questions on our Web site. [1]

If the OCR determines that the medical practice is in willful neglect of HIPAA regulations it could be looking at a fine of $50,000 per incident, up to $1.5 million.

IT'S ALL IN THE BUSINESS ASSOCIATE AGREEMENT

While HIPAA requires covered entities to get signed agreements from business associates stating they will protect patient information, the agreement may not indemnify the covered entity in the event of an OCR investigation because of its business associate's breach. Moreover, unless it's stated in the agreement, a business associate is under no obligation to disclose the breach to his client in a timely manner.

PATIENT DATA *see page* **50**

Quotable

"I think, in the end, it's going to be part of value-based care. I think people are going to use it ... for triage, to add value to services, to get patients evaluated and to the right clinic faster."

Carrie Kovarik, M.D.
Philadelphia

on the future of telemedicine in dermatology

See story page 52

DTExtra

More than half of the physicians across the country who supposedly treat Medicaid patients don't actually do so, a new government report finds. According to a report prepared by the Office of the Inspector General (OIG) of the U.S. Department of Health and Human Services, 43 percent of providers listed by MCOs as accepting Medicaid patients either were not practicing at the location where they were listed or were not participating in the MCO, and another 8 percent were not accepting new patients enrolled in the plan.

READ MORE FINDINGS AND RECOMMENDATIONS: BIT.LY/OIGMEDICAIDREPORT

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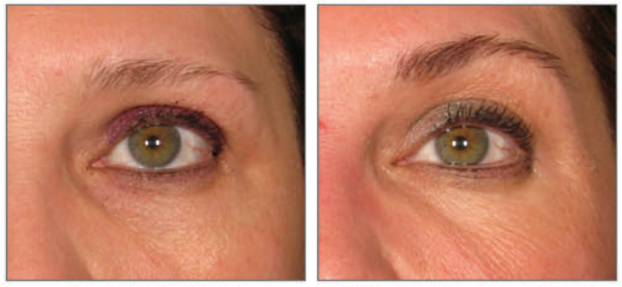
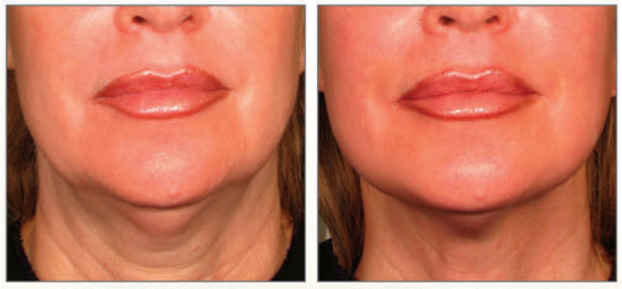


PRE-TREATMENT | DAY 450, *Single Treatment*



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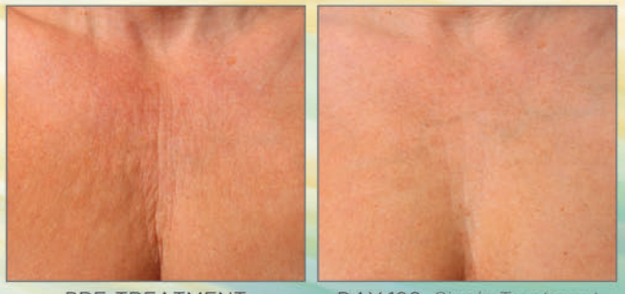

PRE-TREATMENT | DAY 180, *Single Treatment*

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PATIENT DATA:
What to do if your business associate has a HIPAA breach *from page* **48**

Conversely, the covered entity could state in the agreement that if the business associate has a breach, it has to pay the covered entity's fine and indemnify it against any liability. An ironclad agreement like that could make the business associate jittery and reluctant to sign on the dotted line. But, without a Business Associate Agreement, the covered entity won't be able to grant permission to IT companies, medical billers, attorneys, insurance carriers, etc., to handle its clients' health information, virtually cutting off the blood supply to the practice's operation.

To make the agreement fair, both parties need to come to the table, openly discuss the terms of the agreement, and have it reviewed by legal counsel. For starters, the business associate should

A) have proof that the business associate is protecting ePHI;

B) get a breach report to the covered entity within a reasonable time frame, *i.e.*, 10 days. The report should explain what happened, as well as who, how, and what was accessed. The business associate may need time to bring in a forensic IT expert to figure out how the breach happened; on what servers; etc.; And,

C) if the business associate caused the breach, it should indemnify and pay agreed-upon expenses to the covered entity.

Likewise, if the overed entity gets investigated because his business associate was fined, but the practice didn't take the proper steps to comply with HIPAA, it can't use the Agreement to demand that the business associate pay the fine. Business associates are not responsible for making sure their covered entity is HIPAA compliant.

MY TAKEAWAYS:

A) if your business associate commits a breach, the OCR could investigate your practice;

B) be prepared — perform a HIPAA risk assessment; plan and implement security safeguards and provide backup documentation; don't put it off and be caught off guard;

C) provide a Business Associates Agreement that protects your practice, but is fair to your business associate. **DT**

References:
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Dermatology Times (Print: ISSN 0196-6197, Digital ISSN 2150-6523) is published monthly by UBM Advanstar, 131 W. First St., Duluth, MN 55802-2065. Subscription rates: $95 for one year in the United States and Possessions; $140 for one year in Canada and Mexico; all other countries, $185 for one year. International pricing includes air-expedited service. Single copies (prepaid only): $10 in the United States, $15 in Canada and Mexico, $20 all other countries. Back issues, if available, are $20 in the United States and Possessions, $30 in Canada and Mexico, and $40 in all other countries. Include $6.50 per order plus $2 for additional copy for U.S. postage and handling.If shipping outside the United States, include an additional $10 per order plus $3 per additional copy. Periodicals postage paid at Duluth, MN 55806 and additional mailing offices. POSTMASTER: Please send address changes to DERMATOLOGY TIMES, c/o PO Box 6013, Duluth, MN 55806-6013. Canadian G.S.T. number: R-124213133RT001.Publications Mail Agreement Number 40612608. Return undeliverable Canadian addresses to IMEX Global Solutions, P.O. Box 25542, London, ON, N6C 6B2,Canada. Printed in the U.S.A.

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Making telederm work

Q & A

ELAINE SIEGFRIED, M.D.

In part 2 of our "Takeaway" on Telemedicine, ***Dermatology Times*** editorial adviser, Elaine Siegfried, M.D., talks with Carrie Kovarik, M.D., about the nuances of making teledermatology work, what the future may hold, and how to get involved if you're interested. Dr. Kovarik is an associate professor in the Department of Dermatology at the University of Pennsylvania in Philadelphia.

DR. SIEGFRIED: How does recordkeeping for your e-consultation services work?

A Dr. Kovarik: Right now, it's written within the web portal and stored in the cloud within our mobile teledermatology system. This is a medical record within itself.

DR. SIEGFRIED: Does this interface with your hospital EMR?

A Dr. Kovarik: At this point no; however, we do have a new initiative that we're planning. We're currently in discussions with a private insurance carrier as well as our EPIC group to add a teledermatology workflow.

Right now our peripheral primary care offices can send a Consult to Dermatology as an order through EPIC. It comes into our office, we look at it and we try and decide what to do with the patient.

I have colleagues at the University of Texas Southwestern Medical Center in Dallas who have taken that Consult to Dermatology and turned it into a teledermatology consult, similar to our AccessDerm program.

They added the AccessDerm questions that we currently use with Philadelphia and into the Consult to Derm form in EPIC. They've added the ability to insert photos into EPIC and create that teledermatology workflow.

Here, at the University of Pennsylvania, we want to do the same thing, but integrate a mobile workflow. So if you're a PCP and you're in one of the Philadelphia Penn affiliates and you want to send a consult, you'll pull up the Consult to Derm form and fill in a few more questions. Then, to add the pictures, we're hoping to create a mobile interface that will directly integrate into the patient record. So the PCP can use his or her mobile device to take the photos and then send the record as a teledermatology consult. We can then answer the consult and help you treat your patients or we'll have more information to actually get them into the right clinic.

Listen to the discussion.
bit.ly/takeawaytelemedicine

I think using teledermatology as triage and/or treatment through EPIC would really help us enhance our services here. So that is our next project.

DR. SIEGFRIED: What distinguishes an issue that you can treat or triage with teledermatology and one that you can't? Are you aware of anyone who's actually trying to quantify or study that? Have you come up with parameters to distinguish between those cases?

A Dr. Kovarik: Most studies show that about 15 percent of cases need to be seen in person. That's about what we've found in our Philadelphia clinics; whether it's for biopsy, further evaluation or the case is too complex. We also don't want PCPs doing full skin exams and then picking out the lesions to take pictures of and send to us.

There are studies saying that it can be difficult to screen for malignancies; however, there are also good studies showing that dermoscopy works really well. So, if you have the ability to receive dermoscopic photos of pigmented lesions, you can actually screen individual pigmented lesions if you're skilled at looking at these.

You need to know when to search for more; you need to know what you're limitations are.

> "You need to know when to search for more; you need to know what your limitations are."
>
> **Carrie Kovarik, M.D.**
> Philadelphia

DR. SIEGFRIED: It seems to me that teledermoscopy and teledermatopathology may be more amenable than teledermatology, to global use, because the image is two-dimensional and with relatively limited number of views.

A Dr. Kovarik: Pathology, in general, is very amenable to telemedicine. Its very much like radiology, where you have an image and you interpret the image. Same with dermoscopy: you get that image; you interpret it.

DR. SIEGFRIED: So does your system in Africa or Philadelphia incorporate teledermoscopy and teledermatopathology at this point?

A Dr. Kovarik: We've had a wide telepathology system in Botswana since 2009, and I've read about 500 cases. In fact we just published a paper on robotic teledermatopathology.[1]

DR. SIEGFRIED: How do you find that different from standard dermatopathology?

A Dr. Kovarik: It's all limited by the technology. I use a live system, which is really going out of style, because it's all going to slide scanners. But in 2009 en vogue was live robotic telepathology where you put the slide on the scope. The difference is that for live telepathology you need a nice fast Internet connection. Because it's a live streaming connection, I'm moving the slide and I'm seeing it move as the pathologist in his office is watching his microscope move.

TELEDERMATOLOGY *see page* **62**

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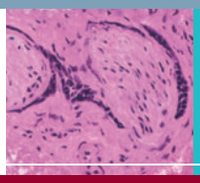

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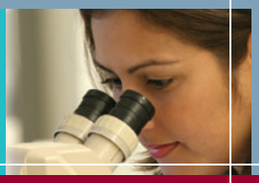

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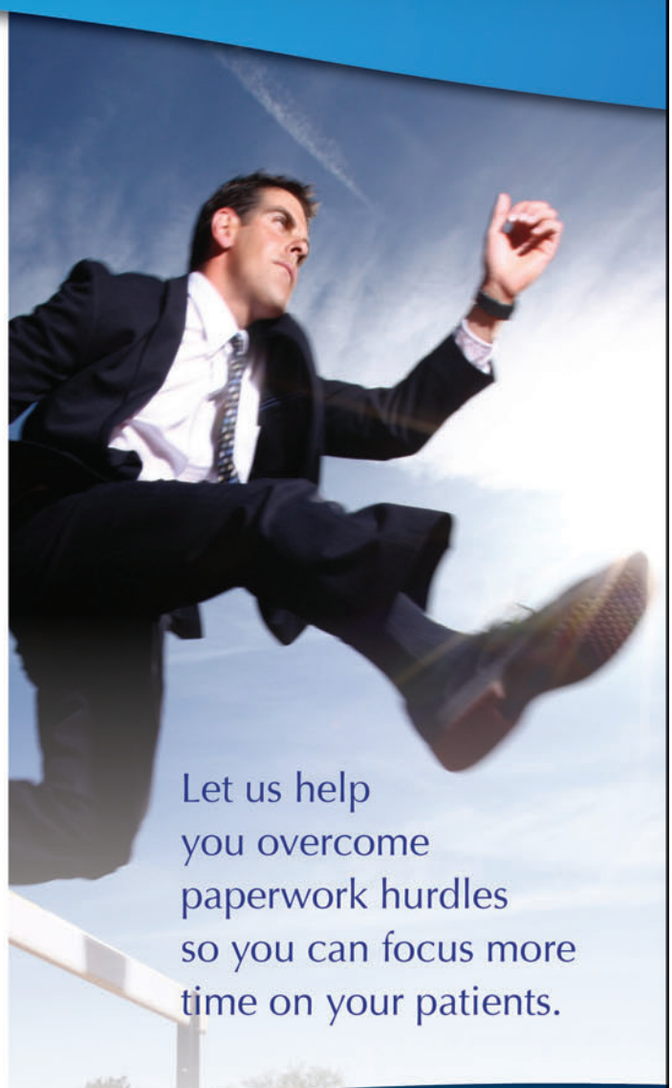

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TELEDERMATOLOGY:
Carrie Kovarik, M.D., discusses experiences with telemedicine in dermatology *from page* **52**

So, I can actually move the stage and move the objective in Botswana, and I can take pictures of it up to 40X. I get great resolution and take beautiful pictures. The limitation is often the slide processing, it's not the microscope. It's the fact that I may get thick sections or fragmented tissue.

What a slide scanner does is that it scans the slide and it generates this massive 60 to 100 MB image, and so to upload that to me from Botswana on that Internet would take all night long. In addition, these slide scanners are really expensive. We are actually working with a hospital in Ethiopia that just bought a four-slide, slide scanner. They have a pretty fast connection; so for the first time we're going to help their hospital to do telepathology using a slide scanner.

DR. SIEGFRIED: Now there are all kinds of little things that you can hook on to your iPhone. Do you have a favorite one? I would imagine that the technology is very similar to doing teledermatology?

A **Dr. Kovarik:** The group in Austria who is actually the group that we did the Africa telederm website with has published some very nice studies on teledermatocopy.[2] They have several iPhone adaptions. It can be done; particularly if you're working in a place where you can't biopsy a lot of lesions and you are good at looking through a dermatoscope.

DR. SIEGFRIED: It seems to me that successful e-consultation from a dermatoscopic digital image taken by a non-dermatologist may be easier than from a clinical image.

A **Dr. Kovarik:** It would be helpful, particularly if they're worried about a certain segment of a lesion.

DR. SIEGFRIED: There's a new code for remote e-consultation, and several states are considering reimbursements for telemedicine. Do you envision future incentives to cover the cost, technology and who will be performing teledermatology once it's well accepted?

A **Dr. Kovarik:** I'm part of a few committees where we're working on reimbursement for telemedicine services. I think as our healthcare reimbursement models change, telemedicine may not be fee-based reimbursement everywhere, but certainly we're still working towards that.

It's reimbursable in many states right now. There are bills up in the majority of states right now to have it reimbursed.

I think in the end it's going to be a part of value-based care. I think people are going to use it, like we talked about Penn using it for triage, to add value to services, to get patients evaluated and to the right clinic faster.

I think people are getting tired of waiting many months to have dermatologic conditions evaluated, and telemedicine is a great way to be triaged or to get an urgent consult. I think it could be bundled into payments for these services. So I think, in the end, it's going to become a very useful part of our healthcare system and certainly patients accept this technology and patients will drive this forward because they like the instant answers.

DR. SIEGFRIED: Reimbursement, I think, is a big barrier to success. Do you see any other barriers to future success?

A **Dr. Kovarik:** Right now some of the barriers are people's anxiety around new technology. I think more education about what telemedicine is would help people understand how it works, how it can be helpful, how it can save money and benefit patients. Right now people think it's heavy technology and expensive equipment and they don't feel they have time for it.

Other barriers: doctors worry about the liability. But, telemedicine has been done for 20 years, and there are less lawsuits percentage-wise that have come up in telemedicine than in other medical care settings.[3] It's definitely not more lawsuit ridden; it's a different way to deliver healthcare, but these fears need to be addressed in order for people to engage.

DR. SIEGFRIED: So how did you introduce it? Do you provide in-service education? Do you send emails? How do you introduce users to the benefits?

A **Dr. Kovarik:** The best way is one-on-one: showing people the app. Other ways that work seem to be in a conference with the residents or a lecture with attendings; showing screenshots and showing them what it's about.

DR. SIEGFRIED: Do you have any suggestions for dermatologists who are interested in setting up a system of teledermatology locally, or getting involved in any way?

A **Dr. Kovarik:** The first thing is figuring out if they're in a state where it reimburses. If they're not, we do have the AccessDerm program through the AAD which they can use for volunteer services. The AAD will help with setting it up. Dermatologists have been using that for some interesting services. In Iowa, for Mohs patients who are elderly and have difficulty coming in for follow up, it has been used to engage the patient's PCP to follow-up with wound care. Dermatologists are welcome to use that platform with patients that may have difficulty with access.

We also have another initiative with the AAD for in-patient teledermatology. We have about 16 groups that are providing in-patient teledermatology services around the country right now. This program is encouraging these groups to set up some type of business contract; so if there's no reimbursement in the state, there are actually many groups that have set up independent contracts to reimburse for telemedicine.

For example, the University of Pittsburgh has set up service agreements with local hospitals in which they provide inpatient and emergency department consultations, home-based primary care consultations, outpatient consultations and dermatologic education.[4] **DT**

[1] Michelett R.G., Steele K.T., Kovarik C.L. Robotic teledermatopathology from an African deratology clinic. J Am Acad Dermatol. 2014;70(5): 952-954

[2] Kroemer S, Frühauf J, Campbell TM, et al. Mobile teledermatology for skin tumour screening: diagnostic accuracy of clinical and dermoscopic image tele-evaluation using cellular phones. Br J Dermatol. 2011;164(5):973-9

[3] Marsch A, High WA. Teledermatology, teledermatopathology, interstate dermatopathology and the law. Semin Cutan Med Surg. 2013;32(4):224-9

[4] English JC, Gehris R, Leyva W. Add Pittsburgh teledermatology "with a twist" to the map!. J Am Acad Dermatol. 2013;68(6):1042

BRIEF SUMMARY OF FULL PRESCRIBING INFORMATION

This Brief Summary does not include all the information needed to use ONEXTON Gel safely and effectively. See full prescribing information for ONEXTON Gel.

ONEXTON™ (clindamycin phosphate and benzoyl peroxide) Gel, 1.2%/3.75%, for topical use

Initial U.S. Approval: 2000

CONTRAINDICATIONS

Hypersensitivity

ONEXTON Gel is contraindicated in those individuals who have shown hypersensitivity to clindamycin, benzoyl peroxide, any components of the formulation, or lincomycin. Anaphylaxis, as well as allergic reactions leading to hospitalization, has been reported in postmarketing use with ONEXTON Gel [see Adverse Reactions]

WARNINGS AND PRECAUTIONS

Colitis/Enteritis

Systemic absorption of clindamycin has been demonstrated following topical use of clindamycin. Diarrhea, bloody diarrhea, and colitis (including pseudomembranous colitis) have been reported with the use of topical and systemic clindamycin. If significant diarrhea occurs, ONEXTON Gel should be discontinued.

Severe colitis has occurred following oral and parenteral administration of clindamycin with an onset of up to several weeks following cessation of therapy. Antiperistaltic agents such as opiates and diphenoxylate with atropine may prolong and/or worsen severe colitis. Severe colitis may result in death.

Studies indicate toxin(s) produced by Clostridia is one primary cause of antibiotic-associated colitis. The colitis is usually characterized by severe persistent diarrhea and severe abdominal cramps and may be associated with the passage of blood and mucus. Stool cultures for Clostridium difficile and stool assay for C. difficile toxin may be helpful diagnostically.

Ultraviolet Light and Environmental Exposure

Minimize sun exposure (including use of tanning beds or sun lamps) following drug application [see Nonclinical Toxicology].

ADVERSE REACTIONS

The following adverse reaction is described in more detail in the Warnings and Precautions section of the label:

Colitis [see Warnings and Precautions].

Clinical Trials Experience

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

These adverse reactions occurred in less than 0.5% of subjects treated with ONEXTON Gel: burning sensation (0.4%); contact dermatitis (0.4%); pruritus (0.4%); and rash (0.4%).

During the clinical trial, subjects were assessed for local cutaneous signs and symptoms of erythema, scaling, itching, burning and stinging. Most local skin reactions either were the same as baseline or increased and peaked around week 4 and were near or improved from baseline levels by week 12. The percentage of subjects that had symptoms present before treatment (at baseline), during treatment, and the percent with symptoms present at week 12 are shown in Table 1.

Table 1: Local Skin Reactions - Percent of Subjects with Symptoms Present. Results from the Phase 3 Trial of ONEXTON Gel 1.2%/3.75% (N = 243)

	Before Treatment (Baseline)			Maximum During Treatment			End of Treatment (Week 12)		
	Mild	Mod.*	Severe	Mild	Mod.*	Severe	Mild	Mod.*	Severe
Erythema	20	6	0	28	5	<1	15	2	0
Scaling	10	1	0	19	3	0	10	<1	0
Itching	14	3	<1	15	3	0	7	2	0
Burning	5	<1	<1	7	1	<1	3	<1	0
Stinging	5	<1	0	7	0	<1	3	0	<1

*Mod. = Moderate

Postmarketing Experience

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

Anaphylaxis, as well as allergic reactions leading to hospitalizations, has been reported in postmarketing use of products containing clindamycin phosphate/benzoyl peroxide.

DRUG INTERACTIONS

Erythromycin

Avoid using ONEXTON Gel in combination with topical or oral erythromycin-containing products due to its clindamycin component. In vitro studies have shown antagonism between erythromycin and clindamycin. The clinical significance of this in vitro antagonism is not known.

Concomitant Topical Medications

Concomitant topical acne therapy should be used with caution since a possible cumulative irritancy effect may occur, especially with the use of peeling, desquamating, or abrasive agents. If irritancy or dermatitis occurs, reduce frequency of application or temporarily interrupt treatment and resume once the irritation subsides. Treatment should be discontinued if the irritation persists.

Neuromuscular Blocking Agents

Clindamycin has been shown to have neuromuscular blocking properties that may enhance the action of other neuromuscular blocking agents. ONEXTON Gel should be used with caution in patients receiving such agents.

USE IN SPECIFIC POPULATIONS

Pregnancy

Pregnancy Category C.

There are no adequate and well-controlled studies in pregnant women treated with ONEXTON Gel. ONEXTON Gel should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Animal reproductive/developmental toxicity studies have not been conducted with ONEXTON Gel or benzoyl peroxide. Developmental toxicity studies of clindamycin performed in rats and mice using oral doses of up to 600 mg/kg/day (240 and 120 times amount of clindamycin in the highest recommended adult human dose based on mg/m^2, respectively) or subcutaneous doses of up to 200 mg/kg/day (80 and 40 times the amount of clindamycin in the highest recommended adult human dose based on mg/m^2, respectively) revealed no evidence of teratogenicity.

Nursing Mothers

It is not known whether clindamycin is excreted in human milk after topical application of ONEXTON Gel. However, orally and parenterally administered clindamycin has been reported to appear in breast milk. Because of the potential for serious adverse reactions in nursing infants, a decision should be made whether to use ONEXTON Gel while nursing, taking into account the importance of the drug to the mother.

Pediatric Use

Safety and effectiveness of ONEXTON Gel in pediatric patients under the age of 12 have not been evaluated.

Geriatric Use

Clinical trials of ONEXTON Gel did not include sufficient numbers of subjects aged 65 and older to determine whether they respond differently from younger subjects.

NONCLINICAL TOXICOLOGY

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity, mutagenicity and impairment of fertility testing of ONEXTON Gel have not been performed.

Benzoyl peroxide has been shown to be a tumor promoter and progression agent in a number of animal studies. Benzoyl peroxide in acetone at doses of 5 and 10 mg administered topically twice per week for 20 weeks induced skin tumors in transgenic Tg.AC mice. The clinical significance of this is unknown.

Carcinogenicity studies have been conducted with a gel formulation containing 1% clindamycin and 5% benzoyl peroxide. In a 2-year dermal carcinogenicity study in mice, treatment with the gel formulation at doses of 900, 2700, and 15000 mg/kg/day (1.8, 5.4, and 30 times amount of clindamycin and 2.4, 7.2, and 40 times amount of benzoyl peroxide in the highest recommended adult human dose of 2.5 g ONEXTON Gel based on mg/m^2, respectively) did not cause any increase in tumors. However, topical treatment with a different gel formulation containing 1% clindamycin and 5% benzoyl peroxide at doses of 100, 500, and 2000 mg/kg/day caused a dose-dependent increase in the incidence of keratoacanthoma at the treated skin site of male rats in a 2-year dermal carcinogenicity study in rats. In an oral (gavage) carcinogenicity study in rats, treatment with the gel formulation at doses of 300, 900 and 3000 mg/kg/day (1.2, 3.6, and 12 times amount of clindamycin and 1.6, 4.8, and 16 times amount of benzoyl peroxide in the highest recommended adult human dose of 2.5 g ONEXTON Gel based on mg/m^2, respectively) for up to 97 weeks did not cause any increase in tumors. In a 52-week dermal photocarcinogenicity study in hairless mice, (40 weeks of treatment followed by 12 weeks of observation), the median time to onset of skin tumor formation decreased and the number of tumors per mouse increased relative to controls following chronic concurrent topical administration of the higher concentration benzoyl peroxide formulation (5000 and 10000 mg/kg/day, 5 days/week) and exposure to ultraviolet radiation.

Clindamycin phosphate was not genotoxic in the human lymphocyte chromosome aberration assay. Benzoyl peroxide has been found to cause DNA strand breaks in a variety of mammalian cell types, to be mutagenic in *S. typhimurium* tests by some but not all investigators, and to cause sister chromatid exchanges in Chinese hamster ovary cells.

Fertility studies have not been performed with ONEXTON Gel or benzoyl peroxide, but fertility and mating ability have been studied with clindamycin. Fertility studies in rats treated orally with up to 300 mg/kg/day of clindamycin (approximately 120 times the amount of clindamycin in the highest recommended adult human dose of 2.5 g ONEXTON Gel, based on mg/m^2) revealed no effects on fertility or mating ability.

PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (Patient Information).

Distributed by:
Valeant Pharmaceuticals North America LLC, Bridgewater, NJ 08807
Manufactured by:
Contract Pharmaceuticals Limited Mississauga, Ontario, Canada L5N 6L6
U.S. Patents 5,733,886 and 8,288,434
Issued 11/2014
9389300
DM/ONX/14/0031(1)

NEW

FOR THE TREATMENT OF COMEDONAL AND INFLAMMATORY ACNE

ONEXTON™

(clindamycin phosphate and benzoyl peroxide) Gel,1.2%/3.75%

For more information, please visit **www.OnextonGel.com**

INDICATION

ONEXTON (clindamycin phosphate and benzoyl peroxide) Gel, 1.2%/3.75% is indicated for the topical treatment of acne vulgaris in patients 12 years of age or older.

IMPORTANT SAFETY INFORMATION

- ONEXTON Gel is contraindicated in patients with a known hypersensitivity to clindamycin, benzoyl peroxide, any component of the formulation or lincomycin.
- ONEXTON Gel is contraindicated in patients with a history of regional enteritis, ulcerative colitis, or antibiotic-associated colitis.
- Diarrhea, bloody diarrhea, and colitis (including pseudomembranous colitis) have been reported with the use of topical or systemic clindamycin. ONEXTON Gel should be discontinued if significant diarrhea occurs.
- Orally and parenterally administered clindamycin has been associated with severe colitis, which may result in death.
- Anaphylaxis, as well as other allergic reactions leading to hospitalizations, has been reported in postmarketing use of products containing clindamycin/benzoyl peroxide. If a patient develops symptoms of an allergic reaction such as swelling and shortness of breath, they should be instructed to discontinue use and contact a physician immediately.
- The most common local adverse reactions experienced by patients in clinical trials were burning sensation, contact dermatitis, pruritus and rash. All occurred in <0.5% of patients.
- ONEXTON Gel should not be used in combination with erythromycin-containing products because of its clindamycin component.
- Patients should be advised to avoid contact with the eyes or mucous membranes.
- Patients should avoid exposure to natural sunlight and avoid artificial sunlight (tanning beds or UVA/B treatment) while using ONEXTON Gel.

Please see Brief Summary of Prescribing Information on the following page.

VALEANT® Dermatology

ONEXTON™
(clindamycin phosphate and benzoyl peroxide)
Gel,1.2%/3.75%