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Clinical Analysis for Today's Skincare Specialists
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Liked or loathed, RUC still relevant

Scott Baltic | Staff Correspondent

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CRITICS: RVUs are seven times likelier to increase than to fall

RUC: Since 2010, of 1,553 codes, only 5% increased, 43% decreased, 34% stayed the same and 18% are still under review

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CRITICS: Certain procedures are overvalued

RUC: The RBRVS as administered by the CMS is budget-neutral, as reflected by annual adjustments in the conversion factor

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RUC see page 61

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Photo courtesy of National Psoriasis Foundation 2012/Billy Delfs Photographer

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ADVANSTAR MEDICAL COMMUNICATIONS GROUP

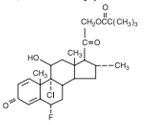
RxOnly

Cloderm® Cream, 0.1%
(clocortolone pivalate)

FOR TOPICAL DERMATOLOGIC USE ONLY–
NOT FOR OPHTHALMIC, ORAL, OR INTRAVAGINAL USE.
WARNING: KEEP OUT OF REACH OF CHILDREN

DESCRIPTION: Cloderm Cream 0.1% contains the medium potency topical corticosteroid, clocortolone pivalate, in a specially formulated water-washable emollient cream base consisting of purified water, white petrolatum, mineral oil, stearyl alcohol, polyoxyl 40 stearate, carbomer 934P, edetate disodium, sodium hydroxide, with methylparaben and propylparaben as preservatives.

Chemically, clocortolone pivalate is 9-chloro-6α-fluoro-11 , 21-dihydroxy-16α methylpregna-1, 4-diene-3, 20-dione 21-pivalate. Its structure is as follows:



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

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

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

Topical corticosteroids can be absorbed from normal intact skin. Inflammation and/or other disease processes in the skin increase percutaneous absorption. Occlusive dressings substantially increase the percutaneous absorption of topical corticosteroids. Thus, occlusive dressings may be a valuable therapeutic adjunct for treatment of resistant dermatoses.
(See **DOSAGE AND ADMINISTRATION**).

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

INDICATIONS AND USAGE: Topical corticosteroids are indicated for the relief of the inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses.

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

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

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

Therefore, patients receiving a large dose of a potent topical steroid applied to a large surface area or under an occlusive dressing should be evaluated periodically for evidence of HPA axis suppression by using the urinary free cortisol and ACTH stimulation tests. If HPA axis suppression is noted, an attempt should be made to withdraw the drug, to reduce the frequency of application, or to substitute a less potent steroid.

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

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

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

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

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

1. This medication is to be used as directed by the physician. It is for external use only. Avoid contact with the eyes.
2. Patients should be advised not to use this medication for any disorder other than for which it was prescribed.
3. The treated skin area should not be bandaged or otherwise covered or wrapped as to be occlusive unless directed by the physician.
4. Patients should report any signs of local adverse reactions especially under occlusive dressing.
5. Parents of pediatric patients should be advised not to use tight-fitting diapers or plastic pants on a child being treated in the diaper area, as these garments may constitute occlusive dressings.

Laboratory Tests: The following tests may be helpful in evaluating the HPA axis suppression:
Urinary free cortisol test
ACTH stimulation test

Carcinogenesis, Mutagenesis, and Impairment of Fertility: Long-term animal studies have not been performed to evaluate the carcinogenic potential or the effect on fertility of topical corticosteroids.

Studies to determine mutagenicity with prednisolone and hydrocortisone have revealed negative results.

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

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

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

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

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

ADVERSE REACTIONS:
The following local adverse reactions are reported infrequently with topical corticosteroids, but may occur more frequently with the use of occlusive dressings. These reactions are listed in an approximate decreasing order of occurrence:

Burning, Itching, Irritation, Dryness, Folliculitis, Hypertrichosis, Acneiform eruptions, Hypopigmentation, Perioral dermatitis, Allergic contact dermatitis, Maceration of the skin, Secondary infection, Skin atrophy, Striae, Miliaria.

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

DOSAGE AND ADMINISTRATION:
Apply Cloderm (clocortolone pivalate) Cream 0.1% sparingly to the affected areas three times a day and rub in gently.

Occlusive dressings may be used for the management of psoriasis or recalcitrant conditions.

If an infection develops, the use of occlusive dressings should be discontinued and appropriate anti-microbial therapy instituted.

HOW SUPPLIED:
Cloderm (clocortolone pivalate) Cream 0.1% is supplied in 30 gram and 75 gram pump bottles, 45 gram and 90 gram tubes.

30 gram pump bottle	NDC-67857-804-30
75 gram pump bottle	NDC-67857-804-51
45 gram tube	NDC-67857-804-45
90 gram tube	NDC-67857-804-90

STORAGE:
Store Cloderm Cream between 15° and 30° C (59° and 86° F).
Avoid freezing.

Distributed by:

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ADVANSTAR MEDICAL COMMUNICATIONS GROUP


THE NEW
TwinPack
Eletone® Cream
Nonsteroidal Dermatitis Therapy
with Hydrolipid Technology
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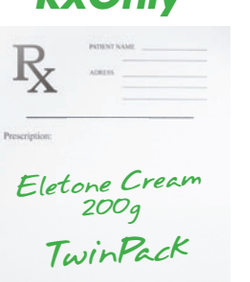
Mission®
PHARMACAL

Now, Therapy that's Always Close at Hand

- Contains **two 100-gram tubes of Eletone** Cream for greater coverage of affected areas during the cold weather season when atopic dermatitis tends to flare most.
- With one prescription, patients can receive twice as much therapy for the same pharmacy co-pay as with the single tube.

RxOnly



ELETONE® CREAM

Nonsteroidal Atopic Dermatitis Therapy

PRODUCT DESCRIPTION: Eletone® Cream is a non-steroidal, lipid-rich, fragrance free emulsion formulated with Hydrolipid Technology for the management and relief of burning, itching, and redness associated with various types of dermatoses. There are no restrictions on age or duration of use and the product has a low potential for irritation.

INDICATIONS FOR USE: Eletone® Cream is indicated for the management and relief of burning, itching, and redness associated with various types of dermatoses, including atopic dermatitis, allergic contact dermatitis, and radiation dermatitis (post-radiation treatment).

CONTRAINDICATIONS: THIS PRODUCT SHOULD NOT BE USED DURING THE PERIOD OF TIME WHEN RADIATION TREATMENT IS OCCURRING BECAUSE OF THE INCREASED RISK OF SKIN TOXICITY WHEN RADIATING THROUGH PETROLATUM AND OIL. Eletone® Cream is contraindicated in patients with a known hypersensitivity to any of the components of the formulation.

PRECAUTIONS: Eletone® Cream is for external use only.

Eletone® Cream does not contain a sunscreen and should always be used in conjunction with a sunscreen in sun exposed areas.

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

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

HOW SUPPLIED: Eletone® Cream is available in a 100 gram tube NHRIC 0178-0368-01. Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature].

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

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

Let your voice be heard, contact us: sthuerk@advanstar.com

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content

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The Business of Dermatology

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The Web can be beneficial for a physician's reputation, but it also can be destructive. Be smarter about the Web to protect your good name.

DermatologyTimes.com/reviews

Will healthcare reform cut costs and improve patient care?

There's little doubt that the way physicians look at costs and decision-making will be subject to change. Physicians may look back on current payment reforms and wonder why they weren't implemented sooner.

DermatologyTimes.com/reform

How to motivate and retain the top employees at your practice

A star player adds up to more than one full-time equivalent on your payroll. Here are tips to cement stars on your team and help good workers become super.

DermatologyTimes.com/motivation

CLARIFICATION

Although vismodegib is currently being investigated in clinical trials for the treatment of nevoid basal cell carcinoma syndrome, it does not currently have Food and Drug Administration approval for this indication. Please read the clarified story at DermatologyTimes.com/vismodegib. *Dermatology Times* regrets the error.

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dermatologytimes.com/differences

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dermatologytimes.com/antibiotics

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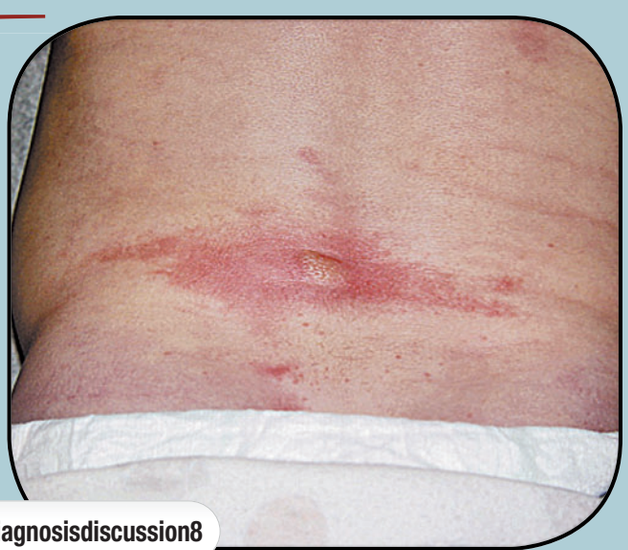

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Brought to you by *Contemporary Pediatrics* magazine

BOTOX® Cosmetic
onabotulinumtoxinA injection

Now approved

For the temporary improvement of moderate to severe lateral with orbicularis oculi activity

BOTOX® Cosmetic (onabotulinumtoxinA) Important Information

Indications

Glabellar Lines

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

Lateral Canthal Lines

BOTOX® Cosmetic is indicated for the temporary improvement in the appearance of moderate to severe lateral canthal lines associated with orbicularis oculi activity in adult patients.

IMPORTANT SAFETY INFORMATION, INCLUDING BOXED WARNING

WARNING: DISTANT SPREAD OF TOXIN EFFECT

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

CONTRAINDICATIONS

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

WARNINGS AND PRECAUTIONS

Lack of Interchangeability between Botulinum Toxin Products

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

Spread of Toxin Effect

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

No definitive serious adverse event reports of distant spread of toxin effect associated with dermatologic use of BOTOX® Cosmetic at the labeled dose of 20 Units (for glabellar lines), 24 Units (for lateral canthal lines), 44 Units (for simultaneous treatment of lateral canthal lines and glabellar lines) have been reported.

Injections In or Near Vulnerable Anatomic Structures

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

in the appearance canthal lines associated in adult patients

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

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

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

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

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

ADVERSE REACTIONS
The most frequently reported adverse event following injection of BOTOX® Cosmetic (onabotulinumtoxinA) for glabellar lines was eyelid ptosis (3%).

The most frequently reported adverse event following injection of BOTOX® Cosmetic for lateral canthal lines was eyelid edema (1%).

DRUG INTERACTIONS
Co-administration of BOTOX® Cosmetic and aminoglycosides or other agents interfering with neuromuscular transmission (eg, curare-like compounds) should only be performed with caution as the effect of the toxin may be potentiated. Use of anticholinergic drugs after administration of BOTOX® Cosmetic may potentiate systemic anticholinergic effects.

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

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

USE IN SPECIFIC POPULATIONS
BOTOX® Cosmetic is not recommended for use in children or pregnant women. It is not known whether BOTOX® Cosmetic is excreted in human milk. Caution should be exercised when BOTOX® Cosmetic is administered to a nursing woman.

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

BOTOX® Cosmetic
onabotulinumtoxinA injection

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

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

WARNING: DISTANT SPREAD OF TOXIN EFFECT

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

INDICATIONS AND USAGE

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

BOTOX® Cosmetic is indicated for the temporary improvement in the appearance of moderate to severe lateral canthal lines associated with orbicularis oculi activity in adult patients.

CONTRAINDICATIONS

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

WARNINGS AND PRECAUTIONS

Lack of Interchangeability between Botulinum Toxin Products

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

Spread of Toxin Effect

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

No definitive serious adverse event reports of distant spread of toxin effect associated with dermatologic use of **BOTOX®**/**BOTOX® Cosmetic** at the labeled dose of 20 Units (for glabellar lines), 24 Units (for lateral canthal lines), 44 Units (for simultaneous treatment of lateral canthal lines and glabellar lines), or 100 Units (for severe primary axillary hyperhidrosis) have been reported.

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

Injections In or Near Vulnerable Anatomic Structures

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

Hypersensitivity Reactions

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

Cardiovascular System

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

Pre-Existing Neuromuscular Disorders

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

Dysphagia and Breathing Difficulties in Treatment of Cervical Dystonia

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

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

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

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

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

Pre-existing Conditions at the Injection Site

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

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

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

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

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

Human Albumin and Transmission of Viral Diseases

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

ADVERSE REACTIONS

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

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

Clinical Trials Experience

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

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

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

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

Glabellar Lines

Table 2 lists selected adverse reactions reported by ≥1% of **BOTOX® Cosmetic** treated subjects (N=405) aged 18 to 75 who were evaluated in the randomized, placebo-controlled clinical studies to assess the use of **BOTOX® Cosmetic** in the improvement of the appearance of glabellar lines.

Table 2: Adverse Reactions Reported by ≥1% of the BOTOX® Cosmetic treated Patients and More Frequent than in Placebo-treated Patients in Double-blind, Placebo-controlled Clinical Studies of Treatment of Glabellar Lines

Adverse Reactions by System Organ Class	BOTOX® Cosmetic (N=405)	Placebo (N=130)
General Disorders and Administration Site Conditions		
Facial pain	6 (1%)	0 (0%)
Nervous System Disorders		
Facial paresis	5 (1%)	0 (0%)
Eye Disorders		
Eyelid ptosis	13 (3%)	0 (0%)
Musculoskeletal and Connective Tissue Disorders		
Muscular Weakness	6 (1%)	0 (0%)

Lateral Canthal Lines

Table 3 lists selected adverse reactions reported within 90 days following injection by ≥1% of **BOTOX® Cosmetic** treated subjects (N=526) aged 18 to 75 who were evaluated in two randomized, double-blind, placebo-controlled clinical studies to assess the use of **BOTOX® Cosmetic** in the improvement of the appearance of lateral canthal lines alone.

Table 3: Adverse Reaction Reported by ≥1% of BOTOX® Cosmetic treated Patients and More Frequent than in Placebo-treated Patients Within 90 Days, in Double-blind, Placebo-controlled Clinical Studies of Treatment of Lateral Canthal Lines

Adverse Reactions by System Organ Class	BOTOX® Cosmetic 24 Units (N=526)	Placebo (N=530)
Eye disorders		
Eyelid edema	5 (1%)	0 (0%)

Immunogenicity

As with all therapeutic proteins, there is a potential for immunogenicity. Treatment with botulinum toxins may result in the formation of neutralizing antibodies that may reduce the effectiveness of subsequent treatments by inactivating biological activity of the toxin.

In three Lateral Canthal Line trials, 916 subjects (517 subjects at 24 Units and 399 subjects at 44 Units) treated with **BOTOX® Cosmetic** had specimens analyzed for antibody formation. Among the 916 **BOTOX® Cosmetic** treated subjects, 14 subjects (1.5%) developed binding antibodies and no subjects (0%) developed the presence of neutralizing antibodies.

The data reflect the subjects whose test results were considered positive or negative for neutralizing activity to **BOTOX® Cosmetic** in a mouse protection assay. The results of these tests are highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to **BOTOX® Cosmetic** with the incidence of antibodies to other products may be misleading.

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

Post-marketing Experience

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

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

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

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

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

Ear and labyrinth disorders
Hypoacusis; tinnitus; vertigo

Eye disorders
Diplopia; strabismus; visual disturbances; vision blurred

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

General disorders and administration site conditions
Denervation; malaise; pyrexia

Metabolism and nutrition disorders
Anorexia

Musculoskeletal and connective tissue disorders
Muscle atrophy; myalgia

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

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

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

DRUG INTERACTIONS

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

Aminoglycosides and Other Agents Interfering with Neuromuscular Transmission

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

Anticholinergic Drugs

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

Other Botulinum Neurotoxin Products

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

Muscle Relaxants

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

USE IN SPECIFIC POPULATIONS

Pregnancy

Teratogenic Effects: Pregnancy Category C.

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

Nursing Mothers

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

Pediatric Use

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

Geriatric Use

Glabellar Lines

In the two initial glabellar lines clinical studies of **BOTOX® Cosmetic**, the responder rates appeared to be higher for subjects younger than age 65 than for subjects 65 years or older *(see Clinical Studies).*

Lateral Canthal Lines

In the two lateral canthal lines clinical studies of **BOTOX® Cosmetic**, the responder rates appeared to be higher for subjects younger than age 65 than for subjects 65 years or older.

OVERDOSAGE

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

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

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

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

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Ronald Wheeland, M.D.,
is a private practitioner in Tucson, Ariz.

Changes and challenges

There have been many changes in the practice of medicine, both big and small, that have occurred during the last few decades.

From legislative federal policy changes to the development of new administrative tools and technologic advances, including drugs and devices. I don't expect to have thought of them all and I'm equally sure there will be many readers who disagree with the level of importance I've assigned them.

At the same time, the more I've thought about these items, I also have realized how dissatisfied I have become with the effectiveness of our elected leadership. They seem more focused on arguing, delaying, obfuscating and generally confusing the electorate than they are in actually working for their constituents. If our representatives would work together on the many important issues that impact access and delivery of healthcare — as well as the ability of physicians to practice high quality medicine in an unimpeded fashion utilizing the many tools, techniques and technologies that have been recently developed — then we physicians could provide better care for our patients. What follows is a list, as I see it, of the most important federal policy changes in healthcare over the past 50 years.

Medicare

When this first federal policy change occurred, I wasn't even a physician but I'm including it here because of its importance, size, longevity and expense.

When President Lyndon Johnson signed into law several amendments to existing Social Security legislation, which established the Social Security Act of 1965, Medicare was established to provide health insurance coverage to people ages 65 and older, with the goal of increasing the availability of affordable healthcare for the elderly. Much like the discussions playing out today in newspapers and on television about the Affordable Care Act (ACA), various politicians predicted that Medicare "wasn't going to work" (Sen. Bob Dole), that it represented "socialized medicine" (George H.W. Bush), that it "took away our personal freedom, would complicate the delivery of healthcare and end the doctor-patient relationship as we know it" (Ronald Reagan).

While I am not sufficiently knowledgeable about all of the economic and social factors regarding Medicare, I believe that during the nearly 50 years it was introduced, it hasn't turned out to be as intrusive as was initially projected, and that the doctor-patient relationship does not seem to have suffered. Furthermore, while this program certainly remains confusing and frustrating to many seniors and their physicians, especially when new programs are added (for example, Medicare Part D), the sheer number of people enrolled in Medicare today can certainly be viewed as one measure of its acceptance and success.

HIPAA

This law was passed in 1996 to ensure that people who were covered under one group health insurance plan would still be able to purchase new health insurance coverage, without being restricted by pre-existing conditions or other long-term health conditions should their employment status change. This law also created certain standards to prevent improper use of medical records and to maintain the privacy of all patients' personal health information. While the implementation came with a significant number of new requirements, I believe that it has proven helpful to these people and also helped to secure the privacy of patients' medical information.

Affordable Care Act

The ACA represents the most comprehensive revision to American healthcare financing. However, it is encumbered with myriad tedious governmental regulations, mandates, conditions and restrictions that will produce dramatic changes (many of which still remain unknown) in the delivery of healthcare once all of its provisions have been fully implemented. Some of the main provisions include: a mandate that requires all individuals to have health insurance coverage or face financial penalties, makes eligibility changes in Medicaid to expand coverage, guarantees availability of health insurance coverage to all citizens of the United States by providing cost-sharing subsidies for those with incomes up to 250 percent of poverty level, imposes fees on employers with more than 50 employees that do not offer medical insurance coverage, establishes state health insurance exchanges, prohibits annual coverage limits and establishes a physician payment system which is tied to the quality of care provided.

As I write, there remain many unanswered questions. In addition, online enrollment has proven frustrating, time-consuming and difficult which has added to the concern of the American public about how well this new program will function when its provisions are fully rolled out. The ultimate acceptance of the provisions of ACA as well as the cost and likelihood of success for this program will require careful scrutiny for years to come. The effect on the patient-physician relationship has also yet to be determined. **DT**

Next month...

Dr. Wheeland will focus on the development of new administrative tools as well as new technologies, drugs and devices that have impacted dermatologic healthcare delivery.

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

Can a derm expert witness be arrested for lying on the stand?

Dr. Skin is a nationally known academic researcher. Because of his expertise he is commonly asked for expert testimony in a large number of medical malpractice cases. He recently testified and was asked about his background. He stated that he was a well-known dermatologist who lectures all over the world. This was true.

When asked about his training, he stated that he went to an Ivy League medical school. In fact, he went to medical school outside of the United States. After the trial is over, it is determined that he lied about his background. He admits this, but contends that his lies as an expert on the stand had no material impact on the trial. His adversaries disagree and file a lawsuit against him. Soon thereafter he is arrested for perjury. He is in disbelief. Can this happen? In fact, it can happen.

Not unprecedented

Such an arrest is not a common headline. But it can happen. Recently, Melvyn Flye, M.D., a St. Louis surgeon, testified in a medical malpractice case involving gallbladder surgery performed in 2010. Media reports noted that Dr. Flye allegedly lied under oath about his own surgical experience, how often he had been sued for malpractice, and the status of his surgical credentials at a St. Louis hospital. He was arrested and subsequently released on $50,000 bond.

Many physician defendants suggest that in their medical malpractice case the physician expert witness lied — and he or she committed perjury. In reality, expert witnesses are generally immune from civil litigation based on their opinions rendered in court. They cannot be sued for malicious prosecution, abuse of process, or defamation.

The reason is simple: In most disputes, there are two sides, and if experts could be sued for their words by the adverse party, there would never be any end to litigation. Because of this, experts can make wild claims on the witness stand with essential civil impunity.

For example, historically, experts can testify that the defendant never received a medical degree; is a pedophile; or has been sued 25 times in the past. While each of these claims is factually false, a party often could not find a remedy in civil court against an adverse expert spouting such lies.

Criminal action

That said, if an expert makes factual claims that are demonstrably false, and these fictions *are materially relevant to the outcome of a case,* action can be taken criminally (alleging perjury). There, the action is propelled by the district attorney. The district attorney would need to be persuaded to take such a case. The bar is high and most such prosecutors take a pass. The few times district attorneys have propelled such cases, they were based on an expert's credentials — for example, an expert misstating his credentials vis à vis board certification or how many procedures he had performed in the past.

An example was a case where, according to a federal prosecutor, a Florida surgeon lied about regularly performing coronary bypass surgery while presenting himself as an expert witness in medical malpractice cases. The doctor denied the accusation. A federal grand jury indicted Alex Zakharia, M.D., on perjury, mail fraud and wire fraud charges, Detroit U.S. Attorney Stephen J. Murphy said in a news release. Dr. Zakharia, 68, is a cardiovascular surgeon licensed in Florida. Mr. Murphy said the doctor lied about his experience to advertise his services as a medical expert in malpractice cases in 2001 to 2003.

With this in mind, preposterous "opinions" are not considered perjury. Fictional factual claims may be actionable as perjury. It appears Dr. Flye joins the list of "experts" whose alleged puffery about his background, training and experience was exposed.

Dr. Skin is entitled to his opinion. A defendant physician may not be happy about this, but cannot do much about it. However, if Dr. Skin's testimony is clearly a lie, he can be arrested for perjury. **DT**

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Melanoma survival up to 10 years for some taking ipilimumab

Presented at European Cancer Congress October 2013

Long-term analysis of patients with advanced melanoma taking ipilimumab demonstrated survival rates of up to 10 years, according to recent research.

A presentation at the 2013 European Cancer Congress suggested a plateau in overall survival starting around the third year and extending through year 10 in patients taking ipilimumab (Yervoy, Bristol-Myers Squibb) for the treatment of melanoma.

Stephen Hodi, M.D., Dana-Farber Cancer Institute, Boston, and colleagues from around the world studied data from 1,861 patients in 12 prospective and retrospective studies of ipilimumab's impact on long-term survival. They also analyzed data from an additional 2,985 patients who had been treated with ipilimumab but were not participants in clinical trials, according to the news release.

Median overall survival for the patients in trials was 11.4 months. Twenty-two percent of these patients were alive after three years, and there were no deaths among patients who survived beyond seven years. Longest overall survival in the database was 9.9 years, according to Dr. Hodi. When factoring in data from patients not in clinical trials, median overall survival was 9.5 months, with a plateau in overall survival at three years for 21 percent of patients.

"This slightly lower survival rate was because there were limited and incomplete data on overall survival," Dr. Hodi says in the news release, "and patients given ipilimumab through the extended access program tended to be more ill and with more advanced disease."

Dr. Hodi notes a limitation in the study is that it did not come from a single, randomized, controlled study but rather from a pooled analysis of phase 2, 3 and observational data. **DT**

Humira effective in early studies for treatment of HS

Presented at 22nd Congress of the European Dermatology and Venereology, October 2013

Results of a post-hoc analysis of an investigational phase 2 study evaluating Adalimumab (Humira, AbbVie) in the treatment of patients with moderate-to-severe hidradenitis suppurativa (HS) after 16 weeks of therapy appear promising, according to a news release.

The analysis found that Humira induced a significant response rate in adult patients at week 16 versus placebo for the two dosing regimens assessed. The efficacy of the drug was re-assessed in this analysis using the Hidradenitis Suppurativa Clinical Response (HiSCR) measure, which is an endpoint defined as at least a 50 percent reduction from baseline in total abscess and inflammatory nodule count, with no increase in counts for abscesses and draining fistulas. Specifically, HiSCR response rates were for HS patients given placebo were 25.6 percent, 33.3 percent for those given Humira every other week, and 54.5 percent for those given Humira weekly.

"Although hidradenitis suppurativa affects a significant number of people, there is no approved treatment option for this underserved patient group," Gregor Jemec, M.D., department of dermatology, University of Copenhagen Roskilde Hospital, says in the news release. "These phase 2 study results suggest Humira could be a promising therapeutic option in patients with moderate-to-severe HS and will be further evaluated in phase 3 trials."

The data substantiate HiSCR as a more responsive method than HS-PGA-based clinical response to determine improvement in patients and demonstrate that HiSCR may be a useful new tool to assess the efficacy of HS therapy in clinical practice and research trials.

"AbbVie developed the HiSCR endpoint to help advance hidradenitis suppurativa research and address the need for a reliable and relatively simple measure of clinical response in HS," AbbVie vice president John Medich, Ph.D., says in the statement. **DT**

Scientists ID 'first responders' in wound healing

Journal of Clinical Investigation, September 2013

http://www.jci.org/articles/view/70064

Researchers have identified a specific type of T cell that summons other immune cells to the site of skin injuries, shedding light on how these "first responders" contribute to wound healing.

Investigators with Scripps Research Institute sought to determine whether dendritic epidermal T cells (DETCs) — which are the only resident T cell population in the epidermis of mice — would produce interleukin-17A in response to a skin injury, according to a news release. IL-17A is considered a recruiter of other immune cells, promoting inflammation in most parts of the body.

In the mouse subjects that lacked IL-17A activity, wounds on their skin healed more slowly than normal, much like the subjects that lacked DETCs, researchers noted. When the scientists applied IL-17A to the skin of these subjects, the wounds were repaired. The rise in local IL-17A levels after skin injury depended on the activation of skin-resident DETCs, researchers found.

Adding normal DETCs from other subjects in the mice lacking IL-17A fully restored their wound-healing capacity.

"Only a subset produces IL-17A upon skin injury, although the surface markers on these cells seem identical to those of other DETCs," Amanda S. MacLeod, M.D., senior researcher associate and lead author of the study, said in the news release. "Why only some DETCs respond to wounds in this way is something we plan to explore further."

In another series of tests, researchers found that DETCs began producing IL-17A as soon as they detected damage signals from nearby keratinocytes. The surge in IL-17A levels induced the keratinocytes to make special proteins known to combat bacteria, viruses and other microbes.

"The 'cross-talk' between skin-resident T cells and nearby keratinocytes is critical for re-establishing the skin barrier following wounding," Dr. MacLeod said. **DT**

Vaccine fails to improve melanoma outcomes

Journal of Clinical Oncology, September 2013

http://jco.ascopubs.org/content/31/30/3831

Vaccinating patients with stage 2 melanoma did not prove beneficial in a recent study by the European Organization for Research and Treatment of Cancer (EORTC). In the study, 657 patients with stage 2 melanomas thicker than 1.5 mm were subcutaneously vaccinated with GM2-KLH-QS21 once a week during the first month, then once every three months during the first two years, and then once every six months during the third year. An observation group (657 stage 2 melanoma patients) did not receive vaccinations. The rationale was to target the GM2 ganglioside antigen, which stimulates the production of antibodies to the GM2 ganglioside, according to the release.

"These results clearly indicate that we do not fully comprehend the impact, on the whole, of multiple vaccinations," said Alexander M.M. Eggermont, M.D., Ph.D., coordinator of the study. "The effects of such vaccinations might well be detrimental as was clear at the time of the interim analysis that stopped this trial." DT

Federal agency funds promising burn treatment

The Biomedical Advanced Research and Development Authority (BARDA) has awarded a contract to Novan Therapeutics to develop a topical nitric-oxide-based burn therapy.

BARDA, an agency of the Department of Health and Human Services, awarded Novan a two-year, $7.8 million contract to fund the development of nitric oxide advanced healing (NOAH) technology, a topical treatment for burns. The grant is intended to cover formulation work, nonclinical toxicology, and proof-of-concept studies in models of deep partial thickness and full thickness thermal injuries, with the goal of enabling future clinical investigation.

Peer-reviewed studies have shown that nitric oxide can speed the migration of epidermal cells, stimulate new blood vessel growth, modulate inflammation and remodel wound beds. The contracted research into nitric oxide-based therapy as a burn treatment will bolster Novan's existing research into NOAH technology as a treatment for combat wounds, multi-drug-resistant infections and chronic wounds.

"We hope to demonstrate that an advanced medical countermeasure can be manufactured, is safe and is effective at healing a wide variety of burn injuries," Nathan Stasko, Ph.D., president and founder of Novan, tells **Dermatology Times**. "That is our goal."

One of the potential uses of NOAH therapy is in case of a mass-casualty event resulting in more burn wounds than present the current burn-treatment infrastructure would be able to handle. **DT**

FDA OKs Esteya system for skin cancer treatment

The Food and Drug Administration has granted 510(k) clearance to Nucletron for Esteya, an electronic brachytherapy system for high-precision skin cancer treatment.

The Esteya system, manufactured by Nucletron, an arm of Stockholm-based Elekta, uses a small high-dose rate (HDR) X-ray source to apply radiation directly to the cancerous site, focusing therapeutic radiation on the disease target and minimizing radiation to surrounding tissues, according to a news release.

Electronic brachytherapy typically achieves a 95 percent cure rate treating skin lesions such as basal cell or squamous cell carcinoma, the company states.

"The interest in Esteya among radiation oncologists during the American Society for Radiation Oncology annual meeting ... in Atlanta was encouraging," John Lapré, executive vice president, brachytherapy, for Elekta, said in the news release. "They appreciated the efficient work flow, easy patient set-up, and the short treatment delivery time. They also cited the accessibility of Esteya — due to its compact design and reduced shielding requirements — allowing treatment to occur virtually anywhere patients are seen within the clinic."

The company says the first installations of Esteya in the United States are scheduled to occur in the next few months. **DT**

Body's circadian rhythms affect skin stem cell regulation

Cell Stem Cell, October 2013

www.sciencedirect.com/science/article/pii/S1934590913004049

New research suggests that the body's internal clock and its circadian rhythms adjust the modulation of skin stem cells based on the time of day — and that disruption to this cycle can cause tissue aging and lead to predisposition to skin cancer.

According to researchers from the Centre for Genomic Regulation (CRG) in Barcelona, during long exposure to pathogens or ultraviolet light, the skin's stem cells will protect themselves. When not exposed to light, the cells produce new keratinocytes — dead cells rich in keratin — that provide a protective layer against harmful agents, according to the study.

"Stem cells have some genes that control their biological clock and that determine peaks of activity and intervals of inactivity over 24-hour periods," study leader Salvador Aznar Benitah, Ph.D., said in a news release. "In this study, we describe how the cells manage to perceive what time of the day it is. This precision allows the stem cells to adapt their activity to the time of day and to its environmental conditions."

In a 2011 study, Dr. Benitah and colleagues described the link between circadian rhythms and the skin's stem cell regulation. That study found that the cells could distinguish between night and day. The new study, funded by the European Research Council and the European Union, monitored the activity of the stem cells — adult stem cells in particular — by the minute to ascertain exactly how they determine the time and use that information to self-regulate and regenerate.

Dr. Benitah's latest study also found that disruptions to the circadian rhythms had serious effects on the proper functioning of skin stem cells, which can lead to tissue aging and possible predisposition to skin cancer. **DT**

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The Only Mid-Potency Topical Steroid Aerosol Spray[1]

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

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

For external use only. Please see full Prescribing Information on reverse and also at KenalogSpray.com.

REFERENCE: 1. Fowler J, Fowler L. Physician and patient assessment of triamcinolone acetonide spray for steroid-responsive dermatoses. *J Clin Aesthet Dermatol*. 2010;3:27-31.

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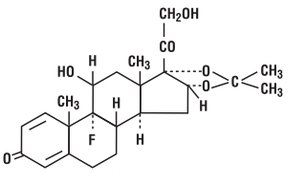
Triamcinolone Acetonide Topical Aerosol, USP (0.147 mg/g)

For dermatologic use only
Not for ophthalmic use

DESCRIPTION

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



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

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

CLINICAL PHARMACOLOGY

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

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

Pharmacokinetics

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

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

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

INDICATIONS AND USAGE

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

CONTRAINDICATIONS

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

PRECAUTIONS

General

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

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

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

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

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

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

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

Information for the Patient

Patients using Kenalog Spray should receive the following information and instructions:

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

Laboratory Tests

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

Carcinogenesis, Mutagenesis, Impairment of Fertility

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

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

Pregnancy: Teratogenic Effects

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

Nursing Mothers

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

Pediatric Use

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

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

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

ADVERSE REACTIONS

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

OVERDOSAGE

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

DOSAGE AND ADMINISTRATION

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

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

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

HOW SUPPLIED

Kenalog Spray (Triamcinolone Acetonide Topical Aerosol, USP)

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

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

Storage and Handling

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

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

RANBAXY
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Revised August 2011

Printed in the USA DERM-3567-1212

FDA OKs Juvéderm Voluma for adult midface volume loss

The Food and Drug Administration has approved the cosmetic filler Juvéderm Voluma XC (Allergan). The hyaluronic acid filler is the first and only filler to be approved for the temporary correction of age-related volume loss in adult patients ages 21 and older, the release states. The product is expected to be available this fall, Allergan says.

Juvéderm Voluma XC, uses Allergan's Vycross technology that results in a smooth gel. It also contains lidocaine to help numb the area during an injection procedure, the company says.

"We're looking at something that has long life, it has reversibility, and it is a product that really is geared in terms of its molecular makeup to robustly treat the cheek in an efficient way," says Chicago-based plastic surgeon Julius Few, M.D., who was one of the clinical site investigators in the study. He is clinical associate, University of Chicago Pritzker School of Medicine, plastic surgery and founder of The Few Institute for Aesthetic Plastic Surgery.

"It is designed to lift," says dermatologist Derek H. Jones, M.D., associate professor of dermatology, University of California, Los Angeles, and medical director of Skin Care and Laser Physicians of Beverly Hills. He also was a clinical investigator in the trial. "What makes it different is that it uses a lower molecular weight hyaluronic acid that allows for increased cross-linking that gives the product an ideal lift capacity for the midface."

The approval follows the results of a single blinded controlled clinical trial conducted at 15 U.S. and two Canadian sites, which demonstrated efficacy and safety. The study was recently published in the *Journal of Dermatologic Surgery*.

Results demonstrated that almost 50 percent of patients were maintaining optimal correction at two years, Dr. Jones says; however, many will maintain the correction longer, he adds. Similarly, Dr. Few says he has patients demonstrating clinically significant results after almost three years.

The study enrolled 282 patients ages 35 to 65 with midface volume deficit. Forty-seven patients were randomized to a control group and 235 patients were treated in one or more of the following midface regions: the zygomaticomalar region, the anteromedial cheek and the submalar region.

Patients received touch-up treatments after 30 days as necessary and were followed up at one month, three months and then quarterly for up to two years, according to the study. Response was determined by two blinded investigators' assessments at six months based on whether the patient had improved by one point or more on a validated six-month Mid-Face Volume Deficit Scale (MFVDS).

Dr. Few says dermatologists and plastic surgeons are going to be most concerned about patient satisfaction. He notes that 90 percent of patients reported feeling that they appeared, on average, five years younger at six months based on analysis of patient diaries. As far out as two years, patient satisfaction was at 76 percent.

The most common adverse effects seen during the clinical trial were injection site tenderness, bruising, redness, discoloration, swelling, lumps/bumps, firmness, itching, and pain that lasted approximately two to four weeks.

The study is available at: *http://onlinelibrary.wiley.com/doi/10.1111/dsu.12343/pdf.* **DT**

FDA approves Cimzia, Stelera for psoriatic arthritis

Cimzia (certolizumab pegol, UCB) as well as Stelara (ustekinumab, Janssen Biotech) alone or in combination with methotrexate have both been approved by the Food and Drug Administration for the treatment of psoriatic arthritis in adult patients.

Certolizumab pegol was approved after results of an ongoing, phase 3, multicenter, double-blind, placebo-controlled study demonstrated patients taking the 200 mg dose every other week had greater reduction in radiographic progression compared to patients taking placebo at 24 weeks. Patients taking 400 mg every four weeks did not demonstrate a greater inhibition of radiologic progression at 24 weeks, however, compared to patients on placebo.

Approval for ustekinumab followed two phase 3, multicenter, randomized, double-blind, placebo-controlled trials. In one trial, 42 percent and 50 percent of patients receiving ustekinumab 45 mg and 90 mg, respectively, achieved at least 20 percent improvement in signs and symptoms of their condition at 24 weeks. Results of the study were published in *The Lancet*.

"Therapy that targets the cytokines interleukin-12 and interleukin-23, two naturally occurring proteins believed to play a role in the development of this debilitating immune-mediated inflammatory disease, could improve patient care," Alice B. Gottlieb, M.D., Ph.D., chief, department of dermatology, Tufts Medical Center, Boston, and study investigator, said in a news release. **DT**

26 SKIN AND GUT
Antibiotic overuse may predispose patients to inflammatory bowel disease

Research sheds light on pathophysiology of acne, rosacea

Ilya Petrou, M.D. | Senior Staff Correspondent

NEW YORK — Although the symptoms of acne and rosacea are well established, clear and definitive etiologies of these conditions have largely been unknown. Recent research, however, has shed new light onto the pathophysiology of these conditions, paving the way for more targeted therapies.

For rosacea, all of the agents currently approved by the Food and Drug Administration (topical metronidazole, azelaic acid 15 percent gel, doxycycline 40 mg modified-release capsule once daily [subantimicrobial dose]) and most studies with nonapproved agents (oral antibiotics, topical calcineurin inhibitors) have been completed in patients with papulopustular rosacea.


Dr. Del Rosso

QUICK READ

Continued research has offered some new insight into the pathophysiology of acne and rosacea, leading to the development of more effective therapies.

"More recent basic science research has shown that rosacea is an inflammatory skin disorder, with neurovascular dysregulation and augmented immune detection and response identified as the two major pathophysiologic components of rosacea," says James Q. Del Rosso, D.O., who spoke at the summer meeting of the American Academy of Dermatology. He is clinical professor (dermatology adjunct faculty), Touro University College of Osteopathic Medicine, and in private practice of dermatology at Las Vegas Skin and Cancer Clinics, Henderson, Nev.

THE CATHELICIDIN PATHWAY

The cathelicidin pathway, a cascade that is present normally in skin to recognize and neutralize invasion by microbial organisms, is upregulated and hyper-reactive in facial skin of rosacea patients, Dr. Del Rosso says. This upregulation produces excess cathelicidin (LL-37), which induces vasodilation of superficial facial vasculature, inflammation and vascular proliferation. The latter effect over time leads to persistent diffuse central facial redness both during and between flares as the dilated and enlarged vessels become fixed.

According to Dr. Del Rosso, it has been shown over the past few years that doxycycline inhibits matrix

RESEARCH see page 25

Quotable

"If an astute dermatologist notices a skin lesion that is highly suggestive of IBD ... the dermatologist may be first to make the diagnosis of IBD."

Anna K. Haemel, M.D.
San Francisco

On the skin-gut connection
See story, page 26

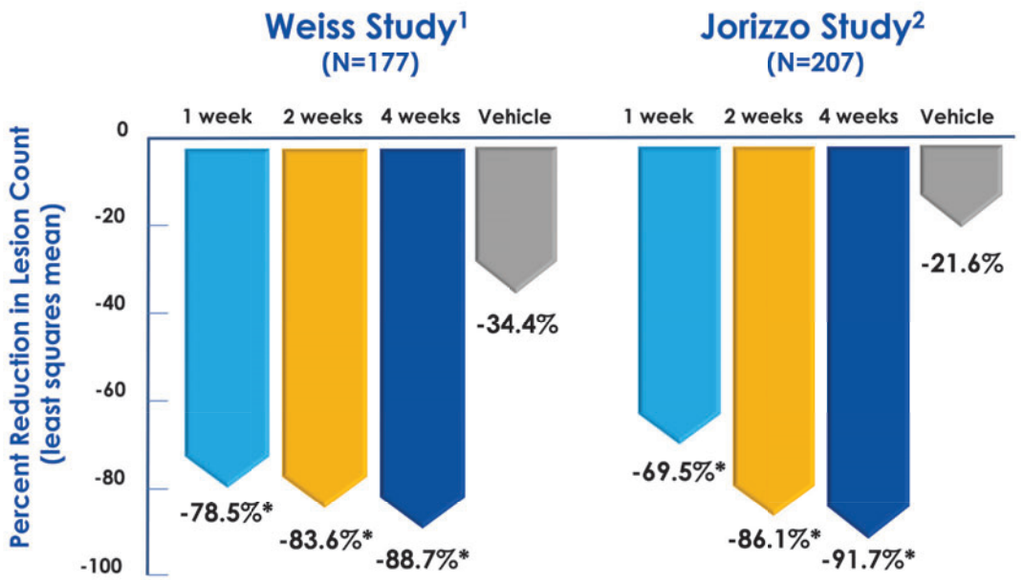
DTExtra

In the 52-week FIXTURE study, secukinumab showed improved efficacy to etanercept beginning as early as week two and confirmed by week 12 when the primary end points were assessed. More patients taking secukinumab experienced almost clear skin (PASI 90) and completely clear skin (PASI 100) compared to etanercept, according to the study. At its peak, the PASI 90 response was over 70 percent and PASI 100 was over 35 percent. At three weeks of treatment, about 50 percent of patients taking secukinumab had a 50 percent reduction in PASI.

READ MORE: DERMATOLOGYTIMES.COM/SECUKINUMAB

once-a-day Carac® fluorouracil cream 0.5%

Significant AK lesion reduction at 1, 2, and 4 weeks



*P<.001 vs vehicle.

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

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

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

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

Important Safety Information

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

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

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

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

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

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

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

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

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

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(fluorouracil cream)

BRIEF SUMMARY

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

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

INDICATIONS AND USAGE

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

CONTRAINDICATIONS

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

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

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

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

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

WARNINGS

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

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

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

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

PRECAUTIONS

General

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

Information for the Patient

Patients using Carac should receive the following information and instructions:

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

Laboratory Tests

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

Carcinogenesis, Mutagenesis and Impairment of Fertility

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

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

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

Pediatric Use

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

Geriatric Use

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

Pregnancy

Teratogenic Effects: Pregnancy Category X

See CONTRAINDICATIONS

Nursing Women

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

ADVERSE REACTIONS

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

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

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

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

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

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

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

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

Adverse Experiences Reported by Body System

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

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

DOSAGE AND ADMINISTRATION

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

OVERDOSE

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

HOW SUPPLIED

Cream - 30 gram tube NDC 0187-5200-30

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

Prescribing Information as of November 2012

Keep out of the reach of children. Rx Only

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CRC-006

RESEARCH:

New insight paves way for more effective acne and rosacea therapies from page 22

metalloproteinase enzymes (MMPs) that are involved early in the activation of the cathelicidin pathway. In addition, azelaic acid has been shown to inhibit the serine protease enzyme, which converts an inactive precursor protein (hCAP18) to active cathelicidin.

"It is interesting that both doxycycline and azelaic acid modulate the cathelicidin pathway at different steps which may explain the observation that the combination of the two agents appears to speed up and augment the therapeutic response as compared to monotherapy in patients with rosacea who have papulopustular lesions," Dr. Del Rosso says.

ADDRESSING FACIAL ERYTHEMA

Topical alpha-adrenergic agonists are becoming of particular interest for the medical management of persistent diffuse central facial erythema of rosacea, which is due to fixed proliferation and enlargement of superficial skin vasculature. These agents stimulate alpha-receptors in the smooth muscle layer of superficial skin vessels resulting in vasoconstriction, Dr. Del Rosso says, leading to reduced facial skin redness over a period of up to 12 hours after a single application.

Oxymetazoline (available in a nasal solution) has been shown to be effective for facial erythema in rosacea patients in a few case reports, he says; however, no studies have been published to date. It is currently under development for this use.

Most recently FDA-approved for treatment of persistent nontransient facial erythema of rosacea in patients age 18 and older, brimonidine tartrate 0.5 percent gel (brimonidine 0.33 percent, Mirvaso, Galderma) applied once daily has been shown to reduce diffuse facial erythema of rosacea with a usual onset within 30 minutes and with peak activity over approximately eight to 10 hours. According to Dr. Del Rosso, the safety profile appears to be favorable, rebound has not emerged as a major problem with this agent, and tachyphylaxis has not been observed.

"This therapy treats the vascular component of rosacea which is not addressed by the therapies which treat the inflammatory component with papulopustular lesions of the disease," Dr. Del Rosso says.

According to Joshua Zeichner, M.D., one of the most difficult challenges in the treatment and management of rosacea is to undo the changes occurring in the skin, making prevention of progression of signs and symptoms a central part of an ideal treatment approach.


Dr. Zeichner

"Up until this point, all we have to treat the background redness of rosacea are laser and light treatments, which are effective," he says. "However, once you treat the redness, it can recur because you are not changing the underlying skin pathophysiology. Now we have the opportunity to use both modalities, meaning laser and light therapies as well as some of these new topicals.

"The goal would be to undo some of the damage, and prevent it from recurring. However, more research needs to be done to see how these vasoconstriction medications change the progression of the disease."

PATHOPHYSIOLOGY OF ACNE

Similar to rosacea, new data is emerging regarding the pathophysiology of acne, showing that inflammation of the skin precedes the development of the microcomedone.

It used to be thought that the microcomedone was the initiating lesion in acne, but according to Dr. Zeichner, who is director of cosmetic and clinical research, department of dermatology, Mount Sinai Medical Center, New York, that might not be the case.

"Interestingly, there is data showing that once the acne improves, there is *still* inflammation in the skin. Current research is looking at why the inflammation is present and differences in patients' inflammatory responses," Dr. Zeichner says.

New isotretinoin formulations have recently become available, he says, such as Zenatane (Promius Pharma), a branded generic bioequivalent formulation of isotretinoin.

The drug is prescribed through a specialty pharmacy that ships the medication to patients overnight via UPS, and assists them to stay on track in the iPLEDGE program. According to Dr. Zeichner, the advantage of using Zenatane is the concierge service that the pharmacy plays and provides, facilitating accessibility and adherence for patients. Absorica (Ranbaxy Laboratories) is another new formulation of isotretinoin that contains Lidose (SMB Laboratories) technology, which facilitates the delivery of the drug.

Isotretinoin is optimally absorbed in the presence of a fatty meal, Dr. Zeichner says, and since patients can be forgetful in when and how to take their medication, formulations that already include the fat component within the matrix of the pill itself can help optimize the absorption of the drug, even on an empty stomach.

"These new medications for acne and rosacea are a step in the right direction that ultimately help us better treat and manage these conditions," Dr. Zeichner says. "I believe that the future will be brighter as we continue to gain a better understanding of the pathophysiology of these conditions, allowing us to develop more targeted treatments and therapeutic options for our patients." **DT**

Disclosures: Dr. Del Rosso has served as a consultant, advisory board participant, clinical investigator, and speaker and is currently active in some or all of these roles for: Allergan, Bayer (Dermatology), Dermira, Ferndale, Galderma, Onset Dermatologics, Promius, Ranbaxy, Taro Pharmaceuticals, Unilever, Valeant, and Warner-Chilcott. He has provided limited professional services within the past three years as a consultant for Anacor, Dermira, Eisai and Primus. He has served as a consultant and speaker for Obagi Medical Products and Pharmaderm. He has also been a consultant and advisory board moderator for Quinnova and a consultant and advisory webcast moderator for Tria-Beauty. Dr. Zeichner has served as a consultant for Promius Pharma and Ranbaxy Laboratories.

Skin-gut connection yields clues in both directions

John Jesitus | Senior Staff Correspondent

New York — Dermatologists should use evolving knowledge about the connections between inflammation in the skin and the gut to their advantage wherever possible, an expert says.

In this regard, "It's important to recognize that inflammatory bowel disease (IBD) is a systemic inflammatory process," says Anna K. Haemel, M.D., an assistant professor of dermatology at the University of California, San Francisco, School of Medicine.

Although researchers previously believed that the gut and the skin possessed separate immune systems, "We now understand that the immune system specific to each organ has significant crosstalk with the immune system in other areas of the body. That's probably one way that the gut can trigger inflammation in the skin."

Some physicians' prescribing practices can influence this delicate balance, Dr. Haemel says. Specifically, "It's becoming increasingly clear that bacteria in both the gut and perhaps the skin may drive the body's inflammatory response. Therefore, when we overuse antibiotics, we may predispose patients to later developing IBD."

Oral antibiotics remain the treatment of choice for serious infections such as Lyme disease and Rocky Mountain spotted fever, she says. However, "Dermatologists often use tetracycline class antibiotics to treat what could be deemed more minor indications, including mild inflammatory acne. We must consider whether we should be reducing our elective use of these antibiotics because there's been some association between doxycycline and IBD," particularly Crohn's disease, in recent literature (Margolis DJ, Fanelli M, Hoffstad O, Lewis JD. *Am J Gastroenterol.* 2010;105(12):2610-2616).

"With both antibiotics and isotretinoin," Dr. Haemel says, "it's not that we don't use them in at-risk patients. But we carefully discuss risks and benefits so that patients are aware of them. Overall, the data on isotretinoin are reassuring."

Additionally, Dr. Haemel says, dermatologists should use caution to protect bone health when prescribing steroids for patients with IBD and celiac disease (CD).

"Commonly, we may start a patient on steroids, then a few months later begin to consider the patient's bone health. But it's something we should think about early on," she says.

QUICK READ

Antibiotic overuse may predispose patients to developing inflammatory bowel disease, an expert says.

> "When we overuse antibiotics, we may predispose patients to later developing IBD."
>
> **Anna K. Haemel, M.D.**
> University of California, San Francisco

Patients with IBD and CD may have lower baseline bone mineral density (BMD) irrespective of prior steroid exposure, she explains. Additionally, BMD has been shown to decline most rapidly in the first three to six months of steroid use.

Accordingly, Dr. Haemel says that in her clinic, "If we anticipate that a patient is going to be on a significant dose of systemic oral or IV glucocorticoids for longer than one to three months, depending on how high-risk the patient is, we follow American College of Rheumatology (ACR) guidelines," which call for initiating bisphosphonate therapy in many cases (Grossman JM, Gordon R, Ranganath VK, et al. *Arthritis Care Res* (Hoboken). 2010;62(11):1515-1526).

"Even if the patient is only going to be on systemic steroids briefly," she adds, "we treat them with calcium and vitamin D," starting on their first day of glucocorticoid use. In such cases, the ACR recommends a daily total calcium intake of 1,200 mg to 1,500 mg, plus 800 international units of vitamin D daily.

Meanwhile, she says, the concept of non-celiac gluten sensitivity is gaining mainstream acceptance. "These are patients who say that they have a reaction to gluten, but they have no clear allergic or autoimmune mechanism" behind it, Dr. Haemel says.

"In dermatology, we think about gluten causing one specific skin disease — dermatitis herpetiformis. Those patients have IgA antibodies to tissue transglutaminase (TTG-IgA)." However, Dr. Haemel says that for years, "I've had patients who say that gluten worsens their eczema. Emerging evidence suggests that may be true — some patients are actually sensitive to gluten but do not have CD."

In diagnosing IBD, she says, the fecal calprotectin test measures neutrophil activity in the stools. As such, "It can be a helpful screening test for patients who have IBD." Patients whom physicians should work up for IBD include those with skin conditions that are highly associated with IBD (such as Sweet's syndrome, pyoderma gangrenosum, severe aphthae, granulomatous cheilitis and cutaneous Crohn's), as well as those with dermatoses sometimes associated with IBD and gastrointestinal symptoms, she says.

"In fact, if an astute dermatologist notices a skin lesion that is highly suggestive of IBD and works the patient up, the dermatologist may be first to make the diagnosis of IBD. Using the skin as a clue to what's going on internally is becoming increasingly important." **DT**

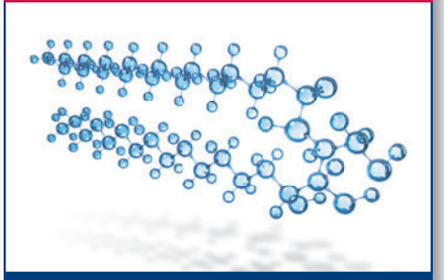
Disclosures: Dr. Haemel reports no relevant financial interests.

THE SCIENCE OF RELIEF

EXPLORING SKIN-SOOTHING AGENTS IN ATOPIC DERMATITIS

How do we deal with the complexities of atopic dermatitis (AD)? Its etiology can include a combination of genetics, environmental triggers, and immunologic and inflammatory pathways. Diagnosis is dependent upon a constellation of both subjective and objective clinical findings. Therapeutic emollients, either as first-line care or in combination with other therapies, have been proven effective in the management and treatment of AD.[1,2] But to truly relieve symptoms and improve the skin barrier for the long term, they should incorporate skin-soothing agents that address the complexities of AD—from the severity of active lesions to the more subtle maintenance of subacute, less symptomatic skin.

CERAMIDES

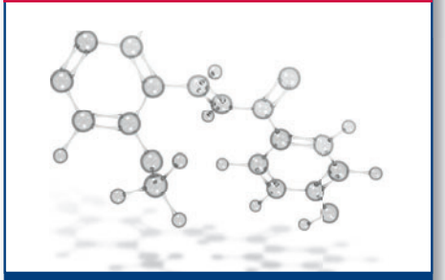


Clinical evidence solidifies the need for ceramides in the treatment of AD: atopic skin, even if non-lesional, usually shows a clear decrease in these intercellular lipids and a consequent increase in transepidermal water loss and impaired barrier. In patients with active lesions in particular, ceramide 3 is significantly lower than in non-symptomatic skin. Impaired skin barrier function leads to increased antigen absorption, which triggers the cutaneous hyperactivity characteristic of AD.[1,3]

COLLOIDAL OATMEAL

With moisturizing, protective, and skin-soothing properties, the active compounds in colloidal oatmeal form an occlusive film, protecting the stratum corneum from outside irritants and allowing for water retention. Proven efficacious and safe in numerous clinical trials, colloidal oatmeal is paramount in relieving one of the most intense symptoms of AD—pruritus. Approved by the FDA, colloidal oatmeal relieves minor skin irritation and itching due to eczema. Clinical trials testing oat-based occlusive creams have improved pruritus as early as 1 week in children and adults.[4,5]

LICOCHALCONE A



Licochalcone A (Lic A), derived from the licorice root *Glycyrrhiza inflata,* is a multipotent ingredient making a powerful impact across the dermatological landscape. A reversely constructed chalcone, or *retrochalcone*, Lic A is a proven inhibitor of proinflammatory reactions, and an antioxidant in both dermal and epidermal cells in vitro. It has served as a skin-soothing agent in emollients, visibly reducing the appearance of redness in razor burn, UV-induced erythema, and in patients with rosacea. Formulations with Lic A, ceramide 3, and oatmeal have eased visible redness and the itch-scratch cycle in adults and children with AD, and improved overall quality of life.[6]

ADVANCING SKIN SCIENCE THROUGH INNOVATION

At Beiersdorf, we are constantly exploring promising ingredients to help improve the quality of life in patients with chronic skin conditions. Our commitment to research has produced a continuous line of innovations that have fueled our passion for skin science for more than 125 years.

1. Leung DY, Boguniewicz M, Howell MD, Nomura I, Hamid QA. *J Clin Invest.* 2004;113(5):651-657. **2.** Buys LM. *Am Fam Physician.* 2007;75(4):523-528. **3.** Coderch L, López O, de la Maza A, Parra JL. *Am J Clin Dermatol.* 2003;4(2):107-129. **4.** Fowler JF, Nebus J, Wallo W, Eichenfield LF. *J Drugs Dermatol.* 2012;11(7):804-807. **5.** Food and Drug Administration, US Department of Health and Human Services. *Fed Regist.* 2003;68(107):33362-33381. **6.** Kolbe L, Immeyer J, Batzer J, et al. *Arch Dermatol Res.* 2006;298(1):23-30.

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PSORIASIS:

Researcher investigates role of nervous system from page 1

2013 by Dr. Ward and colleagues, not only follows up on her previous work, but could also open the door to new therapies for chronic psoriasis sufferers.

> "There are certain cells that change in a predictable temporal manner following denervation. What we're going to do is figure out how these molecules are actually driving the disease."
>
> **Nicole Ward, Ph.D.**
> Cleveland

Dr. Ward, associate professor of dermatology at Case Western Reserve University School of Medicine, Cleveland, has received three NIH grants to study the mechanisms of psoriasis. The most recent is to investigate the nervous system's role in the disease.

Dr. Ward says her work in psoriasis started almost by accident.

"When I started my own research lab, I was interested in studying how blood vessels and nerves in the skin interacted, and why they seemed to pattern each other. In developing experimental methods to study how those two systems interacted, I serendipitously created my first mouse model of psoriasis, which was the KC-Tie2 mouse. That's the mouse model that I originally published and still study to this day," Dr. Ward says. "That started my interest in studying inflammation, and how it's sustained and initiated specifically with respect to psoriasis."

IDENTIFYING PROTEIN CULPRITS

In 2011, Dr. Ward and colleagues used the KC-Tie2 mouse model and developed a surgical method to mimic what doctors had been talking about anecdotally (Ostrowski SM, Belkadi A, Loyd CM, et al. *J Invest Dermatol*. 2011;131(7):1530-1538).

"We surgically went in and eliminated the nerves from the skin and, lo and behold, the disease in the mouse model went away," Dr. Ward says. "We were able to figure out what's going on in the cell bodies of those nerves in the skin, which are actually found along the spine in a structure called the dorsal root ganglion (DRG)."

The researchers dissected the cell bodies of the nerves to study gene expression changes and identified two molecules that were increased: calcitonin gene related peptide (CGRP) and substance P.

"We were able to put (the proteins) back into the mouse skin under denervated conditions (when the nerves were surgically removed), and showed the disease came back. And we were able to inhibit those proteins in the mouse when the nerves were present and showed that the disease got better," she says.

These proteins, according to Dr. Ward, appear to drive and maintain skin inflammation. The most recent NIH grant allows Dr. Ward and colleagues to determine these molecules' direct and indirect effects on cells.

"We know there are certain cells that change in a predictable temporal manner following denervation. What we're going to do is try and figure out how these molecules — how these proteins — are actually driving the disease," Dr. Ward says.

The research team's goal is to better understand, at the basic science level, how CGRP and substance P are critical for psoriasis pathogenesis. The long-term goal is to potentially develop drugs or therapeutic targets that can directly inhibit these proteins or modify the actions these proteins have with individual cells, according to Dr. Ward.

The new two-year study Dr. Ward and colleagues started only months ago is considered translational research. Part of the work involves growing cells from mice and looking at how these proteins directly cause changes in the cells. The researchers will then retrieve skin cells and immune cells from psoriasis patients and controls and conduct similar experiments using cells isolated from those subjects.

> "We surgically went in and eliminated the nerves from the skin and, lo and behold, the disease in the mouse model went away."
>
> **Nicole Ward, Ph.D.**
> Cleveland

Dr. Ward's hope is that the findings obtained from her basic science work will be useful for practical applications that enhance human health and well-being. **DT**

Disclosures: Dr. Ward is a consultant to Novartis, Amgen, Eli Lilly and Galapagos.

A CLASS 1, SUPER-POTENT SPRAY

For plaque psoriasis

Topicort®
(desoximetasone)
Topical Spray 0.25%

0.25%
SPRAY

Important Safety Information

- Topicort® Topical Spray is a topical corticosteroid indicated for the treatment of plaque psoriasis in patients 18 years of age or older.
- Topicort® Topical Spray is a topical corticosteroid that has been shown to suppress the hypothalamic-pituitary-adrenal (HPA) axis.
- Systemic absorption of topical corticosteroids can produce reversible HPA axis suppression with the potential for glucocorticosteroid insufficiency. This may occur during treatment or upon withdrawal of the topical corticosteroid.
- Because of the potential for systemic absorption, use of topical corticosteroids may require that patients be periodically evaluated for HPA axis suppression.
- Local adverse reactions may be more likely to occur with occlusive use, prolonged use or use of higher potency corticosteroids. Reactions may include atrophy, striae, telangiectasias, burning, itching, irritation, dryness, folliculitis, acneiform eruptions, hypopigmentation, perioral dermatitis, allergic contact dermatitis, secondary infection, and miliaria. Some local reactions may be irreversible.
- Safety and effectiveness of Topicort® Topical Spray in patients younger than 18 years of age have not been studied; therefore use in pediatric patients is not recommended.

TaroPharma®

See brief summary of Prescribing Information on reverse side.

AD100-0033 July 2013

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

BRIEF SUMMARY

1 INDICATIONS AND USAGE

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

4 CONTRAINDICATIONS

None

5 WARNINGS AND PRECAUTIONS

5.1 Effect on Endocrine System

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

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

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

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

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

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

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

5.2 Local Adverse Reactions with Topical Corticosteroids

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

5.3 Allergic Contact Dermatitis with Topical Corticosteroids

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

5.4 Concomitant Skin Infections

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

5.5 Flammable Contents

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

ADVERSE REACTIONS

6.1 Clinical Trials Experience

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

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

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

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

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

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

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

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

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

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

8.3 Nursing Mothers

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

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

8.4 Pediatric Use

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

8.5 Geriatric Use

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

10 OVERDOSAGE

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

17 PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (Patient Information and Instructions for Use)

Inform patients of the following:

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

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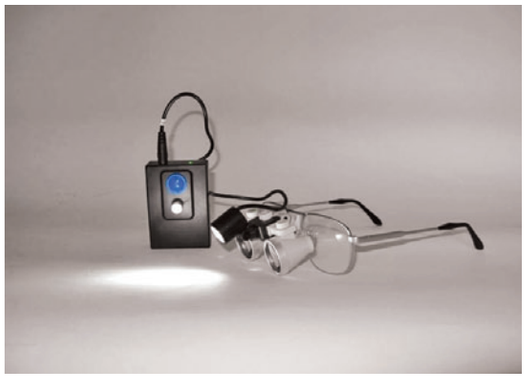


VISION USA

Loupes are waterproof, feature clip-on light

The new Task Vision loupes are waterproof, dust-proof and include an LED headlight that clips to the top. The platinum frame includes a side shield and is available for prescription lenses, according to the company. The waterproof loupe is adjustable and is available in 2.5x or 3.5x. The clip-on LED light has a variable intensity control (0-100 percent) 50,000 LUX.

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

SKIN FOR LIFE

Sun-protective shirt provides coverage during outdoor activities

The Skin For Life shirt is a long-sleeve breathable garment that was created by Mott 50 and dermatologist Amy Forman Taub, M.D. The shirt includes thumb holes so wearers can also keep their hands protected from harmful UV rays, the company states. The shirt is UPF50.

The Skin For Life shirt is effective for up to 60 washes, and comes in sizes extra small to extra large. It is available at Dr. Taub's Skinfo Specialty Skincare Boutique.

FOR MORE INFORMATION:
www.skinfo.com

HEALFAST SKINCARE

Cream formulated to prevent scarring

Scarblock is formulated to help prevent scarring after patients undergo cosmetic procedures or suffer from injuries. The cream contains proprietary Ovasome Technology and helichrysum italicum (everlasting) flower oil.

Ovasome in the HealFast SkinCare product line incorporates whole egg into topical creams, serums and lotions to allow its nutrients to remain active.

Helichrysum helps to encourage scar fading and to reduce scar tissue while also stimulating the growth of new skin tissue, according to the company.

The product also helps to promote collagen production and could help to improve the appearance of older scars when the cream is used regularly. It is appropriate for all skin types, contains no synthetic fragrances and is not tested on animals. The cream is also paraben-free.

FOR MORE INFORMATION:
www.healfastskincare.com

EPOCRATES

Directory connects physicians to each other

The Provider Directory allows Epocrates members to identify other clinicians for consultations and patient referrals. More than 700,000 clinician profiles on the application can be searched by name, location or specialty, according to the company.

Providers who already use the Epocrates Rx or Epocrates Essentials apps can find full profile listings, which include clinicians' practice information, for thousands of dermatologists in the U.S. After a clinician has found a provider, the Directory allows users to easily share that information with a colleague or patient via email.

To ensure accuracy, clinicians are able to edit and confirm their own profiles at any time. Directory users can build a list of "favorites" that they reference frequently in order to pull up those profiles even more quickly.

FOR MORE INFORMATION:
www.epocrates.com/company

Dermatology Times

Midface descent strikes in 60s, 70s

John Jesitus | Senior Staff Correspondent

ASPEN, COLO. — The key to addressing midfacial descent and overall fat loss in patients in their 60s and 70s is staging treatments appropriately and matching patient expectations, according to experts who offered solutions at Cosmetic Boot Camp, held here.

"In the sixth and seventh decades," says Wendy E. Roberts, M.D., "men and women have different issues. But what we're really addressing is midfacial descent. In men, in particular, it leads to a heavier cutis" that often creates very prominent nasolabial folds. Other common concerns in men of this age group include prominent frontalis wrinkles, says Dr. Roberts, a dermatologist in private practice in Rancho Mirage, Calif.

"The most important take-home point in the sixth and seventh decades is that you can't do it all in one session," Dr. Roberts says.

QUICK READ

Midface descent and overall fat loss can be corrected in patients in their 60s and 70s with appropriate staging treatments and understanding patient expectations.

Patients in this age group require significant volume, she adds, so she sets a global price for her "liquid facelift."

ADDRESSING MIDFACIAL DESCENT

Starting at the midface, she performs tear trough rejuvenation with Juvéderm XC (hyaluronic acid/HA, Allergan) or another HA.

"I do a retrograde injection at the tear trough. And I like to visualize the cannula when I'm injecting this area — I like to see the depth at which I'm injecting," Dr. Roberts says. She performs these injections in two stages: superficially with HA and, in some severe cases, periosteally with microdrops of diluted Sculptra (poly-L-lactic acid/PLLA, Valeant Aesthetics).

With Sculptra, Dr. Roberts injects a deep subcutaneous depot at the temporal fossa.

"I give a robust amount both in the temporal fossa and in the deep dermal subcutaneous malar prominence, which will lift that area. I also like to work in the hairline area, in the deep plane, directing the Sculptra upward to again achieve some midface lifting. Injecting this area is great for women because their hair covers the injection sites," she says. Typically, Dr. Roberts also uses another injection point in the center of the zygomatic/cheek area.

MIDFACE see page 38

Quotable

"Patients want tattoos removed and don't understand the difficulties involved. They believe the tattoo will go away as if by magic."

Terrence A. Cronin, M.D.
Melbourne, Fla.

On body modifications
See story, page 44

DTExtra

An injectable therapy under study and not yet approved by the Food and Drug Administration has potential as a noninvasive treatment option for submental fat. As a proprietary formulation of deoxycholic acid, a bile salt that naturally occurs in the body, ATX-101 (Kythera Biopharmaceuticals) has been studied in clinical trials, with results most recently presented at this year's meeting of the American Society of Dermatologic Surgery in Chicago. Two identical phase 3 pivotal trials met all predefined primary and secondary endpoints and demonstrated high statistical significance across these measures ($p<0.001$), according to the company.

READ MORE AT: DERMATOLOGYTIMES.COM/DOUBLECHIN

Finacea® (azelaic acid) Gel, 15% is a topical prescription medication used to treat inflammatory papules and pustules of mild to moderate rosacea.

Rosacea is with her wherever she goes. So is Finacea®.

Finacea® (azelaic acid) Gel, 15%

It's true. Rosacea is complex and it's with them for life. Finacea® treats the papules and pustules with associated erythema of mild to moderate rosacea. Although some reduction of erythema which was present in patients with papules and pustules of rosacea occurred in clinical studies, efficacy for treatment of erythema in rosacea in the absence of papules and pustules has not been evaluated.

You have made Finacea® the #1 Dermatologist-prescribed topical brand.[1]

INDICATION & USAGE

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

IMPORTANT SAFETY INFORMATION

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

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

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

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

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

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

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.

1. According to IMS NPA™ (National Prescription Audit) July 2010-September 2013

Finacea®
(azelaic acid) Gel, 15%

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

BRIEF SUMMARY
CONSULT PACKAGE INSERT FOR FULL PRESCRIBING INFORMATION

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

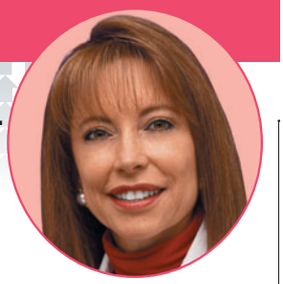
Manufactured for:
Bayer HealthCare Pharmaceuticals
Bayer HealthCare Pharmaceuticals Inc.
Wayne, NJ 07470
Manufactured in Italy
6706805BS

Q & A

TEMPLE REJUVENATION

Experts discuss best practices and techniques at the 2013 Vegas Cosmetic Surgery and Aesthetic Dermatology meeting.

Q: What product do you choose for temple revolumization, what device do you use to inject, and in what plane do you inject?



Susan Weinkle, M.D.

A: Amy Taub, M.D., dermatologist, Chicago: For the temple, I inject deeply to bone and use a bolus technique. The two fillers I use on the temple are Perlane (hyaluronic acid/HA, Medicis/Valeant) and Sculptra (poly-L-lactic acid, Valeant), depending on the patient. I slowly advance the needle until I hit bone and then pull back on the needle to make sure I am not in a vessel. I inject slowly and let the material gradually fill in the hollow. Assess, mold, and, if necessary, reinject.

A: Michael Persky, M.D., plastic surgeon, Encino, Calif: If the patient has time I prefer Sculptra in the temple area. I inject deep, supraperiosteally, with a 25-gauge 1-1/2 inch needle. If the patient's daughter or son is getting married in a month or two and they want an immediate, quick filling of their temple, then I like to use either Radiesse (calcium hydroxylapatite, Merz), or a mixed Juvéderm (cross-linked HA, Allergan) or Perlane with saline and lidocaine. I inject those fillers with a cannula more superficially — on top of the temporalis fascia. When I use a cannula I dilute all of the products. Val Lambrose, M.D., a plastic surgeon in Newport Beach, Calif., has done great work in this area using one part Juvéderm, one part saline and one part 1 percent lidocaine without epinephrine. He has gotten incredible results. The products seem to last long and it also makes it a lot easier to inject. Radiesse has much better flow when it is diluted with lidocaine.

A: Rebecca Fitzgerald, M.D., dermatologist, Los Angeles: I use a couple of things in the temple. I do the Val Lambros dilution solution technique, too, where you can do a two to one dilution with a hyaluronic acid. I use a cannula and I put it on the superficial temporalis fascia. That works very well for me right around the temporal crest. And I use a lot of Sculptra deeply underneath the temporalis fascia. I use it with a needle and I reflux before I put the Sculptra in. And I just want to share experience — in the HIV clinic, we would sometimes inject 12 or 18 people a day, and we'd do it a couple of times a week.

We were using a long needle and we were right on periosteum. We did that for years and it was not uncommon to reflux blood. It wasn't every day that you'd reflux blood, but it wasn't uncommon. What I speculate is that we were pushing the vessel down and pinning it, and then you would pull back blood. But I think that you can hit a vessel down

TEMPLE see page 36

Dermatology Times presents a panel discussion (right) at the annual Vegas Cosmetic Surgery and Aesthetic Dermatology annual meeting. Here, panel members discuss best practices and techniques when injecting in the temple.

VIDEO dermatologytimes.com/temple

TEMPLE:

Experts discuss techniques and best practices for revolumizing in the temple from page 35

there. And we know that the external and internal carotid circulation is all intermixed. And we know that there have been cases of blindness reported with injectables all over the face and that area is no exception to the rule. So you just want to do anything you can not to inject intravascularly.

A: Welf Prager, M.D., dermatologist, Hamburg, Germany: I used to inject Radiesse on a deep plane close to the bone but I found out that the surface — the transitions from the cheekbones to the forehead — was not as smooth as I would wish and so I changed to a subdermal injection with blunt cannulas. The product I mainly use is Belotero Balance (HA, Merz) because it has the viscosity where you can smooth it out nicely and get the transitions to the eyebrow, to the forehead, and also to the cheekbones evened out.

A: Derek Jones, M.D., dermatologist, Los Angeles: This is such an excellent question and I have really firm ideas on this. The temple is really easy if you do it properly. In my opinion, you want to be right down on bone. My needle is usually three quarters of an inch to an inch, minimum. I inject pretty much in bolus. I might put a few aliquots around but you're right down on bone. If you were anywhere more superficial than that, sitting somewhere in the middle ground, there are a lot of vessels tracking in and around there — I have some interesting reports coming out on that — I think you're asking for a problem. My problem with injecting more superficially and we've seen injectors at this course treating this way and some of our own panelists doing it. There are a lot of vessels there and I have had a lot of patients who come into my office who have been injected elsewhere superficially and there are contour irregularities. It's pretty thin skin up here on the temple on a lot of individuals, especially older individuals. So it's just like the tear trough, if you're injecting something superficially, once everything settles down the contour may not be just perfect. I do a lot of temporal injections. I go straight down the bone and I use a fairly high G prime line product like Radiesse. I think (Juvéderm) Voluma (Allergan) will be very promising there.

> "In my opinion, you want to be right down on bone. My needle is usually three quarters of an inch to an inch, minimum."
>
> **Derek Jones, M.D.**
> Los Angeles

A: Michael Kane, M.D., plastic surgeon, New York: I think temples are probably technically the easiest area of the face to inject as long as you don't make a contour irregularity. I would inject any product there — calcium or HA. If given my first choice of what looks best, I think it's Sculptra, but I don't inject it deeply. I inject it superficially. When I'm injecting Sculptra I try to scrape right along the undersurface of the dermis because that's where the fibroblasts are. And I like to try to thicken that dermis. I think you can hide some of the vessels there.

And I think the key to reducing embolic phenomena, which is what we're talking about, is really a slow rate of injection. I'm generally not an aspirator but then I do not inject with my needle in one place. I'm constantly, constantly moving the needle and I inject at a very, very slow rate. So in the one-in-a-million chance I cannulate an arteriole, I'm out of it in a second without an appreciable amount of product being in there.

A: Susan Weinkle, M.D., dermatologist, Bradenton, Fla.: I personally like to inject both deep and superficial. I think one concern we need to have when we're teaching our colleagues in terms of deep injections is the needles that come in the package with an HA often are a half-inch needle, and it is very difficult in some patients to get all the way down to that supraperiosteal plane with that short needle. I think you're at much greater risk if you are not on the supraperiosteal plane to have an inadvertent injection of the deep temporal artery.

I recently did a cadaver dissection in Shanghai and almost fell over when I realized where the deep temporal arteries are located. It is vitally important, as we've all discussed on this panel, that when doing a deep injection to get down to the bone, feel the bone, and know where you are.

I reflux as well and then do a bolus injection in the deep plane. I find that some patients still need a superficial injection if they have a lot of loss. However, with those thin-skinned elderly patients that I have, there have been a few times where I have not reconstituted the product and I was not happy with the irregular contour. So live and learn. I think that's the exciting thing about a panel like this where we can really share tips that have helped us.

I utilize a deep injecting and sometimes an icing-on-the-cake superficial injection. If injecting superficially, I would recommend reconstituting and thinning an HA or Radiesse in order to obtain a smooth, even contour. **DT**

MIDFACE:

Staging treatments and matching patient expectation are key

from page 32

Mary P. Lupo, M.D., says that in her experience, Sculptra injections in this area don't cause pain — until the next day, when patients feel soreness chewing or opening their mouths widely. She and Dr. Roberts agree that massaging the area right after treatment helps minimize this discomfort. "We must prepare patients for this, and talk them through it," says Dr. Lupo, who is a New Orleans-based dermatologist in private practice.

SELECTING THE RIGHT HA

For the canine fossa, which also features thicker skin in males, Dr. Roberts often chooses Perlane (HA, Medicis) or Radiesse (calcium hydroxylapatite, BioForm/Merz). "We need that lift and G prime."

Perlane is slightly easier to mold than Radiesse, she says, which can be important around the oral commissure, a high-motion area. In contrast, "Radiesse can get a little bulky in the commissure area," although it's well suited for the top of the nasolabial folds, where thicker skin necessitates a more robust filler.

The angular artery passes through the nasolabial fold area, Dr. Roberts says, "And with Radiesse, you cannot aspirate. So I use very slow injections. The key is not to place too much volume here too quickly."

Typically, she places three injection points that form a triangle slightly below the edge of the nostril. After these vertical injections, Dr. Roberts carefully cross-hatches the remaining length of the nasolabial fold, injecting small depots very superficially to provide lift. Massage follows the injections in this area.

Some patients also benefit from a layer of Belotero (HA, Merz) just above the cross-hatched injections of Radiesse, running essentially parallel to the nasolabial fold, Dr. Roberts says.

"Belotero works well for superficial etched vertical cheek rhytids," she says. As a further hedge against the dynamic motion here, "I take a multilevel approach; I start deep, then raise the fold through more superficial injections."

ACCENTUATING THE POSITIVE

Jonathan Sykes, M.D., says he bases his filler recommendations on the patient's age and amount of existing facial fat. A 67-year-old female patient he treated had a higher right eyebrow, which he says commonly comes with lower-lid ptosis on the same side, plus a thinner upper eyelid. But overall, he adds, this patient had an attractive facial bone structure he wanted to accentuate rather than obscure. Dr. Sykes is director, facial plastic and reconstructive surgery, University of California-Davis, and a Cosmetic Boot Camp co-director.

This patient's treatment involved PLLA injections along the mandibular line, Juvéderm around the mouth and in selected rhytids, plus diluted Restylane (HA, Medicis) in the periocular area to lift the ptotic lid, all performed under local anesthesia mixed with epinephrine for vasoconstriction.

Dr. Sykes says he typically dilutes a vial of PLLA with about 2 cc of lidocaine without epinephrine, and about 7 cc of sterile water. "I always start with an injection from the side, using a 1.5 inch, 25-gauge needle," injecting on bone along the mandibular line. When performing these injections, "You must know where the masseter is, because the facial artery lies at the front of the masseter."

> "It's important to get a feel for what your patients want. This patient made it clear that she would rather have a wrinkle or two than look unnatural."
>
> **Jonathan Sykes, M.D.**
> Davis, Calif.

He also injected this patient's preauricular sulcus. In this area, "We must be more careful because there is no deep plane — we are not injecting on bone." Therefore, he injects smaller amounts, more superficially, in this area. He also injected PLLA in a vertical line up toward the ear, then into the pyriform aperture to reach the medial fat pad of the cheek.

"This is the only injection I perform perpendicular to the skin, because I want to know exactly where I'm injecting," Dr. Sykes says. When injecting the upper cheek, he adds, "At no time do I inject the eyelid, which is only 400 to 500 µ thick." All told, he typically injects two vials of PLLA per session; this patient required five vials total.

For the tear trough, Dr. Sykes says he injected small amounts of Restylane diluted 50:50 with saline, also on the bone and slightly above it (using

MIDFACE see page 41

> "I do a retrograde injection at the tear trough. And I like to visualize the cannula when I'm injecting this area — I like to see the depth at which I'm injecting."
>
> 
>
> **Wendy Roberts, M.D.**
> *Rancho Mirage, Calif.*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MIDFACE:

Staging treatments and matching patient expectation are key from page 38

progressively smaller amounts for the more superficial injections).

"The closer you put the product to the dermis, the more effect you'll see, but you'll also see more complications," he says. To lift this patient's ptotic lower lid, he adds, "I injected a little closer to the lid than I normally would."

Next, he injected undiluted Juvéderm Ultra around the patient's mouth, starting just below the corners of mouth (subcutaneously) to correct a slight downturn here. Regarding injection volumes, he generally uses one to 1.5 syringes total around the mouth.

Additionally, Dr. Sykes injected a little more HA to slightly plump this patient's lower lip. In such areas, "It's important to get a feel for what your patients want. This patient made it clear that she would rather have a wrinkle or two than look unnatural." **DT**

Disclosures: Dr. Lupo is a trainer and clinical investigator for Allergan, and a trainer for Medicis/Valeant, but has no ownership interests in these companies. Dr. Roberts is a consultant, speaker and/or advisory board member for Valeant, Allergan, L'Oreal, Neostrata, Skin Medica, TopMD and Theraplex. Dr. Sykes has received research support from Kythera, and is an advisory board member for Allergan and a speaker for Merz and Valeant.

Fat pad overlooked in facial rejuvenation

John Jesitus | Senior Staff Correspondent

ASPEN, COLO. — Physicians offering rejuvenation treatments to patients in their 50s frequently overlook the lateral temporal-cheek fat pad, says Timothy M. Greco, M.D., an expert in the aging face.

Dr. Greco says that common problems for patients in their 50s include midface asymmetry, brow ptosis, and temporal, lateral cheek and lateral mandibular hollowing. In addressing these issues, his approach centers largely around the lateral temporal-cheek fat pad.

"It starts in the temple, then proceeds in front of the ear over the parotid gland, and extends to the neck," he says. Dr. Greco believes it's one of the most neglected areas when injecting the face. He is a facial cosmetic plastic surgeon based in Bala Cynwyd, Pa., who is double board-certified by the American Board of Facial Plastic and Reconstructive Surgery and the American Board of Otolaryngology-Head and Neck Surgery.

When addressing this pad with Juvéderm Ultra Plus (hyaluronic acid/HA, Allergan) injected through a 27-gauge cannula, he starts by making a minute injection site in the midface with a 25-gauge needle — which he leaves in place so he can find the opening when later injecting the nasolabial folds. He typically uses approximately 1 cc per lateral temporal-cheek fat pad.

To elevate the corner of the lip with Juvéderm Ultra Plus, Dr. Greco says he uses a deep lateral injection to lay linear threads in a crosshatching fashion in this area with a cannula.

"Lips are great to inject with a cannula. I just make a small injection site at the lateral commissure; my first pass is below the vermilion-cutaneous border. I make sure I inject the medial tubercle and the two lateral tubercles. These tubercles are derived from the three embryological units from which the upper lip develops. Then I'll actually flip the patient's lip up. From the same injection site at the lateral commissure, I can inject anterior to the frenulum. That creates eversion of the lip," he says. He typically injects 0.1 cc in this area.

If patients can feel the material with their tongue, Dr. Greco says, "I massage the region." He uses a similar technique for the lower lip, injecting perhaps 0.1 cc on each side of the frenulum through a single injection point.

Dr. Greco injects the lower lip in a similar fashion, but only two tubercles are injected (the lower lip develops from two embryological units). In this regard, "It is important to maintain a subtle central cleft when injecting the lower lip."

For the temporal hollows, he typically injects Radiesse (calcium hydroxylapatite, BioForm/Merz) using a needle. To help locate veins in this area, "Just take the skin and stretch it using your thumb and forefinger while illuminating the area with a bright light. You can see the temporal veins more easily with this technique. Then I can safely inject into the temporal fossa with minimal bruising," Dr. Greco says.

To add volume in the cheek and midface region, Dr. Greco might inject a point at the height of the cheekbone, which allows him to inject deeply, right onto bone. Also in this area, he will direct the cannula medially to augment the sub-orbicularis oculi fat pad, which sits just below the orbital rim.

"There's always an indentation right where the infraorbital nerve emerges. I put a small amount of Radiesse in this region to provide volume that also improves the anterior projection of the cheek. Then I'll inject inferiorly, going after the deep cheek fat pad that sits below the nasolabial fold. I find that placing product in this region gives effective volume restoration — which may result in less product being injected into the nasolabial folds." **DT**

Disclosures: Dr. Greco is a speaker and consultant with Merz and Valeant/Medicis and a speaker, consultant and researcher with Allergan.

Examining molecular influences on aging

Stephanie Skernivitz | Staff Correspondent

WAILEA, HAWAII — How do we age? That was the weighty question to kick off a presentation by Barbara A. Gilchrest, M.D., Boston University School of Medicine, who presented at MauiDerm 2013 earlier this year.

In the skin there are two distinct components of aging: intrinsic and extrinsic aging processes, Dr. Gilchrest notes. Intrinsic aging entails the clinical, histologic and physiologic changes realized in sun-protected skin of older adults. Extrinsic aging is what is commonly called photoaging, or the clinical, histologic and physiologic changes seen in the habitually sun-exposed skin of older adults.

"There is a striking contrast clinically between these two processes," she says.

CONSEQUENCES OF PHOTOAGING

Intrinsic skin aging has relatively minor impact on skin appearance, according to Dr. Gilchrest, but there are well-documented functional deficits that range from poor healing, poor thermal regulation and compromised immune function.

"Photoaged skin, in contrast, has major impact on appearance. There is further loss of immune function and other physiologic deficits. Very importantly, it is associated with photocarcinogenesis — a huge problem in our practices," Dr. Gilchrest says.

Another concept widely held in the gerontology community, she says, is that aging and photoaging are consequences of safeguarding the genome. From this perspective, cancer is the failure of this safeguard mechanism.

Major mechanisms of skin aging, according to documented literature in the late 20th and early 21st centuries, include changes in signaling, oxidative stress and cumulative DNA damage. Lastly, and of great importance to Dr. Gilchrest, is telomere shortening and dysfunction. These mechanisms are inter-related, and among them, telomere signaling offers the most comprehensive and unifying framework.

QUICK READ

A researcher examines the critical role telomeres play in skin aging.

Telomeres are the ends of chromosomes. At the very tips of all eukaryotic chromosomes are telomeres. In human cells, telomeres are 7,000 to 10,000 base pairs in length. Their job is to cap chromosome ends.

"If you remove telomeres experimentally from chromosomes, the chromosomes fuse and it's a catastrophic event for cells," Dr. Gilchrest says.

THE BODY'S BIOLOGICAL CLOCK

Researchers have shown that telomeres function to limit cell division and are essentially the biologic clock (Harley CB, Futcher AB, Greider CW. *Nature*. 1990;345:458-460).

"Because of the end replication problem, every time the cell divides it's not possible to replicate the final 50 to 100 base pairs at the end of the chromosome," she says. "The telomeres shorten each time the cell divides. And ultimately telomeres reach a critically short length after which the cell will never divide again no matter what mitotic signals are provided."

More recently, laboratories have been examining the important function of telomeres in triggering DNA damage responses. For example, Rockefeller University's de Lange Laboratory has shown disruption of the telomere loop causes DNA damage signaling.

"A thought that is critical to consider in skin aging is that telomeres are excellent targets for DNA damage. The TTAGGG sequence is completely conserved in all mammalian organisms. TT (adjacent thymidines) are the target for a great majority of UV-induced DNA damage. Guanine is half of the telomere sequence, and is the target for almost all oxidative damage.

"It's been shown experimentally by groups examining DNA damage for other reasons that if you use any agent to damage the DNA in a cell, you'll damage DNA throughout the genome, of course, but you get much more damage in the telomeres," she says. "Nature has given us a wonderful mechanism for sensing when damage is occurring."

TIES TO HUMAN AGING

Dr. Gilchrest also notes that telomeres have been strongly implicated in human aging. Telomeres are known to shorten with age both *in vitro* and *in vivo*. Telomeres shorten progressively over the life span and shortening is associated with age-associated diseases, such as cardiovascular disease and diabetes.

> "If you use any agent to damage the DNA in a cell, you'll damage DNA throughout the genome, but you get much more damage in the telomeres."
>
> **Barbara Gilchrest, M.D.**
> Boston

Telomere length also correlates with longevity. In recent studies, it has been shown that if you take a group of people at age 60 and measure their telomeres and wait and see how long these individuals live, those with longer telomeres at age 60 average a longer life span (Cawthon RM, Smith KR, O'Brien E, et al. *Lancet*. 2003;361(9355):393-395; Valdes AM, Andrew T, Gardner JP, et al. Lancet. 2005;366(9486):662-664).

Additionally, virtually all diseases of premature aging are all characterized by very short telomeres. Those include Werner syndrome, progeria and other progeroid syndromes.

One other molecule critical in the telomere story, according to Dr. Gilchrest, is telomerase, the enzyme complex responsible for lengthening

TELOMERES see page **46**

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AD100-0033 July 2013

Body modifications pose challenges for treating skin

John Jesitus | Senior Staff Correspondent

QUICK READ

Recognizing the messages sent by tattoos and body adornments can help dermatologists educate and treat patients with these skin decorations.

NEW YORK — Dermatologists are best positioned to treat and educate patients whose tattoos, piercings and other body adornments are causing problems, an expert says.

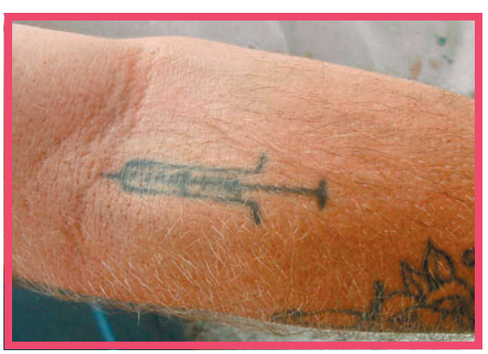
"Most tattoos are there for exhibitionistic reasons — to send a message for the viewer. Often they tell you something about a person. As dermatologists, we can get clues about their health and psyche," says Terrence A. Cronin Jr., M.D. He is a dermatologist in private practice in Melbourne, Fla., and assistant professor, department of dermatology and cutaneous surgery, University of Miami Miller School of Medicine.

> "Everyone who does tattoo removal would be wise to lower patients' expectations — it may take multiple treatments."
>
> **Terrence A. Cronin Jr., M.D.**
> Melbourne, Fla.

The body of the 5,300-year-old "Iceman" found in the Italian Alps in 1991 bore several small tattoos over joints where he was found to have arthritis. "Archaeologists believe they were there for shamanistic or medicinal reasons." Conversely, Dr. Cronin says, the Maori of New Zealand used facial tattoos to indicate their jobs within the community.

TATTOO'S BEGINNINGS

The word "tattoo" entered the English language in the mid-



A 42-year-old male former drug user shows his tattoo. Photos: Terrence A. Cronin Jr., M.D.

voice of the dermatologist

"... So we are left with a choice of aging or cancer until we learn how to manipulate the system better."

Barbara A. Gilchrest, M.D., on the role of telomeres in skin aging, page 42

1700s, when Capt. James Cook used it to describe Tahitian natives' practice of tapping ink into the skin with tiny bamboo needles. "Before that, 'tattoo' was always used to describe the beating of a drum," Dr. Cronin says.

Today's tattoo wearers probably don't know that the concentric circle motif of so-called tribal tattoos was originally patterned after the whorled appearance of skin afflicted by tinea imbricata, Dr. Cronin adds. Other popular trends include the following:

- Tattoos with fluorescent inks that glow under special lighting;
- Overtattooing — placing a new tattoo over an old one that has faded or no longer holds meaning to the wearer;
- Innovative cosmetics designed to camouflage tattoos at work or in formal environments.

Nowadays, "Tattoos show everything, from the names of family members to gang affiliations." Other tattoos may indicate solidarity with sociopolitical movements or causes, Dr. Cronin says. And when a dermatologist sees the image of a hypodermic needle tattooed on an IV drug abuser's forearm, "That opens up a line of thought — has the person been exposed to hepatitis or HIV? As dermatologists, we like to be able to read the skin. Sometimes when you see a tattoo, it's already spelled out for you."

Increasingly, Dr. Cronin says, dermatologists must treat infections caused by tattoos and skin decorations. Additional side effects can include granulomas and allergic reactions to pigments and metals. In the former area, he says, the red pigment cinnabar frequently causes granulomas, although it's mostly used in Asia.

REALISTIC EXPECTATIONS

In other cases, "Patients want tattoos removed and don't understand the difficulties involved. They believe the tattoo will go away as if by magic" after one treatment, Dr. Cronin says. "Everyone who does tattoo removal would be wise to lower patients' expectations — it may take multiple treatments. And those treatments are expensive," he says.

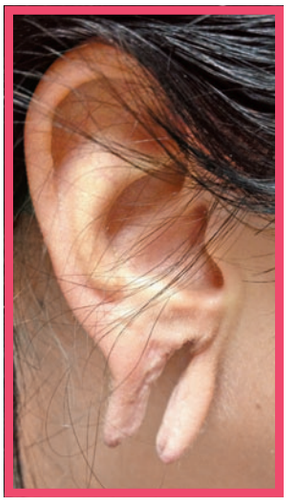
Showing sequential before and after photos clarifies the challenges of tattoo removal, Dr. Cronin says.

"You can say, 'Here's the tattoo after one treatment, five treatments, and 10 treatments.' When they hear 10 treatments, that's scary to them because usually they're paying out-of-pocket." Regarding lasers, he says alexandrite lasers are the best type to use for tattoo removal, although different colors respond to different wavelengths.

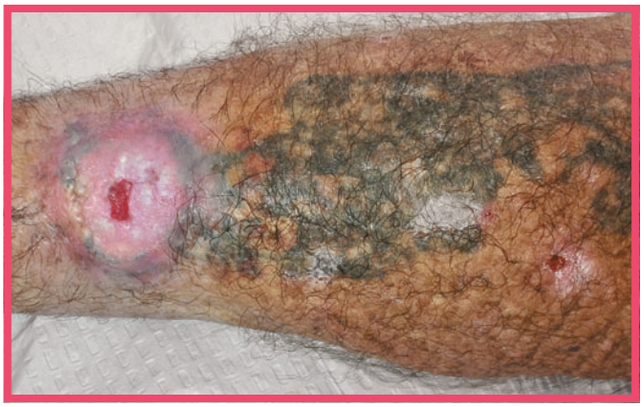
Also of concern is the practice of gauging, or stretching the earlobe or other appendage using progressively larger jewelry over time. Treating the aftereffects of this practice requires surgical repair, including tissue removal and multilayered closure, he says. Additionally, Dr. Cronin says, any skin piercing creates the possibility of traumatic removal, or having the jewelry accidentally ripped out the earlobe, nipple or other body location, a problem that also requires surgical repair.

"Tattoos and skin decorations teach us a lot about patients and society. And dermatologists are at the forefront of understanding the human condition," he says. "Every day we see more tattoos. There's a lot we can do to help tattooed patients with their skin — whether it's removing the tattoos with lasers or treating the infections, keloids and hypertrophic scars they may cause." **DT**

Disclosures: Dr. Cronin reports no relevant financial interests.



A 24-year-old female patient who suffered traumatic removal of her gauged jewelry presents with a torn earlobe.



A 50-year-old male landscaper presents with an aggressive squamous cell carcinoma growing out of a tattoo on his forearm.

TELOMERES:

Protective region at end of chromosones plays specific role in skin aging

from page 42

telomeres. This enzyme complex is expressed in germline cells, stem cells, and greater than 90 percent of malignant cells, where it maintains telomere length. Importantly, it also slows but does not prevent telomere shortening in normal somatic cells.

SLOWING AGING

What is the consequence of activating or upregulating this telomerase enzyme activity?

"If you activate telomerase, you immortalize cells. They will then divide indefinitely in a culture dish, and they do not age," Dr. Gilchrest says.

There is a downside, however. Stewart et al found that if you activate telomerase in an organism, you also promote carcinogenesis, "because you have removed the safeguard against infinite proliferation of abnormal cells. That was very unfortunate," Dr. Gilchrest says (Stewart SA, Hahn WC, O'Conner BF, et al. *Proc Natl Acad Sci U S A*. 2002;99(20):12606-12611).

In another study, it was shown that when examining skin explant models, activating telomerase results in tissue rejuvenation by a number of criteria (Funk WD, Wang CK, Shelton DN, et al. *Exp Cell Res*. 2000;258(2):270-278).

More recently, increased telomerase activity in combination with cancer resistance appears to delay aging in a mouse model (Tomas-Loba A, Flores I, Fernández-Marcos PJ, et al. *Cell*. 2008;135(4):609-622). According to Dr. Gilchrest, by activating telomerase to a moderate level in a mouse experiment, study authors found no increase in incidence of cancer, median and maximum life span was substantially increased, there was decrease in clinical and molecular aging markers, and telomere length in cells in animals was lengthened.

"At least in a mouse model, it gets around the yin/yang issue of aging and cancer," she says.

TELOMERASE ACTIVATION

The telomerase activation in mice also resulted in much less inflammation in skin, epidermis and subcutaneous fat layers were thicker, and there was increased resistance to ulcer formation. Further, senescent markers for DNA damage signaling were much decreased in skin.

Dr. Gilchrest cites another mouse model of aging in which researchers genetically deleted the telomerase-active enzyme in these animals, such that there was no telomerase activity (Rudolf et al. *Cell*. 1999).

"In the first generation of the mice, the animals seemed completely normal. But as they bred them, by the fourth generation, animals aged very prematurely. They were disease prone, infertile, unhealthy and died at a much younger age," Dr. Gilchrest says.

> "The mechanism by which stress interacts with aging process remains largely unknown."
>
> **Barbara Gilchrest, M.D.**
> Boston

In this model of mice with short telomeres and no ability to lengthen because of no telomerase activity, what was interesting was what happened if telomerase was reintroduced into these mice. In as little as four weeks, "there is a striking change in the animals. Telomeres are lengthened, fibroblasts are proliferative, fertility increases and litter sizes increased," she says.

Additionally, when the animals were assessed for rejuvenation psychologically, the animals with longer telomeres were much more youthful in responses to olfactory stimuli, and they lived longer. According to Dr. Gilchrest, the animals did not develop cancers in this four-week period. Also, there was less DNA damage signaling (indicative of cell senescence) in tissues.

"We now know that telomere shortening leads to apoptosis or senescence of cells in skin and other tissues, but what causes aging of remaining cells?" Dr. Gilchrest says.

She cites more work showing that as telomeres shorten, their gene expression patterns change (Lou Z, Wei J, Riethman H, et al. *AGING*. 2009;1(7):608-621). Telomere dysfunction (or shortening) can also compromise cellular metabolism by activating p53, according to study findings, which, in turn, compromises mitochondrial energy production (Sahin E, Colla S, Liesa M, et al. *Nature*. 2011;475:254).

IMPACT OF STRESS

Lastly, how does stress spur aging?

"The mechanism by which stress interacts with aging process remains largely unknown," Dr. Gilchrest says. Epel et al. looked at the effect of stress on aging from the perspective of the telomere (Epel ES, Blackburn EH, Lin J, et al. *Proc Natl Acad Sci U S A*. 2004;101(49):17312-17315). A total of 58 healthy women were recruited for the study, 19 of who had a healthy child, while 39 had a chronically ill child. Study authors measured peripheral blood lymphocytes for these women for their telomere function and length.

Researchers found a "statistically significant difference" in telomere length between two groups. "Stressed mothers have shorter telomeres and lower telomerase activity," Dr. Gilchrest says. "These women have compromised ability to maintain telomere length."

Future studies may examine how to find a balance between slowing aging and preventing cancer, she says.

"Telomere-based signaling acts first to reduce DNA damage, slow senescence and protect the genome. Telomerase is documented to be critical for genome protection, cancer prevention and regulating aging. So we are left with a choice of aging or cancer until we learn how to manipulate the system better," Dr. Gilchrest says. "Fortunately, means of achieving a better balance seem possible, at least in mice." **DT**

Disclosures: Dr. Gilchrest reports no relevant financial interests.

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The cream is exclusive to physicians and can be used alone or as part of a clinician-recommended adjunctive at-home skincare regimen to prepare for or following in-office skin resurfacing treatments such as peels and laser treatments.

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SOCIÉTÉ

System firms, hydrates skin

iComplete is two-step system to enhance the effects of injectable treatments using "neurotoxin-like" peptides with its proprietary Intra-Cell technology, according to the company.

Step one is the Intense Firming Complex/Anti-Wrinkle Serum, designed to reduce muscle contractions, helping to diminish the appearance of wrinkles and fine lines. It also hydrates and plumps the skin, and the serum contains a proprietary collagen-boosting peptide complex. Hyaluronic acid and antioxidants in the serum work to promote healthy skin.

The Skin Hydration Complex in step two helps to calm, soothe and hydrate post-procedure skin and helps to reduce irritation and redness. It should be applied to clean skin, after toner and the Intense Firming Complex. The hydration complex helps to boost skin recovery and it contains vitamin C and hyaluronic acid.

The system is available at physician offices only.

FOR MORE INFORMATION:
www.societeskincare.com

DERMELECT COSMECEUTICALS

Serum designed to revive skin for youthful glow

The Outcrease Retinol Trifecta Serum takes aim at sun-damaged skin, fine lines and wrinkles, giving the skin a healthier, more luminous glow, according to the company.

The anhydrous formulation was created in a silicone matrix to preserve the efficacy of the retinols, the company states. It contains retinol for increased cellular turnover, retinyl palmitate to soften tough skin, and retinyl acetate to restore sun-damaged skin and improve cell integrity. The serum allows gentle exfoliation to restore clarity and reduce the appearance of age spots and enlarged pores. A multi-peptide helps to decrease wrinkle volume and density.

The serum can be used on the face in the morning and evening after cleansing, by applying a drop to the forehead, chin, under the eyes and on each cheek. The serum will be available in January 2014.

FOR MORE INFORMATION:
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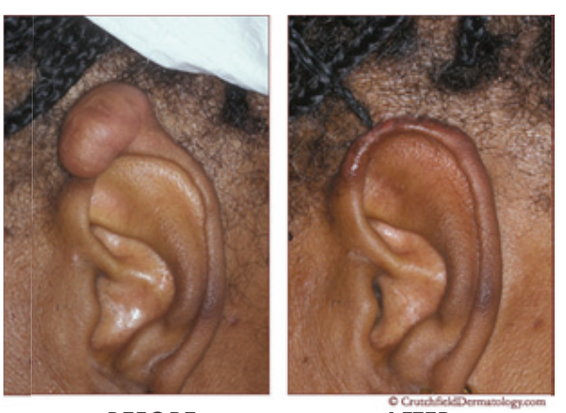

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Dermatology Times

Topical treatment alone insufficient for many NMSCs

John Jesitus | Senior Staff Correspondent

NEW YORK — Except in limited instances, an expert says, topical therapies for medical management of nonmelanoma skin cancers (NMSCs) work best as adjuncts to surgery.

As monotherapy, says Fiona O'Reilly Zwald, M.D., "I typically use topical agents (off-label) for AKs, superficial basal cell carcinomas (BCCs) and perhaps squamous cell carcinoma (SCCs) *in situ*. However, I would not use topical agents for more invasive SCC or nodular BCC. That's where surgery is needed." Dr. Zwald is a Mohs surgeon based in metro Atlanta whose practice revolves around the care of high-risk skin cancers associated with organ transplant recipients.

Only when a patient is not a surgical candidate should dermatologists consider topical treatment alone for more aggressive skin cancer, Dr. Zwald says.

QUICK READ

Encouraging results of some newer topical therapies for skin cancer notwithstanding, such treatments should rarely be used as monotherapy, an expert says.

"Treatment of field disease is another area that's very important for preventing the progression of skin cancer," she says. Topical agents can provide benefits here because they can be used over wide body surface areas.

As adjunctive therapies, Dr. Zwald says, topical agents can be used before or after surgical removal of skin cancers. Overall, topical agents "will probably help to clear the skin in many instances. But they're not supposed to be used as a replacement for surgery," she notes.

EYE ON IMMUNOSUPPRESSION

When treating immunosuppressed patients such as those who have received organ transplants, Dr. Zwald says, "I'll often treat them surgically, while also having them on a regimen of topical therapies." Using topical agents presurgically can reduce the need for more invasive treatments, and the attendant potential for scarring, she says.

"I tell patients that if any lesion pops through while they're on the topical regimen, they need to get biopsied," Dr. Zwald says.

As for specific topical treatments, "Efudex (5-fluorouracil/5-FU, Valeant) and Aldara (imiquimod, Medicis/Valeant) are the major

NMSC see page 52

Quotable

"We strongly recommend that these patients be seen every six months for follow-up in order to hopefully diagnose any invasive tumor as early as possible."

Marcia Ramos-e-Silva, M.D., Ph.D.
Rio de Janeiro

On identifying oral lesions see story, page 53

DTExtra

A laparoscopic procedure to remove lymph nodes reduces the chance of infection and cuts the recovery time in half, according to a Northwestern Memorial Hospital news release. A surgical oncologist at the hospital in Chicago performed the surgery on a 24-year-old female patient who was diagnosed with malignant melanoma that had spread to her lymph nodes. Instead of a five-day hospital stay after a lymphadenectomy, she was able to go home the day after the surgery, according to the release.

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voice of the dermatologist

"The best approach is to step up our screening efforts and detect these lesions early in their development."

Marcia Ramos-e-Silva, M.D., Ph.D., on the early detection of oral lesions, page 53

NMSC:

Topical therapies for skin cancer should rarely be used as monotherapy from page 50

agents we've used for many years now," she says. Patients typically must apply these drugs daily for six to eight weeks to see results.

"I tell patients that if any lesion pops through while they're on the topical regimen, they need to get biopsied."

Fiona O'Reilly Zwald, M.D.
Atlanta

Dermatologists also may use 5-FU in the form of chemo wraps, she says.

"We clean the skin, then apply 5-FU directly on the area being treated, and wrap the skin with Kerlix (Covidien) gauze embedded in a zinc oxide paste," Dr. Zwald says. After applying a layer of petroleum jelly over this layer, another layer of Kerlix follows, and then an outer layer of Coban (3M). Patients leave the wrap on for a week before returning to the office.

Additionally, Dr. Zwald says she occasionally prescribes oral 5-FU (capecitabine) — usually in conjunction with a medical oncologist, who checks the patient's kidney and liver functions before treatment and monitors these functions during treatment. "Because it's hard to tolerate, we use it only for who don't have other options. Some patients do very well on it," she says.

Capecitabine causes very strong inflammatory reactions, according to Dr. Zwald.

"Patients also experience significant desquamation on the hands and feet," which helps to reduce actinic keratoses (AKs) and pre-skin cancers, she says. A typical regimen consists of four weeks on therapy, alternating with four weeks off.

TRYING PDT AND TOPICAL GELS

Topical therapies gaining increased attention include photodynamic therapy (PDT) and Picato gel (ingenol mebutate, Leo). Unlike 5-FU and imiquimod, Dr. Zwald says, ingenol mebutate only requires application for two to three days. A prospective study has shown that around 57 days later, "There is a complete response rate of around 42 percent in patients who have had it used on the face, scalp, trunk and extremities (Lebwohl M, Swanson N, Anderson LL, et al. *N Engl J Med*. 2012;366(11):1010-1019)."

In a recent study, patients applied ingenol mebutate gel to skin cancers of the face and scalp for three days, or cancers of the trunk and extremities for two days. At 12 months post-treatment, 87 percent of patients with cancers of the face and scalp remained completely cured, as did 86 percent with cancers of the trunk and extremities (Lebwohl M, Shumack S, Stein Gold L, et al. *JAMA Dermatol*. 2013;149(6):666-670).

Drawbacks of topical agents include patient compliance and persistence, she says. For example, "Ingenol mebutate causes a tremendous local skin reaction. But it is efficacious. So the more reaction a patient gets, the better the outcome. Not every patient can go through that," Dr. Zwald says.

"Ingenol mebutate causes a tremendous local skin reaction. But it is efficacious."

Fiona O'Reilly Zwald, M.D.
Atlanta

Somewhat similarly, she says, PDT causes a sunburn-like reaction that desquamates superficial skin layers.

"If patients forget to apply sunblock after PDT, they're going to have a pretty extensive reaction," she says. Accordingly, Dr. Zwald says that any nonsurgical therapy requires thorough patient education, particularly regarding how to protect treated skin from the sun, and which lesions require evaluation by a dermatologist. **DT**

Disclosures: Dr. Zwald reports no relevant financial interests.

Early detection, treatment critical for oral lesions

Ilya Petrou, M.D. | Senior Staff Correspondent

NEW YORK — Cancers and precancers of the oral mucosa are notoriously challenging to treat and, according to one expert, a heightened vigilance spanning different specialties remains key in reducing the morbidity and mortality in patients.

"The early diagnosis of precancerous and cancerous lesions in the oral cavity is absolutely critical. Despite the advances in surgery, radiation and chemotherapy, these treatment approaches may only have a palliative effect in many cases and often prove to be too little, too late for a large majority of unfortunate patients," says Marcia Ramos-e-Silva, M.D., Ph.D., associate professor and head, sector of dermatology, School of Medicine, Federal University of Rio de Janeiro.

Cancers of the oral cavity constitute 3 to 5 percent of all cancers and result in 50 percent mortality in five years, underscoring the importance for physicians to arrive at an accurate and early clinical diagnosis of suspicious lesions. In order to better understand the dynamic of oral cancers, it is paramount to diagnose premalignant conditions and premalignant lesions before they worsen, says Dr. Ramos-e-Silva, who spoke at the American Academy of Dermatology summer conference in New York.

PREMALIGNANCIES IN ORAL CAVITIES

Premalignant or precancerous lesions are morphologically altered tissue in which cancer occurs with a greater frequency than normal tissue. In the oral cavity, these include leukoplakia, erythroplakia, leukoplakia candidiasis, cutaneous horns, actinic cheilitis, compound and junctional nevi, and lentigo maligna.

QUICK READ

The early diagnosis of precancerous and cancerous lesions and conditions in the oral cavity can help minimize the morbidity and mortality in affected patients.

In contrast, a premalignant condition is a generalized state that is significantly associated to an increased risk of cancer, including Plummer-Vinson syndrome, atrophic glossitis of tertiary syphilis, xeroderma pigmentosum (XP), lichen planus and lupus erythematosus. The latter two conditions remain controversial and a gray area, Dr. Ramos-e-Silva says, in terms of their potential to undergo malignant transformation.

Some conditions can be more serious than others in terms of their potential for malignancy, such as erythroplakia. According to Dr. Ramos-e-Silva, 91 percent of cases that are diagnosed as erythroplakia have already progressed to epithelial dysplasia, carcinoma *in situ* or invasive cancer.

Though still considered controversial as to whether they can undergo malignant transformation, Dr. Ramos-e-Silva says lichen planus — which can present as reticulate, linear or annular, atrophic, erosive or ulcerative, among other forms — is one common premalignant condition of which to be particularly wary. Up to 2.8 percent of all cases can turn malignant.

Similarly, up to 75 percent of patients with systemic lupus erythematosus and up to 25 percent of patients with discoid lupus erythematosus have oral lesions, Dr. Ramos-e-Silva says, and theoretically, any number of these lesions could turn malignant, further stressing the need for extreme vigilance in affected patients.

"As there is a potential for these diagnosed premalignant conditions to turn malignant, and surgery or other therapeutic modalities are often not the first choice of management, we strongly recommend that these patients be seen every six months for follow-up in order to hopefully diagnose any invasive tumor as early as possible," Dr. Ramos-e-Silva says.

> "For more advanced (oral cancer) cases, anything you do will be mutilating in order to adequately remove the tumor with significant collateral damage to surrounding tissues."
>
> **Marcia Ramos-e-Silva, M.D., Ph.D.**
> Rio de Janeiro

Leukoplakia is a common premalignant lesion, particularly among the elderly, and occurs in up to 5 percent of the general population. While 20 percent of cases can undergo spontaneous involution, up to 23 percent can progress to epithelial dysplasia, carcinoma *in*

ORAL see page **54**

ORAL:

Early diagnosis can minimize morbidity, mortality from page 53

situ or invasive cancer. Therefore, Dr. Ramos-e-Silva recommends that patients with leukoplakia be treated and managed as if the lesions could turn malignant.

STARTING TREATMENT EARLY

Regardless of the premalignant lesion or condition, the key is to initiate treatment as soon as possible, she says, which can range from local or oral corticosteroid therapy for conditions such as lichen planus, to electrocoagulation and curettage or even surgery for leukoplakia.

The most common cancer in the oral cavity by far is squamous cell carcinoma, constituting 90 percent of all malignant neoplasia of the mouth.

The most common cancer in the oral cavity by far is squamous cell carcinoma, constituting 90 percent of all malignant neoplasia of the mouth, followed by others cancers such as basal cell carcinoma (by contiguity), melanoma and distant metastases.

"The choice of treatment for oral cancer greatly varies from case to case. Particularly true for more advanced cases, anything you do will be mutilating in order to adequately remove the tumor with significant collateral damage to surrounding tissues, especially if the cancer is large," she says. "So, the best approach is to step up our screening efforts and detect these lesions early in their development.

Physicians of different medical disciplines, including dermatologists, general practitioners, head and neck surgeons, dentists, and ear-nose-throat specialists could help by simply asking the patient of any suspicious lesion or problem they may have noticed in their mouth during a regular consultation or physical examination.

According to Dr. Ramos-e-Silva, 50 percent of lesions in the oral cavity are asymptomatic and it is

possible that what the patient sees as "nothing" could turn out to be the beginning of a cancerous process.

"This is a multidisciplinary area and there are many specialists that patients see who could diagnose something in the patient's mouth, and then refer them onwards to the appropriate specialist for further scrutiny and treatment of the lesion," she says. "Asking the patient is all that it takes sometimes to help detect these lesions early." **DT**

Disclosures: Dr. Ramos-e-Silva reports no relevant financial interests.

Erivedge® (vismodegib) capsule

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

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

WARNING: EMBRYO-FETAL DEATH AND SEVERE BIRTH DEFECTS

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

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

1 INDICATIONS AND USAGE

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

2 DOSAGE AND ADMINISTRATION

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

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

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

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Embryo-Fetal Death and Severe Birth Defects

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

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

5.2 Blood Donation

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

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

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

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

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

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

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

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

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

[1]aBCC = Advanced Basal Cell Carcinoma.

[2]MedDRA = Medical Dictionary for Regulatory Activities.

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

Amenorrhea:

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

Laboratory Abnormalities:

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

7 DRUG INTERACTIONS

7.1 Effects of Other Drugs on Vismodegib

Drugs that Inhibit or Induce Drug Metabolizing Enzymes

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

Drugs that Inhibit Drug Transport Systems

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

Drugs that Affect Gastric pH

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

7.2 Effects of Vismodegib on Other Drugs

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

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

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category D

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

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

8.3 Nursing Mothers

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

8.4 Pediatric Use

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

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

8.5 Geriatric Use

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

8.6 Females of Reproductive Potential and Males

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

Female patients

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

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

Male patients

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

8.7 Hepatic Impairment

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

8.8 Renal Impairment

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

10 OVERDOSAGE

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

17 PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (Medication Guide).

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

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Synergy between UVA, UVB linked to UV-induced immunosuppression

Louise Gagnon | Staff Correspondent

MONTREAL — The sun protection factor (SPF) is not the only measure that should be guiding the formulation of new sunscreens, according to the senior manager, worldwide regulatory affairs, L'Oreal Research and Innovation, Paris.

Individuals with darker skin phototypes are more susceptible to persistent pigment darkening (PPD) that is induced by exposure to ultraviolet A (UVA) radiation, and they need to take extra care to ensure protection against UVA, says Dominique Moyal, Ph.D.

"There is a persistent pigment darkening that is easily induced in skin phototypes III to V because of the higher content of melanin in the skin," Dr. Moyal says.

Speaking here at an update on therapeutics in dermatology, Dr. Moyal notes that skin types are classified based on the capacity to burn and to tan and that conditions such as melasma occur in patients of darker skin types, such as Asian or Indian patients.

UVA, UVB FILTERS

A biological endpoint, PPD, is being used to assess UVA photoprotection, Dr. Moyal says. A unique property of UVA is that it penetrates deeper into the skin than does UVB, and UVA irradiance is at least 17 times higher than UVB irradiance. To adequately cover the complete range of harmful radiation, sunscreens should contain both UVA and UVB filters, she says.

The growing concern about the deleterious impact of UVA is leading some researchers to look at additional measures in developing sunscreens. One of those measures is UVA protection factor (UVAPF). A sunscreen can carry a particular SPF but possess insufficient protection against UVA.

"You can have two sunscreens that offer SPF of 30, but the protection factor of UVA may be different," Dr. Moyal says. "Only a well-balanced product is able to decrease UVA-induced pigmentation."

Well-balanced protection is defined by a UVAPF at least one-third of the SPF, and products that fulfill this criterion are identified with a UVA logo, Dr. Moyal says.

Factors that contribute to that difference include if the UVA filters are subject to degradation when exposed to UV. Consequently, a filter such as avobenzone should ideally be paired with a UVB filter such as octocrylene to ensure avobenzone's efficacy in terms of its protection against UVA, Dr. Moyal says.

QUICK READ

Sunscreens need to provide adequate protection against the full range of UVA, and to ward off UV-induced immunosuppression, patients must defend themselves from UVA and UVB radiation.

> "You can have two sunscreens that offer SPF of 30, but the protection factor of UVA may be different."
>
> **Dominique Moyal, Ph.D.**
> Paris

Full protection over the entire UVA range, effective absorption in both the long UVA and short UVA, is required, Dr. Moyal adds.

PHOTOIMMUNOSUPPRESSION

Like UVB, UVA is involved in the induction of photoimmunosuppression, according to Dr. Moyal.

A study published in the *British Journal of Dermatology* showed that human epidermal Langerhans cells were modified with a single exposure to either UV solar simulated radiation, or ultraviolet B and UVA or UVA radiation alone (Seité S, Zucchi H, Moyal D, et al. *Br J Dermatol*. 2003;148(2):291-299).

To protect patients against UV-induced immunosuppression, they need to be protected against UVA and UVB, according to Robert Bissonnette, M.D., F.R.C.P.C., a dermatologist based in Montreal, with Innovaderm Research.

"You don't need (to be exposed to) a high dose of radiation to create UV immunosuppression," says Dr. Bissonnette, noting the impact of UV radiation on Langerhans cells has been well-studied. "There appears to be a synergistic effect between UVA and UVB."

The mechanisms involved in UV immunosuppression are fairly complex, Dr. Bissonnette says.

"Immunosuppressive effects of UV radiation could explain the association between sun exposure and a decrease in the incidence of other diseases like multiple sclerosis," Dr. Bissonnette says. "Some studies suggest that sun exposure in childhood has a protective effect against such diseases."

Dermatologists should individualize their treatment plans around the issue of photoprotection for their patients, Dr. Bissonnette explains.

"The impact of UV-induced immunosuppression is different from one patient to another," he says. "The approach I would take with a patient who has a phototype II skin type and works outdoors is different from what I would do with a patient who has a phototype VI skin type and who spends most of his time indoors." **DT**

Disclosures: Dr. Bissonnette has received honoraria and/or research grants from Pierre-Fabre, L'Oreal and La Roche-Posay.

64 CPT CODES
Figure shows how a CPT code's Medicare allowable is determined

Thriving amid office politics requires a reality check

John Jesitus | Senior Staff Correspondent

MIAMI BEACH, FLA. — Making office or organizational politics work for your group requires acceptance, transparency and relationship-building, an expert says.

"Politics are part of every group or organization," says Diane R. Baker, M.D., a dermatologist in private practice in Lake Oswego, Ore. However, she adds, the fact that some politics are productive and necessary for meeting group goals initially may appear counterintuitive.

Definitions of politics run the gamut — from any struggle for power in any group setting, to the ways in which people recognize and reconcile differences to get things done in business or volunteer settings.

Moreover, "In every group, some people have more power for a variety of reasons — not necessarily because they're leaders, but perhaps because they've been there a long time and know the history of the group or organization" better than others, she says.

QUICK READ

Not all office politics are inherently bad — the key is how individuals in a group work together to meet common goals, according to an expert.

Additionally, "People within an organization have different interests. They will work to satisfy their own interests, as well as those of the organization. Politics aren't a bad thing necessarily, because your interests might be the same as the organization's." By the same token, Dr. Baker says, someone's desire to become president of an organization provides a valuable service to the group in a way that other members might be unwilling or unable to.

THE GREATER GOOD

Politics only becomes a negative force when it involves gaining advantage at the expense of others, or of the greater good, she says. In this regard, she says, there's a big difference between "dirty politics," or self-serving schemes that advance one person's interests regardless of what's good for the group, and "clean" politics. The latter type of politics may feature struggles between individuals who have the organization's best interests at heart but disagree on how to serve these interests, or perhaps even about what those interests are.

"That's actually what we want in an organization," a free-flowing discussion regarding shared decisions that

POLITICS see page 60

Quotable

"Have a slide that you know should appear about five minutes before you're done, and if necessary, skip some slides to get there."

Ilona Frieden, M.D.
San Francisco

On tips for successful, engaging presentations

See story, page 60

DTExtra

Most physicians read online reviews that patients write about them and monitor the reviews of their competitors, according to a new survey. Results of the first-annual Digital Doctor Survey conducted by ZocDoc showed that 85 percent of physicians and other providers read their online reviews and 36 percent glanced at the reviews of competitors and fellow physicians, as well. Most physicians surveyed (85 percent) said most patient reviews were "very fair" or "fair." Only 15 percent did not consider the reviews fair.

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"The RUC is a purely advisory committee to CMS ... " The RUC's job is to "take every current procedural terminology (CPT) code and decide how much work the code is worth relative to the work involved in every other code."

Daniel M. Siegel, M.D., American Academy of Dermatology (AAD) adviser to the RUC page 70

POLITICS:

Acceptance, transparency, relationship-building are keys to coming together from page 58

involve the good of the group, Dr. Baker says. Though it's not always obvious whether a maneuver represents self-interest or not, she says, "Often we have a gut feeling about that."

Furthermore, Dr. Baker says that attempting to avoid politics "doesn't work very well. Whether you're comfortable with it or not, politics will always be there in group settings. Pericles said that just because you don't take an interest in politics doesn't mean politics won't take an interest in you."

ROLE RECOGNITION

It's also important to recognize the role or roles played by each member of a group and how those roles may help or hinder an organization's ability to achieve its goals, she says. Group members may assume one particular role — such as devil's advocate — most of the time, adds Dr. Baker, or they may play different roles depending on the discussion or circumstances. Examples of roles that group members assume are those of the "dominator," the "distractor," the "compromiser," the "brainstormer" and the "blocker."

To illustrate the effect of different role players and politics on group dynamics, attendees at a Forum on Leadership held at the American Academy of Dermatology (AAD) annual meeting participated in a mock task force discussion. It focused on the appropriateness or inappropriateness of the establishment of a category of membership in the AAD for mid-level practitioners who have been trained by and are supervised and employed by board-certified dermatologists. Attendees role-played pro and con positions, while others observed the role players and attempted to discern the hidden agendas behind their pro or con positions.

"Politics aren't a bad thing necessarily, because your interests might be the same as the organization's."

Diane R. Baker, M.D.
Lake Oswego, Ore.

It's important to recognize the role or roles played by each member of a group and how those roles may help or hinder an organization's ability to achieve its goals.

Regardless of your role in a group or organization, Dr. Baker says, a better understanding of the inevitability of politics, an acceptance of the differences in motivation of group members and an appreciation of the usefulness of diverse opinions about methods to achieve goals all contribute to the success of the organization. **DT**

Disclosures: Dr. Baker reports no relevant financial interests.

RUC:

Participants and critics have polarizing views, so what's the real role? from page 1

What is most important to note is the broad influence RUC has on how much physicians get paid both in the Medicare program directly and in the private market. While the committee makes recommendations for relative value, those recommendations carry great weight as industry-wide benchmarks for actual-dollar payment rates.

Those who participate in the RUC and those who are critics of it have polarizing views, and there is a need to discover RUC's role in the real world of healthcare, both today and for the future. We hope this article produces more light than heat, which might be an improvement over recent mainstream media coverage that over the past few years has explained, and to varying extents, excoriated the RUC.

For example, an article in the Feb. 20, 2007, issue of *Annals of Internal Medicine* discussing the income gap between primary care and medical specialties took the committee to task for failing to do more to close that gap. Specifically, the article blamed the overrepresentation of specialty physicians on the RUC for the lower incomes of primary care providers (PCPs). The article did note other factors, however, such as private insurers "reimbursing specialists at large percentages and primary care providers at small percentages over Medicare rates."

Perhaps the most vilifying headline appeared on a July/August 2013 article in *Washington Monthly*: "Special Deal: The shadowy cartel of doctors that controls Medicare." It and other articles are clear on a number of criticisms.

Critics: There is weak representation of primary care on RUC, therefore RUC is skewed in favor of specialists.

Taken as a whole, the negative articles criticize RUC based largely on the same perceptions. Much of the focus specifically falls on the committee's purported effects on reimbursements for PCPs.

The committee is, in fact, heavier on medical specialists than PCPs by head count, which at least encourages the ongoing tendency for procedural CPT codes to be reimbursed more generously than cognitive codes, such as those for patient Evaluation and Management (E/M). And since primary care physicians tend to engage in a higher proportion of activities that fall under E/M codes, a related criticism is that the updating process undervalues the work of primary care physicians.

Even so, there are also persistent issues around payments for procedural codes versus those for cognitive codes.

"RUC represents that tension, but it doesn't define it," says David Muhlestein, director of research for healthcare consultants Leavitt Partners LLC.

RUC: Primary care compensation is increasing appropriately.

From 1991 to 2011, the portion of Medicare money paid to primary care increased from 37 percent to 43 percent while the portion going to surgical specialties dropped from 32 percent to 21 percent, according to William L. Rich III, M.D., F.A.C.S., an ophthalmologist and former RUC chairman. Similarly, reimbursement for routine office visits with established patients (E/M code 99213) has risen from $32 to $66 since 1995, he says.

"There has been a redistribution of valuation by the RUC," Dr. Rich says. "There has been an absolute shift of dollars to primary care, appropriately."

He adds that in the past two years and on its own initiative, RUC has added valuations for care coordination, team education and phone calls.

There are still, however, "some distortions" in pay, he says. Cardiology, gastroenterology and orthopedic/spine surgery, for example, "pay substantially more than primary care or general surgery."

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RUC:

Participants and critics have polarizing views, so what's the real role? from page 61

SPECIALTIES VS. PRIMARY CARE

Glen Stream, M.D., past-president and former board chairman of the American Academy of Family Physicians (AAFP), counters that though the tide is turning back toward primary care, it's only "to a small and inadequate degree."

He points out that the common codes (E/M 99213 and 99214, which includes moderate-complexity medical decision-making) are also embedded into many codes for surgical procedures, such as for pre-op and follow-up visits. Therefore, increasing the pay for common codes helps primary care physicians less than might initially seem the case.

AAFP has recommended to CMS that the agency create primary care-specific E/M codes. The academy's position is that evaluation and management work in primary care is more demanding and complex than in specialties, especially with an aging population that often presents with multiple or chronic conditions.

But the whole idea behind RUC and its value determinations is to arrive at relatively fair compensation for time and skill. Each CPT code — created exclusively by AMA to document healthcare services for the purpose of reimbursement — has a Relative Value Unit (RVU) assigned to it. When the RVU is multiplied by a conversion factor and a geographical adjustment, it creates the baseline for compensation for a particular service.

RVU numbers are translated into actual reimbursement dollars by the CMS conversion factor, which is flat, or the same for all specialties, says Barbara S. Levy, M.D., the current RUC chairwoman and vice president of health policy for the American College of Obstetricians and Gynecologists. She adds that private insurers' conversion factors are affected by market forces, such as the availability of a given specialty in a certain area, and so aren't necessarily flat.

Although it's not the only formula, private insurers often use the actual rates paid by Medicare as a baseline for their separately negotiated rates with providers. Market forces, quality programs, pay for performance and other factors figure in, as well.

Critics: Service time metrics can become out-of-date with medical advances.

Other criticisms of the RUC cover a wide range of issues. For example, the amount of time attributed to many procedures has remained high even as the procedures have advanced to become more routine and to require less of the physician's time than previously documented.

A *Washington Post* article noted that 78 physicians in Florida had — on paper — performed at least 24 hours worth of procedures in a single workday based on RVU figures, which would be clearly impossible in the real world. And reportedly, certain ophthalmologists performed 30 to 40 procedures in a single day, which would have been 30-plus hours worth of work based on RVU figures.

RUC: The numbers must be examined in context.

In a press release shortly after the article appeared, the AMA stated that it had asked to see the magazine's cited data for the Florida physicians, but that the documentation was not provided. Regarding the ophthalmologists, the association noted that the procedures cited appeared to have included LASIK, for which RVU values have never been determined, because the procedure is not covered by Medicare.

As to the system not addressing procedures that have become more efficient, Dr. Rich says that over a 10-year period, he went from doing three cataract surgeries in about seven hours to doing 10, but his reimbursement per surgery declined significantly. The Medicare reimbursement for cataract surgery was $941 in 1995 and is $578 currently (figures not adjusted for inflation), Dr. Rich says.

Critics: RVU numbers assigned to procedures always go up.

Reimbursement just keeps growing over time, the critics say. A *Washington Post* analysis of records for 5,700 procedures reportedly showed that work RVUs are seven times likelier to increase than to fall.

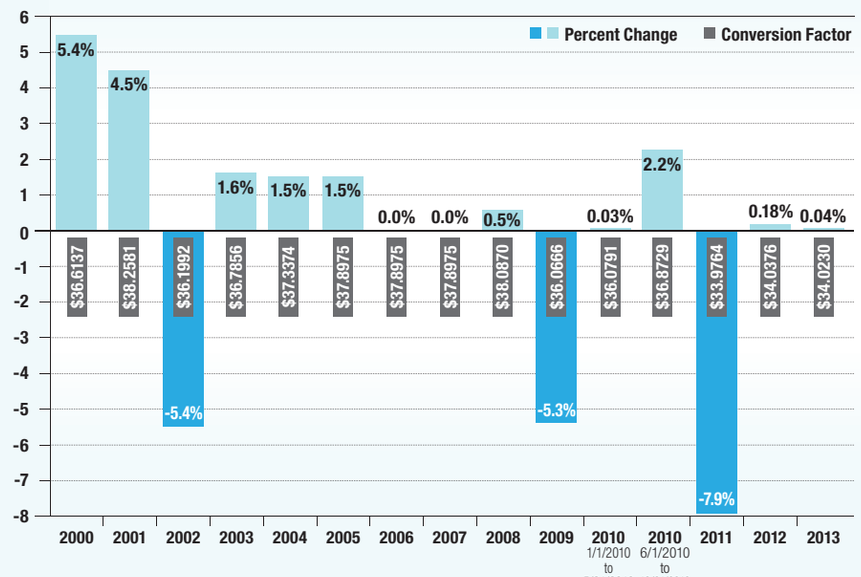
RUC: The values are relative.

The AMA and RUC have repeatedly emphasized that the RBRVS and its updates are based on relative values. In other words, if everything is inflated by a similar factor, the RVU figures are still valid, compared to each other. And RUC leadership insists that the committee's RVU recommendations are largely in line with each other in those relative relationships.

It's a common misperception that RUC is somehow jacking up physicians'

RUC see page 64

CMS conversion factors: 2000-2013



Source: American Medical Association

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RUC:

Participants and critics have polarizing views, so what's the real role? from page 62

fees in absolute terms, according to AMA. With the various steps between an RVU allocation by the RUC and a final dollar figure in the following year's Physician Fee Schedule, accusations of "price-fixing" are off the mark.

"The RUC does not control revenue," Dr. Rich says, "it just determines valuation."

Further, Dr. Rich says, since 2010, RUC has reviewed 1,553 codes. Of those, only 5 percent increased, 43 percent decreased, 34 percent stayed the same and 18 percent are still under review. Most of the redistribution of value was to primary care, he says.

Critics: There is overvaluation of certain procedures.

Overvaluation encourages overuse, not only under Medicare, but under private insurance, too. Many insurers use the RBRVS as a baseline for their own payment scales, with some using a percentage of actual Medicare payment as a final rate. This "Medicare spillover" effect does exist, Mr. Muhlestein says. Medicare is the payer with the most clout, and its rates do indeed influence private insurers.

RUC: The RBRVS as administered by the CMS is budget-neutral, as reflected by annual adjustments in the conversion factor.

The amount that Medicare spends on physician fees, even fees per patient, continues to rise drastically, of course, but that's being driven by other factors, such as utilization increasing overall.

As for private insurers, the RUC has no control over whether they use the RBRVS values or whether or how they modify them.

Critics: CMS essentially rubber-stamps the RUC's recommendations.

Historically, CMS has approved more than 90 percent of RUC recommendations. The raw numbers are hard to argue with, but the reasons for them are hotly debated. Many question whether new payment models will force CMS to push back on some of the RUC determinations.

RUC: The committee is doing its job well.

The fact that CMS accepts the vast majority of the committee's recommendations is an indication of how carefully and fairly the RUC does its job, according to AMA.

In addition, RUC leadership points to the fact that CMS "listens to every debate," Dr. Rich says. So what the committee does and how it does it is completely transparent to CMS.

Dr. Stream does agree that CMS has been "more discerning" lately about accepting the RUC's valuations.

CRITICS: RUC IS 'SECRETIVE'

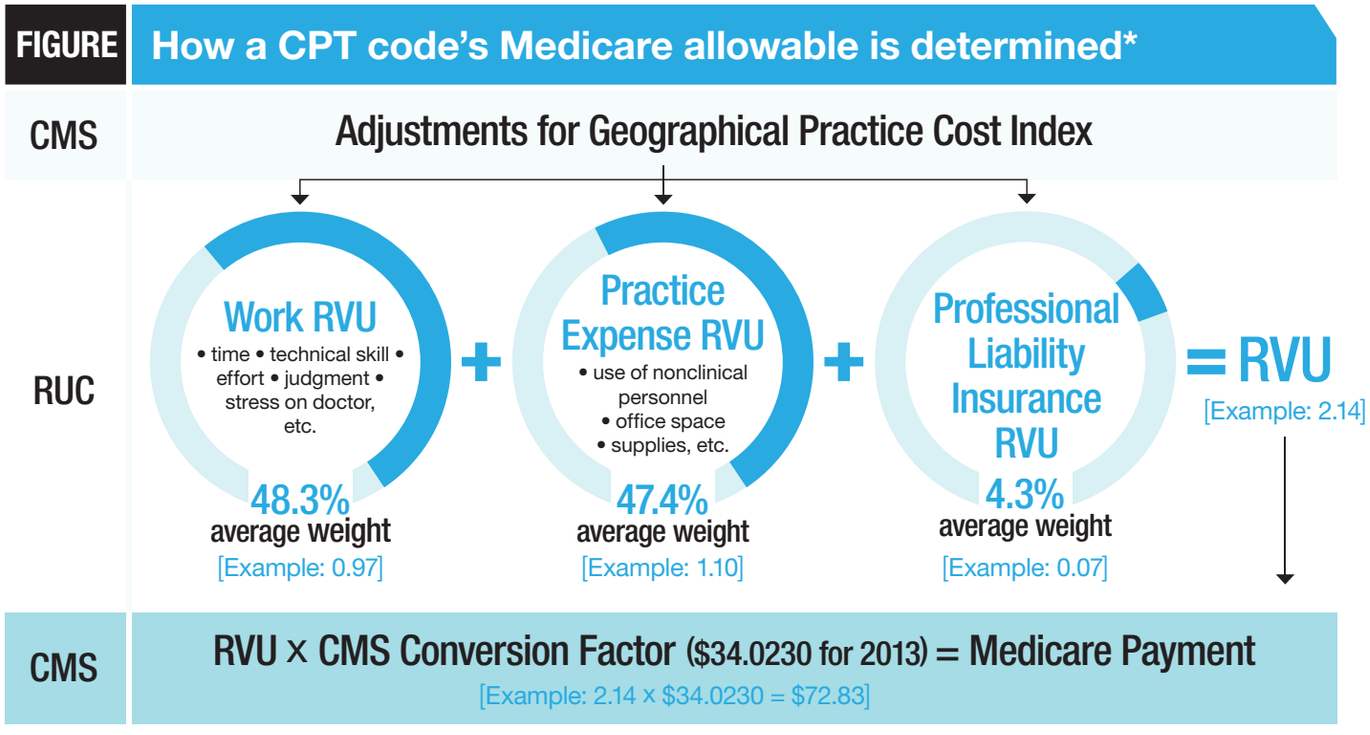
In not publishing the results of RVU votes and in requiring a broad nondisclosure agreement from any non-members allowed to attend a meeting, RUC appears to be less than transparent in its decision-making process.

The lack of transparency engenders much of the distrust of the committee, says Dr. Stream, who adds that the AAFP has pushed for more transparency within RUC and outside of it.

Medicare is becoming somewhat more open about what it pays providers

RUC see page 66

FIGURE How a CPT code's Medicare allowable is determined*



Abbreviations: **CMS:** Centers for Medicare and Medicaid Services **RUC:** American Medical Association (AMA)/Specialty Society Relative Value Scale Update Committee **RVU:** Relative Value Unit

*Example based on CPT code 99213

Source: American Medical Association

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RUC:

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since a federal judge lifted a 1979 injunction that prohibited CMS from disclosing Medicare payments. In May, CMS released hospital charge data for 100 common procedures, but physicians remain divided on the issue of making the information public.

The biggest favor RUC could do for itself would be more transparency, Mr. Muhlestein agrees.

RUC: Some information is better kept within the committee.

RUC meetings are closed for good reasons, principally that new CPT codes requiring an RVU recommendation often involve new medical devices, and RUC doesn't want its deliberations to become fodder for the stock market.

"They (CMS) don't want Wall Street responding to the debates in that room," Dr. Rich says.

The AMA also notes that RUC meetings typically are attended by 300 people, so the attendees hardly comprise a small, clandestine "cartel."

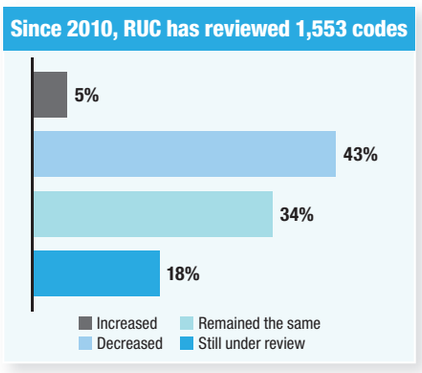
TRANSFORMING RUC FROM THE INSIDE

So is the RUC deservedly as controversial as mainstream media portrays? Or is it more of a lightning rod for a variety of contentious, persistent issues around Medicare reimbursements specifically and concerns around fee-for-service payments generally?

In a September post on the American College of Physicians' ACP Internist Blog, Robert M. Centor, M.D., F.A.C.P., an academic general internist and associate dean at the University of Alabama School of Medicine, Birmingham, writes: "... the RUC did not create the system. They try hard to balance a system that is designed to achieve the wrong outcomes. The RUC has become a very easy and attractive kicking post, but the problem comes from the idea of resource-based relative value units ..."

He goes on to say he does not blame RUC. Although it is not perfect, members are working to patch a flawed concept.

And RUC leadership has been moving to address at least a couple of the concerns highlighted by recent media coverage. For example, one allegation has been that RUC members vote in blocs and that the surgeons or other specialties agree to vote in concert.



Around 1999 and 2000, Dr. Levy says, "there were factions" that would meet separately the night before a meeting to plan their votes, but both she and Dr. Rich worked hard to drive that attitude out.

Dr. Levy says she tells RUC members, "When you sit on the RUC, you're representing the house of medicine," not a particular society or specialty. "People are not voting in blocs," currently, she says, adding, "Most of our votes are overwhelming. Generally it's not close."

CULTURAL SHIFT

One way she and Dr. Rich brought about a cultural shift, Dr, Levy says, was procedural. The typical agenda book for a RUC meeting is massive, at about 2,000 to 3,000 pages, so this material is now divided up and assigned to advance reviewers who are from specialties different than the specific codes they're reviewing. These reviewers also become the lead commenters on those codes during the meeting.

The result has been more-informed discussion, Dr. Levy says. "People don't come in as fearful."

In another change, she says, RUC votes will be published for the first time after CMS publishes its final rule — likely in November. The votes will be reported only as totals for and against a given RVU assignment, however, not as individual voting records.

"We have to have" that level of anonymity, Dr. Levy says. She doesn't want to risk RUC members being punished for voting against their specialty society's narrow interests, which she says happens commonly.

The RBRVS update process is based entirely on effort, so it's lacking any elements connected with health outcomes or the value to a patient of a procedure or E/M. RUC's leadership and outside observers agree — although it's an improvement — the change is unlikely to happen any time soon.

Physician payments should be based to an extent on effort, as they currently are, says Roy Poses, M.D., a clinical associate professor of medicine at Brown University, Providence, R.I., an internist and blogger who has followed the RUC for half a dozen years. But the most important thing to add to the RBRVS, he says, would be "some measure of value for the patient ... Ideally, effectiveness ought to be part of it."

"The problem is, that's really hard to measure," Dr. Poses continues, and "Right now, I don't think we know enough" about outcomes.

When the RUC was established, there was supposed to be a valuation proposition to it, Dr. Rich says, but the committee didn't have such tools in 1989.

"We're starting to find ways to measure value to the patient," such as quality-of-life scores or patient-related outcomes, he says.

Dr. Levy says if she could recommend changes to RBRVS, she'd like to add factors for relative patient benefit, as shown by outcomes research, and add a factor for cost-effectiveness.

By law, however, the only factors that can be considered currently in the RBRVS are work, practice expenses and malpractice insurance expenses, along with "a bit of a geographic modifier," Dr. Levy says. As a result, the RUC can't yet consider a procedure's value to the patient or to society.

TRANSFORMING RUC FROM THE ONSIDE

Section 3134 of the Affordable Care Act mandates that CMS establish a process to validate RVUs of Physician Fee Schedule services, and the agency has contracted with the Urban Institute and the RAND Corp. to do so.

The Urban Institute project is intended to give CMS a way to review proposed work RVUs, assess how reasonable they are in terms of external data, and ensure that the overall RBRVS fee schedule is internally consistent

RUC see page 68

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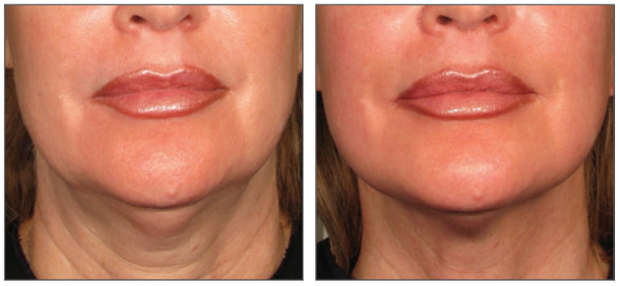

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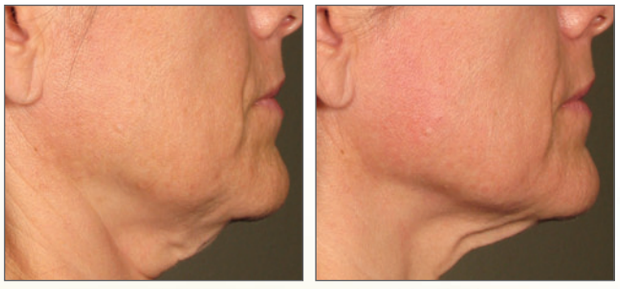

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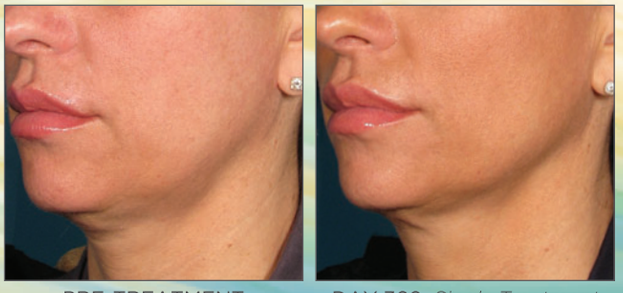

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RUC:

Participants and critics have polarizing views, so what's the real role? from page 66

within families of services and specialties. The project will examine the work RVUs for 100 services in the Physician Fee Schedule. Clinical panels made up of physicians from a range of specialties will review the new data regarding the time necessary to perform specific services and procedures.

Over a two-year period, the RAND project will build a validation model to predict work RVUs and their time and intensity components. "The model design will be informed by the statistical methodologies and approach used to develop the initial work RVUs and to identify potentially misvalued procedures under current RUC and CMS processes," according to RAND. CMS will provide a sample of CPT codes to test the model.

WHO COULD DO IT BETTER?

One of the issues underlying these efforts seems to be the question of who would be better qualified to determine physician work values than the physicians themselves? To put it another way: Could a body substantially different from RUC do the same job, but better?

Dr. Levy is skeptical, noting that almost everyone on RUC is a practicing physician. She questions how a non-physician could set RVUs, particularly the aspects of a procedure's intensity and the potential harm that might result.

She says she would be more optimistic about changing other aspects of Medicare payment policy. For example, there's a policy related to implantable defibrillators. Costing more than $100,000 installed, the devices are indicated only for congestive heart failure, but their use has over time been extended to other conditions without supporting evidence.

CMS has tried to rein in the extended use, she says, "but they get tremendous pressure" from Congress.

Health services researchers originally developed the RVU concept, so presumably they would be qualified to do RUC's work, Mr. Muhlestein says, though he isn't aware of any significant current research efforts along this line.

"It's hard to get non-physicians really interested" in this kind of work, he adds.

On one hand, Mr. Muhlestein explains, the reported $7 million that the AMA spends annually to operate RUC is roughly one ten-thousandth of the approximately $60 billion a year that Medicare pays for physicians fees, so more effort in ensuring that RVU allocations are accurate wouldn't be a big hit on the federal budget.

On the other hand, he says, Congress has never given CMS the resources to replace or supplement the RUC.

RUC PROCEDURES

Calling RUC's procedures "complicated and opaque," Brown University's Dr. Poses says RBRVS should be updated by a formal federal advisory committee whose members are appointed by the federal government; which accepts open, public comments; and which includes "some representation by patients and taxpayers." He envisions something along the lines of the Patient-Centered Outcomes Research Institute, whose board includes representatives from patient-advocacy groups.

A potential step in the direction that Mr. Muhlestein and Dr. Poses suggest was taken in June, when U.S. Rep. Jim McDermott (D-Wash.) introduced a bill that would create a new panel to oversee the RUC.

In a news release, Rep. McDermott's office said the RUC "is unevenly weighted by procedural specialists over primary care doctors and relies heavily on anecdotal and self-serving survey evidence, rather than forensic data."

"Medicare certainly needs clinical expertise in order to fairly set reimbursements, but an outside organization ... needs checks and balances," Rep. McDermott said. "No matter how well-intentioned, structural biases are inevitable and we're seeing that effect as new doctors flock toward specialty care and away from primary care."

Rep. McDermott is a psychiatrist and the ranking member of the House Ways and Means Subcommittee on Health.

Based on a recommendation from the Medicare Payment Advisory Committee, the Accuracy in Medicare Physician Payment Act of 2013 introduced by Rep. McDermott in June would establish a panel of independent experts within CMS "to identify distortions in the fee schedule and develop evidence to justify more accurate updates."

The panel's members would include patient representatives, and the group would be subject to the Federal Advisory Committee Act, which requires such bodies to hold open meetings and publish their minutes.

Under the bill, Medicare could continue to request work from the RUC, but the new panel would both initiate such requests and review the RUC's work.

THE FUTURE OF THE RBRVS

It's clear that RUC is, for better or worse, handcuffed to the RBRVS, which was built on a fee-for-service (FFS) model. With or without major changes, what might the future hold for the RBRVS?

Even within group practices, accountable care organizations (ACOs) and other care models, rewards need to be divvied up somehow, Dr. Rich says, either by RVU or some equivalent, and the current RVU assignments are already very commonly used for such purposes.

"These are not going away. They're always going to be needed," he says, even if the FFS model fades somewhat.

Dr. Levy adds that in addition to being part of how ACOs apportion salaries, the RBRVS is likely to be part of any bundled-payment valuations.

The RVU is "the default standard" for such purposes, Muhlestein agrees. He notes that Leavitt Partners' Center for Accountable Care Intelligence has been tracking ACOs and their payment arrangements for about three years and concludes that most contracts are still fee-for-service based. In addition, the ACOs in the Medicare Shared Savings Program are all based on FFS, he says.

Catalyst for Payment Reform (CPR), a national, not-for-profit collaborative of large employers, in March found that 10.9 percent of commercial healthcare payments today are tied to value rather than volume.

The biggest take-away from the current controversy about RBRVS and its updates, Mr. Muhlestein says, is simply that "RUC is still very relevant and will be relevant for a long time." **DT**

In your opinion, is there a better qualified body to determine physician work values? E-mail editor@dermatologytimes.com

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FUNCTIONAL:

RUC role complex, not perfect, but better than proposed alternatives, some say from page 1

RUC, he has served on its practice advisory committee and chaired its research subcommittee. He is also a clinical professor of dermatology and director of the procedural dermatology fellowship at the State University of New York Downstate Medical Center, Brooklyn, and AAD immediate past-president.

Mark D. Kaufmann, M.D., adds, "There's been a lot of criticism of the RUC," ranging from its influence on the Centers for Medicare and Medicaid Services (CMS) to its apparent secrecy. To such charges, he replies, "The RUC is continually evolving and is always attempting to improve itself." He is an associate clinical professor, department of dermatology, Icahn School of Medicine at Mount Sinai, New York, and the American Society for Dermatologic Surgery (ASDS) adviser to the RUC.

IT'S ALL RELATIVE

By definition, Dr. Siegel says, "The RUC is a purely advisory committee to CMS," which ultimately sets prices. As such, he says, the RUC's job is to "take every current procedural terminology (CPT) code and decide how much work the code is worth relative to the work involved in every other code." After considering the time, intensity, complexity and physician risk involved, he explains, the RUC assigns numerical values that allow between-specialty comparisons.

Dr. Kaufmann says that the average dermatologist may have an inkling about what the RUC does, but few appreciate the intricacies of RUC rules or how the committee functions.

Fitzgeraldo A. Sanchez, M.D., co-chair of the AAD Resource-Based Relative Value Scale (RBVS) committee, says that when he attended his first RUC meeting while serving as a fellow under the supervision of Dr. Siegel, "I found it incredible that they put so much detail into developing the value of a code," down to the 14 cents worth of gauze a procedure might require. He is also adjunct clinical assistant professor of dermatology at the University of Florida College of Medicine, Gainesville.

The process demands such detail, Dr. Kaufmann says, because RUC advisers understand that "The more value that goes to their procedures, the less is available for others, and vice versa." Overall, though, "The RUC strives to be fair and allows specialties to tell their side of the story." Additionally, he says, RUC advisers know that — because of checks and balances within the system — what they request must be realistic.

In this regard, he says that he — along with Dr. Siegel and advisers from the Society for Investigative Dermatology and the American College of Mohs Surgery — jointly develop strategies for presenting and defending codes. If RUC dermatologist surveys reveal that 70 percent of dermatologists do a follow-up visit within the 10-day global period allowed after wart destruction, for example, "That's very good evidence to take to the RUC showing that the value that's been assigned to that global period deserves to be there."

RUC surveys don't always work as intended, however. Despite AAD efforts to educate members about the RUC, Dr. Siegel says, dermatologists' misunderstanding or disbelieving AAD missives amounts to ignorance. When ignorance causes physicians to answer surveys lazily or inaccurately, he says, "People suffer," via reduced reimbursements.

Regarding the objectivity of the RUC process, Dr. Siegel says that when a dermatology code comes up for review, "The dermatologist on the committee is not reviewing it. Codes are primarily scrutinized and reviewed by people who do not have interest in that code."

As for characterizations of RUC meetings as obscure and boring, Dr. Siegel says, "They're actually rather exciting. Thirty-one of the brightest minds in medicine gather around the table to work these things out." This figure includes three nonvoting members; RUC recommendations to CMS require a two-thirds majority.

Regarding the RUC's appearance of secrecy, Dr. Siegel says, "The only reason the meeting is closed is that some people might be able to use what happens there unfairly." A tip from behind closed doors might result in "fire sales" on stocks of companies involved with a particular procedure, he explains.

To boost transparency, Dr. Kaufmann says, the RUC now releases vote totals after its meetings (without revealing how individual members voted). Since its inception, Dr. Siegel notes, "The efforts of the RUC are revealed in both the annual proposed and final fee schedules published in the Federal Register."

FIXES MISS THE MARK?

Remedies proposed to eliminate perceived RUC problems fall short, Drs. Siegel, Kaufmann and Sanchez say. For example, Dr. Siegel says, the RVU validation model being built by the RAND Corporation is "potentially useful from the perspective of cutting expenditures, but does nothing for quality or outcomes. They're not getting input from people who actually practice medicine."

A similarly purposed Urban Institute project is "The cause of many significant cuts to values including phototherapy for psoriasis," he adds. Mandated with saving money, "The Urban Institute has come up with methodologies for trying to level payments regardless of site of service — hospital or office — that make no sense. Essentially they're responding to the government's desire to let a third party inflict pain, without a logical model."

Dr. Sanchez adds, "They want to review some of the dermatology codes, but they're not asking dermatologists to get involved. They're asking family practitioners, who aren't the typical practitioner" who uses those codes.

Dr. Kaufmann says that as a participant in the RUC process, he would prefer that these determinations remained under the RUC purview. However, he says, the specialty of dermatology will "have to abide by whatever recommendations these projects make to the RUC if CMS tells us we have to."

Additionally, the American Academy of Family Physicians (AAFP) has proposed that CMS create primary-care-specific E/M codes with higher relative values to reflect more demanding E/M requirements in primary care versus specialties. However, Dr. Kaufmann says, dermatology opposes specialty-specific codes.

"From the RUC perspective," he says, "an office visit is an office visit, no matter who's doing it."

Dr. Siegel adds, "The primary-care-as-gatekeeper model was tried in the

1990s and for an assortment of reasons fell out of favor."

Addressing the concern that RVUs always ascend over time, Dr. Siegel counters, "That's not true." Specialties in which payments have declined in recent years include pathology and cardiology, he says.

Furthermore, he says CMS does not simply rubber-stamp RUC recommendations. In fact, Dr. Kaufmann says that the percentage of RUC recommendations adopted by CMS has fallen from greater than 90 percent to 87 percent for 2012.[1]

Taken together or separately, Dr. Siegel says, the many proposed RUC remedies are all worrisome. "You never know which one the government is going to let grow legs."

Accordingly, he advises all physicians to become proactive in protecting codes they rely on. "And if things aren't working well, don't simply complain to your specialty society. Make it known to your congressman that they're tampering with things that don't need tampering." The best way to do this is "through a polite, well-constructed message that the AAD can provide. Your support of SkinPAC, the only political action committee dedicated to the interests of dermatology, is also critical."

Within the RUC, Dr. Kaufmann says, all specialties must follow the same rules. "As long as no one has a perceived advantage at the table, it seems to work." As such, he says, "It's a process we're happy to be involved with. We would be upset if these things were being determined without the specialty societies' input."

For more than two decades, Dr. Siegel adds, the RUC has managed to value CPT codes in such a way that all specialties that use a particular code — and those that don't — have been relatively happy. Accordingly, he says, "It's a functional system that's better than many other possibilities, such as the ones being put forth where the government arbitrarily decides things based on whimsy."

Perhaps Dr. Sanchez best sums up experts' attitude: "The RUC system could be better, but it could be a lot worse." **DT**

Dr. Siegel is the AAD adviser to the RUC. Dr. Kaufmann is the ASDS RUC adviser. Dr. Sanchez co-chairs the AAD RBVS committee.

Reference:

1. American Medical Association. RVS update process 2013. www.ama-assn.org/resources/doc/rbrvs/ruc-update-booklet.pdf. Accessed Oct. 14, 2013.

For more information:
www.ama-assn.org
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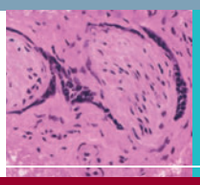

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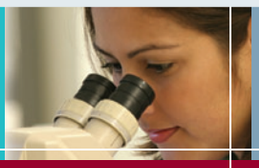

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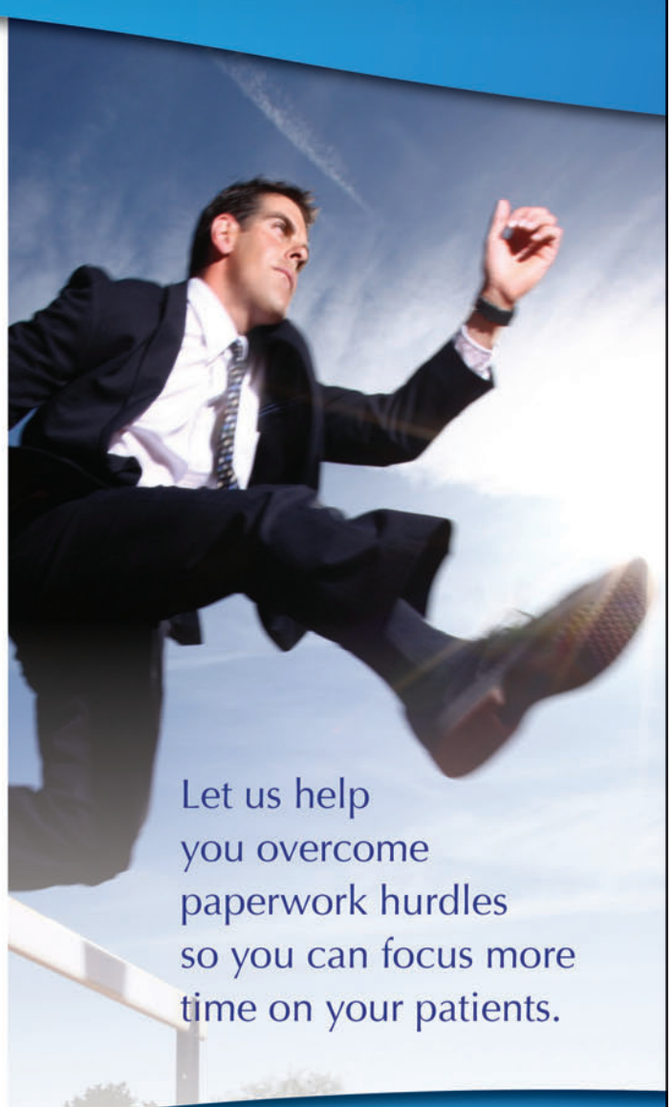

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4 DRUG RESOURCE APPS THAT AID PATIENT CARE

1 EPOCRATES RX

THIS APP helps dermatologists deliver accurate drug-related information to patients at the point-of-care. It's a quick reference tool that incorporates association guidelines, reference tables and calculator tools. It also gives access to prescribing and safety information for thousands of brand, generic and over-the-counter drugs, such as dosing for drugs that are approved by the Food and Drug Administration and those with off-label indications, black box warning, adverse reactions, drug interactions, pregnancy risk categories and more.

The app offers the ability to identify pills based on color, shape and imprint code. You can quickly find the drug-drug interactions for up to 30 drugs at one time. In addition, dermatologists can search an extensive listing of more than 700 physicians by specialty and clinical interest for referral or consult.

www.epocrates.com

2 LOCAL ANESTHESIA

THIS QUICK-reference calculator helps guide dermatologists in dosing with one or multiple local anesthetics. After inputting relevant patient information, the physician selects the agent and receives the maximum recommended dose in milligrams, maximum number of cartridges, the maximum dose milligrams/kilogram of patient weight, and milligrams/cartridge.

An overdose section allows dermatologists to calculate toxicity of one or more drugs and receive information detailing maximum toxic doses for each agent used.

www.altrasolution.com

3 MICROMEDEX DRUG INFORMATION

VISUALIZE Micromedex's suite of evidence-based findings as an easy to navigate mobile tool that allows dermatologists access to concise drug information, including dosing, indications, black box warnings, contraindications, drug interactions and adverse effects. It can be searched by using more than 4,500 search terms.

www.micromedex.com

4 TARASCON PHARMACOPOEIA

ANOTHER portable drug reference resource, this app also aims to help dermatologists make better decisions at the point of care by distilling and organizing hard-to-remember clinical information. This mobile-friendly version of its portable print pocket resource includes 47 drug reference tables, 15 calculators and peer-reviewed information on Food and Drug Administration-approved and off-label drug dosing, trade and generic formulations, and safety information.

www.tarascon.com

IMPORTANT INFORMATION ABOUT

Mirvaso®

(Brimonidine) Topical Gel, 0.33%*

*Each gram of gel contains 5 mg of brimonidine tartrate, equivalent to 3.3 mg of brimonidine free base

BRIEF SUMMARY

This summary contains important information about MIRVASO (Mer-VAY-Soe) Gel. It is not meant to take the place of the full Prescribing Information. Read this information carefully before you prescribe MIRVASO Gel. For full Prescribing Information and Patient Information please see package insert.

WHAT IS MIRVASO GEL?

MIRVASO (brimonidine) Topical Gel, 0.33% is a prescription medicine that is used on the skin (topical) to treat facial redness due to rosacea that does not go away (persistent).

WHO IS MIRVASO GEL FOR?

MIRVASO Gel is for use in adults ages 18 years and older.

WHAT WARNINGS AND PRECAUTIONS SHOULD I BE AWARE OF?

MIRVASO Gel should be used with caution in patients that:

- have depression
- have heart or blood vessel problems
- have dizziness or blood pressure problems
- have problems with blood circulation or have had a stroke
- have dry mouth or Sjögren's Syndrome
- have skin tightening or Scleroderma
- have Raynaud's phenomenon
- have irritated skin or open sores
- are pregnant or plan to become pregnant. It is not known if MIRVASO Gel will harm an unborn baby.
- are breastfeeding. It is not known if MIRVASO Gel passes into breast milk. You and your female patient should decide if she will use MIRVASO Gel or breastfeed. She should not do both.

Ask your patient about all the medicines they take, including prescription and over-the-counter medicines, skin products, vitamins and herbal supplements. Using MIRVASO Gel with certain other medicines may affect each other and can cause serious side effects.

Keep MIRVASO Gel out of the reach of children.

If anyone, especially a child, accidentally swallows MIRVASO Gel, they may have serious side effects and need to be treated in a hospital. Get medical help right away if you, your patient, a child, or anyone else swallows MIRVASO Gel and has any of these symptoms:

- **Lack of energy, trouble breathing or stops breathing, a slow heart beat, confusion, sweating, restlessness, muscle spasms or twitching.**

WHAT ARE THE POSSIBLE SIDE EFFECTS OF MIRVASO GEL?

The most common side effects of using MIRVASO Gel include:

- redness, flushing, burning sensation of the skin, skin irritation

Skin redness and flushing may happen about 3 to 4 hours after applying MIRVASO Gel. Ask your patients to tell you if they get skin redness and flushing that is uncomfortable.

MIRVASO Gel can lower blood pressure in people with certain heart or blood vessel problems. See **"What warnings and precautions should I be aware of?"**

These are not all of the possible side effects of MIRVASO Gel. Remind your patients to call you for medical advice about side effects.

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

HOW SHOULD MIRVASO GEL BE APPLIED?

- Remind your patients to use MIRVASO Gel exactly as you instruct them. They should not use more MIRVASO Gel than prescribed.
- Patients should not apply MIRVASO Gel to irritated skin or open wounds.
- **Important**: MIRVASO Gel is for use on the face only. Patients should not use MIRVASO Gel in their eyes, mouth, or vagina. They should also avoid contact with the lips and eyes.
- Instruct your patients to see the detailed Instructions for Use that come with MIRVASO Gel for information about how to apply MIRVASO Gel correctly.

GENERAL INFORMATION ABOUT THE SAFE AND EFFECTIVE USE OF MIRVASO GEL

Remind your patients not to use MIRVASO Gel for a condition for which it was not prescribed and to not give MIRVASO Gel to other people, even if they have the same symptoms. It may harm them.

WHAT ARE THE INGREDIENTS IN MIRVASO GEL?

Active Ingredient: brimonidine tartrate
Inactive Ingredients: carbomer homopolymer type B, glycerin, methylparaben, phenoxyethanol, propylene glycol, purified water, sodium hydroxide, titanium dioxide.

WHERE SHOULD I GO FOR MORE INFORMATION ABOUT MIRVASO GEL?

- Go to **www.mirvaso.com** or call **1-866-735-4137**

GALDERMA LABORATORIES, L.P.
Fort Worth, Texas 76177 USA
Revised: August, 2013
HCP

MIRVASO® (brimonidine) topical gel, 0.33%

GALDERMA Committed to the future of dermatology

Galderma Laboratories, L.P.
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Fort Worth, TX 76177
MIR-164B Printed in USA 08/13

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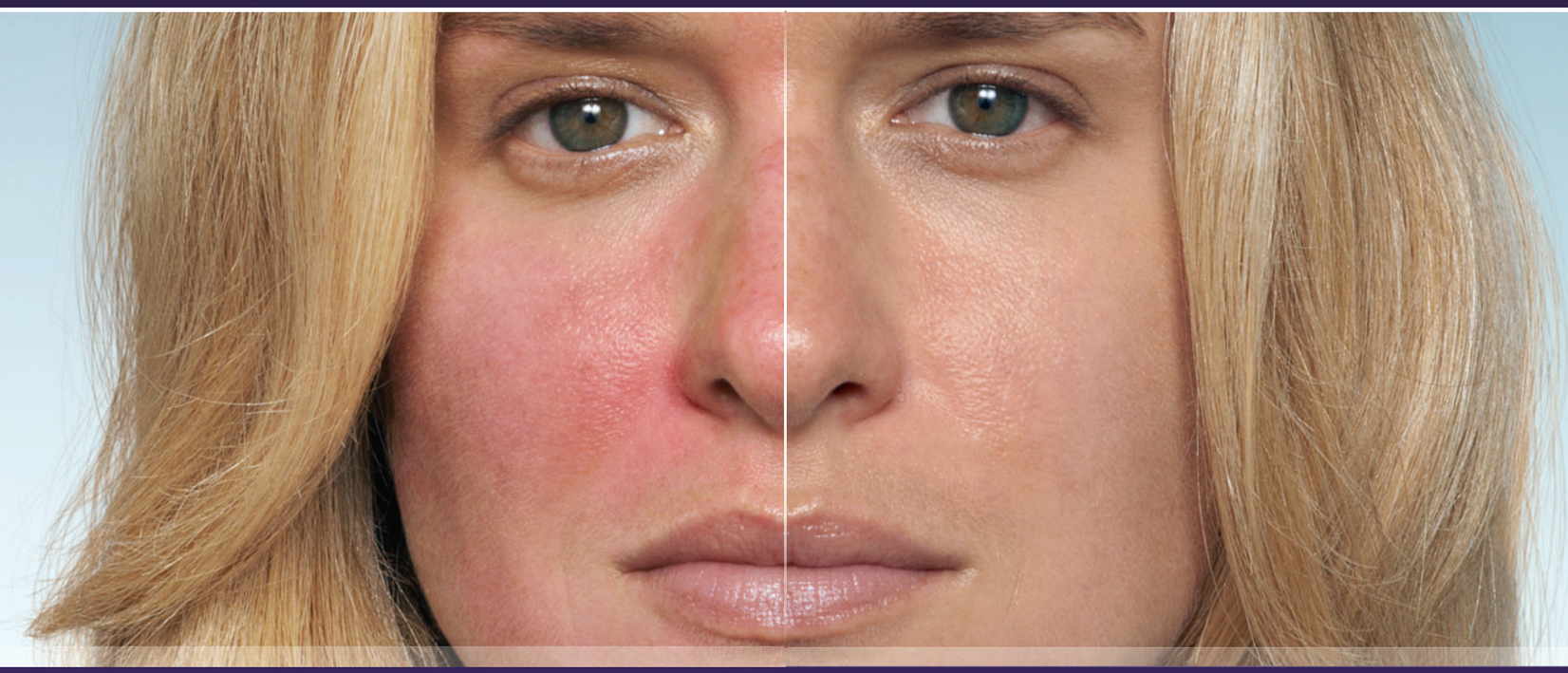
References: 1. Fowler J Jr, Jackson JM, Moore A, et al; Brimonidine Phase III Study Group. Efficacy and safety of once-daily topical brimonidine tartrate gel 0.5% for the treatment of moderate to severe facial erythema of rosacea: results of two randomized, double-blind, vehicle-controlled pivotal studies. *J Drugs Dermatol.* 2013;12(6):650-656. **2.** Mirvaso [package insert]. Galderma Laboratories, L.P. Fort Worth, TX; 2013.

Help your patients with facial erythema of rosacea experience...

THE MIRVASO EFFECT



Not an actual patient. Individual results may vary. Results are simulated to show a 2-grade improvement of erythema. At hour 12 on day 29, 22% of subjects using Mirvaso Gel experienced a 2-grade improvement of erythema compared with 9% of subjects using the vehicle gel.*

RAPID AND SUSTAINED ERYTHEMA REDUCTION BROUGHT TO YOU BY MIRVASO® (brimonidine) TOPICAL GEL, 0.33%†

- The **first** and **only** FDA-approved topical treatment specifically developed and indicated for the facial erythema of rosacea[1]
- Fast results that last up to **12 hours**[1]
- The most commonly reported adverse events in controlled clinical studies included erythema (4%), flushing (2%), skin-burning sensation (2%), and contact dermatitis (1%)[2]

Important Safety Information

Indication: Mirvaso® (brimonidine) topical gel, 0.33% is an alpha-2 adrenergic agonist indicated for the topical treatment of persistent (nontransient) facial erythema of rosacea in adults 18 years of age or older. **Adverse Events:** In clinical trials, the most common adverse reactions (≥1%) included erythema, flushing, skin-burning sensation, and contact dermatitis. **Warnings/Precautions:** Mirvaso Gel should be used with caution in patients with depression, cerebral or coronary insufficiency, Raynaud's phenomenon, orthostatic hypotension, thromboangiitis obliterans, scleroderma, or Sjögren's syndrome. Alpha-2 adrenergic agents can lower blood pressure. Mirvaso Gel should be used with caution in patients with severe or unstable or uncontrolled cardiovascular disease. Serious adverse reactions following accidental ingestion of Mirvaso Gel by children have been reported. **Keep Mirvaso Gel out of the reach of children.** Not for oral, ophthalmic, or intravaginal use.

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

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

See for yourself. Visit **www.mirvaso.com/hcp**.

MIRVASO®
(brimonidine) topical gel, 0.33%

*Phase 3 clinical studies of 553 subjects 18 and older. Subjects were randomized 1:1 to either Mirvaso Gel or vehicle for 29 days. Subjects and clinicians were asked to grade the improvement they saw at 30 minutes and hours 3, 6, 9, and 12 following application.

†Each gram of gel contains 5 mg of brimonidine tartrate equivalent to 3.3 mg of brimonidine free base.