# Follow Hemangiomas; Outcome Not Guaranteed

BY SHERRY BOSCHERT

San Francisco Bureau

LAS VEGAS — Telling parents that an infant's facial hemangioma will go away and doesn't need follow-up is no longer acceptable, Dr. Edward D. Buckingham said at an international symposium sponsored by the American Academy of Facial Plastic and Reconstructive Surgery.

Older studies that support the leave-italone approach defined "acceptable" cosmetic outcomes in ways that don't meet today's higher standards, said Dr. Buckingham of Austin, Tex.

Hemangiomas are benign tumors that evolve from an initial proliferative phase to a second phase of involution, in which the tumor gradually disappears. Complications can include scars from ulcerations, epidermal atrophy from thinning of the skin as the tumor grows, cosmetic distortion of facial features, residual telangiectasias, redundant skin after involution, or cartilage destruction by some hemangiomas around the ear or nose.

In the half of children with hemangiomas who show significant ("early") involution before age 5, 38% had "imperfect" cosmetic outcomes, one 1983 study found. In the other half of children whose hemangiomas did not show significant ("late") involution by 5 years of age, 80% had imperfect cosmetic outcomes.

Once the hemangioma stops proliferating, the rate of involution can give a sense of the likelihood of an acceptable cosmetic outcome without medical or surgi-

Observation alone may be adequate management for small hemangiomas in clinically insignificant cosmetic areas, but this does not mean forgetting about the lesion. All birthmarks that develop during the first month of life should be evaluated by a specialist and followed through serial evaluations, Dr. Buckingham said.

There are reasons to treat many hemangiomas during the proliferative or involution phases with the goals of preventing the lesion from getting larger than it needs to be and achieving the best cosmetic results by age 2 or 3 years, when children begin to form a self-image, he said.

Evaluation by a specialist also is key to proper diagnosis of hemangiomas, which commonly are confused with port wine stains, said Dr. Marcelo Hochman. Port wine stains are venous malformations. not tumors, and require different and more difficult treatment.

Hemangiomas occur in 4%-10% of white newborns, with girls four times more likely than boys to develop the lesions. Most hemangiomas develop on the head or neck. Diagnosis is made by histo-Continued on following page

# **Hemangiomas:** Fact vs. Fiction

onfusion about the differences between vascular malformations and hemangiomas abound. Many physicians entertain the following common misconceptions about hemangiomas, Dr. Hochman said:

Myth: Hemangiomas are big bags of blood, so surgical resection carries a big risk of bleeding.

Reality: Hemangiomas are solid tumors. Surgical removal is relatively

Myth: There are numerous and tortuous feeder vessels in hemangiomas that require embolization.

Reality: Hemangiomas typically have one feeder vessel that's easily isolated. "This is very low-tech surgery," Dr. Hochman said.

Myth: Hemangiomas infiltrate surrounding tissues and are difficult

Reality: Hemangiomas can push tissue out of the way, giving the impression of infiltration, but there is always a plane between the tumor and surrounding normal tissues. Dissection is relatively easy in discrete planes that occur naturally and can be created between the superficial and deep components of the hemangioma, or in the deep component, or within the fibrofatty residuum of skin and scar tissue.

Dr. Hochman cautioned that while these myths don't apply to apply to hemangiomas, they may apply to malformations like port wine

# BRIEF SUMMARY

Revised: January 2006

# Protopic<sup>®</sup>

FOR DERMATOLOGIC USE ONLY NOT FOR OPHTHALMIC USE

RX Only
See boxed WARNING concerning long-term safety of topical calcineurin inhibitors

topical calcineurin inhibitors

INDICATIONS AND USAGE
PROTOPIC Ointment, both 0.03% and 0.1% for adults, and only 0.03% for children aged 2 to 15 years, is indicated as second-line therapy for the short-term and non-continuous chronic treatment of moderate to severe atopic dermatitis in non-immunocompromised adults and children who have failed to respond adequately to other topical prescription treatments or adoptic dermatitis, or when those treatments are not advisable.

PROTOPIC Ointment is not indicated for children younger than 2 years of age (see boxed WARNING, WARNINGS and PRECAUTIONS: Pediatric Use).

CONTRAINDICATIONS
PROTOPIC (tacrolimus) Ontment is contraindicated in patients with a history of hypersensitivity to tacrolimus or any other component of the ointment.

# WARNING

# Long-term Safety of Topical Calcineurin Inhibitors Has Not Been Established

Although a causal relationship has not been established, rare cases of malignancy (e.g., skin and lymphoma) have been reported in patients treated with topical calcineurin inhibitors, including PROTOPIC Ointment.

- nerefore:
  Continuous long-term use of topical calcineurin inhibitors including PROTOPIC Dintment, in any age group should by avoided, and application limited to areas of involvemen with atopic dermatitis.

Prolonged systemic use of calcineurin inhibitors for sustained immunosuppression in animal studies and transplant patients following systemic administration has been associated with an increased risk of infections, lymphomas, and skin malignancies. These risks are associated with the intensity and duration of immunosuppression.

- If signs and symptoms of atopic dermatitis do not improve within 6 weeks, patients should be re-examined by their healthcare provider and their diagnosis be confirmed (see PRECAUTIONS: General).
- The safety of PROTOPIC Ointment has not been established beyond one year of non-continuous use.

  (See boxed WARNING, INDICATIONS AND USAGE, and DOSAGE AND ADMINISTRATION).

# PRECAUTIONS

General The use of PROTOPIC Ointment should be avoided on pre-malignant and malignant skin conditions. Some malignant skin conditions, such as cutaneous T-cell lymphoma (CTCL), may mimic atopic dermatitis.

patients with generalized erythroderma. The use of PROTOPIC ointment may cause local symptoms such as skin burning (burning sensation, stinging, soreness) or pruritus. Localized symptoms are most common during the first tew days of PROTOPIC ointment application and typically improve as the lesions of atopic dermatitis resolve. With PROTOPIC ointment 0.1%, 90% of the skin burning events had a duration between 2 minutes and 3 hours (median 15 minutes), 90% of the pruritus events had a duration between 3 minutes and 10 hours (median 20 minutes). (see ADVERSE REACTIONS).

(INEURIA 20 INITIOLES), (See ADVENSE REACTIONS).

Bacterial and Viral Skin Infections

Before commencing treatment with PROTOPIC Ointment, 
cutaneous bacterial or viral infections at treatment sites should be 
resolved. Studies have not evaluated the safety and efficacy 
of PROTOPIC Ointment in the treatment of clinically infected 
variety demotifies.

of PROTUPIC Unturieur in the adoption of PROTUPIC Unturieur in the adoption dermatitis.

While patients with atopic dermatitis are predisposed to superficial skin infections including eczema herpeticum (Kaposi's varicelliform eruption), treatment with PROTOPIC Ointment may be independently associated with an increased risk of varicella zoster virus infection (chicken pox or shingles), herpes simplex virus infection, or eczema herpeticum.

virus inection, or eczema nerpeticum.

Patients with Lymphadenopathy
In clinical studies, 112/13494 (0.8%) cases of lymphadenopathy
were reported and were usually related to infections, Garicularly
of the skin) and noted to resolve upon appropriate antibiotic
therapy, Of these 112 cases, the majority had either a clear etiology
or were known to resolve. Transplant patients receiving
immunosuppressive regimens (e.g., systemic lacrolimus) are at

increased risk for developing lymphoma; therefore, patients who receive PROTOPIC Dintment and who develop lymphadenopathy should have the etiology of their lymphadenopathy in the absence of a clear etiology for the lymphadenopathy, or in the presence of acute infectious mononucleosis, PROTOPIC Dintment should be discontinued. Patients who develop lymphadenopathy should be monitored to ensure that the lymphadenopathy resolves.

Immunocompromised Patients
The safety and efficacy of PROTOPIC Ointment in immunocompromised patients have not been studied.

The safety and emicacy or PROTOPIC Unimment in immunocompromised patients have not been studied.

Renal Insufficiency

Rare post-marketing cases of acute renal failure have been reported in patients treated with PROTOPIC Ontiment. Systemic absorption is more likely to occur in patients with epidermal barrier defects especially when PROTOPIC is applied to large body surface areas. Caution should also be exercised in patients predisposed to renal impairment.

Information for Patients
(See Medication Guide)
Patients using PROTOPIC Ointment should receive and
understand the information in the Medication Guide. Please refer
to the Medication Guide for providing instruction and information to
the partient.

to the patient.

What is the most important information patients should know about PROTOPIC Dintment?

The safety of using PROTOPIC Ointment for a long period of time is not known. A very small number of people who have used PROTOPIC Ointment have had cancer (for example, skin or lymphoma). However, a link with PROTOPIC Ointment has not been shown. Because of this concern, instruct patients:

Do not use PROTOPIC Ointment continuously for a long time.

Use PROTOPIC Ointment only on areas of skin that have eczema.

Do not use PROTOPIC Ointment on a child under 2 years old.

PROTOPIC Dintment comes in two strenaths:

- PROTOPIC Ointment comes in two strengths:
  Only PROTOPIC Ointment 0.03% is for use on children aged 2 to 15 years.
- Either PROTOPIC Ointment 0.03% or 0.1% can be used by adults and children 16 years and older.

Advise patients to talk to their prescriber for more information.

# How should PROTOPIC Ointment be used? Advise patients to:

- Use PROTOPIC Ointment exactly as prescribed.
- . Use PROTOPIC Ointment only on areas of skin that
- Use PROTOPIC Ointment for short periods, and if needed, treatment may be repeated with breaks in between.
- Stop PROTOPIC Ointment when the signs and symptoms of eczema, such as itching, rash, and redness go away, or as
- Follow their doctor's advice if symptoms of eczema return after treatment with PROTOPIC Ointment.
- Call their doctor if:
- Their symptoms get worse with PROTOPIC Ointment. . They get an infection on their skin.
- Their symptoms do not improve after 6 weeks of treatment. Sometimes other skin diseases can look like eczema.

# To apply PROTOPIC Ointment:

- Apply a thin layer of PROTOPIC Ointment twice daily to the areas of skin affected by eczema.

  Use the smallest amount of PROTOPIC Ointment needed to control the signs and symptoms of eczema.
- through the signs and symptoms on exemia. If they are a caregiver applying PROTOPIC Ointment to a patient, or if they are a patient who is not treating their hands, wash their hands with soap and water after applying PROTOPIC. This should remove any ointment left on the hands.
- Do not bathe, shower, or swim right after applying PROTOPIC. This could wash off the ointment.
- This could wash off the ointment.

  Moisturizers can be used with PROTOPIC Ointment. Make sure they check with their doctor first about the products that are right for them. Because the skin of patients with ezema can be very dry, it is important to keep up good skin care practices. If they use moisturizers, apply them after PROTOPIC Ointment.

# What should patients avoid while using PROTOPIC Dintment?

- Do not use ultraviolet light therapy, sun lamps, or tanning beds during treatment with PROTOPIC Ointment.
- Limit sun exposure during treatment with PROTOPIC Ointment even when the medicine is not on their skin. If patients need to be outdoors after applying PROTOPIC Ointment, wear loose fitting clothing that protects the treated area from the sun. Doctors should advise what other types of protection from the sun patients should use.
- waps: Talicitis can wear from a cooling.

  Avoid getting PROTOPIC Ointment in the eyes or mouth. Do not swallow PROTOPIC Ointment. Patients should call their doctor if they swallow PROTOPIC Ointment.

they swallow PROTOPIC Ointment. **Drug Interactions**Formal topical drug interaction studies with PROTOPIC Ointment have not been conducted. Based on its extent of absorption, interactions of PROTOPIC Ointment with systemically administered drugs are unlikely to occur but cannot be ruled out. The concomitant administration of known CYP3A4 inhibitors in patients with widespread and/or enythrodermic disease should be done with caution. Some examples of such drugs are erythromycin, itraconazole, ketoconazole, fluconazole, calcium channel blockers and cimetidine.

Carcinogenesis, Mutagenesis, Impairment of Fertility
No evidence of genotoxicity was seen in bacterial (Salmonella and
E. coli) or mammalian (Chinese hamster lung-derived cells) in
vitro assays of mutagenicity, the in vitro CHO/HGPRT assay
of mutagenicity, or in vivo clastogenicity assays performed in
mice. Tacrolimus did not cause unscheduled DNA synthesis in

Reproductive toxicology studies were not performed with

Pregnancy
Teratogenic Effects: Pregnancy Category C
There are no adequate and well-controlled studies of topically administered facorilmus in pregnant women. The experience with PROTOPIC Ointment when used by pregnant women is too limited to permit assessment of the safety of its use during pregnancy. to permit assessment or the salety of us be during prejaratory. There are no adequate and well-controlled studies of systemically administered tacrolimus in pregnant women. Tacrolimus is transferred across the placenta. The use of systemically administered tacrolimus during pregnancy has been associated with neonatal hyperkalemia and renal dysfunction. PROTOPIC Ointment should be used during pregnancy only if the potential benefit to the mother justifies a potential risk to the fetus.

Nursing Mothers
Although systemic absorption of tacrolimus following topica applications of PROTOPIC Ointment is minimal relative to applications of PROTOPIC Ointment is minimal relative to systemic administration, it is known that tacrollimus is excreted in human milk. Because of the potential for serious adverse reactions in nursing intents from tacrollimus, 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.

Pediatric Use

Pediatric Use
PROTOPIC Ointment is not indicated for children less
than 2 years of age.

Only the lower concentration, 0.03%, of PROTOPIC Ointment is
recommended for use as a second-line therapy for short-term and
non-continuous chronic treatment of moderate to severe adopt
cermatitis in non-immunocompromised children 2 to 15 years of
age who have failed to respond adequately to other topical
prescription treatments for atopic dermatitis, or when those
treatments are not advisable.
The long-term safety and effects of PROTOPIC Ointment
on the developing immune system are unknown (see

NARNING, WARNINGS and INDICATIONS AND USAGE:

The most common adverse events associated with PROTOPIC Dintment application in pediatric patients were skin burning and pruritus (see ADVERSE REACTIONS). In addition to skin burning and pruritus, the less common events (< 5%) of varicella coster (mostly chicken pox), and vesiculobulous rash were more frequent in patients treated with PROTOPIC Dintment 0.03% compared to vehicle. In the open-label safely studies, the incidence of adverse events, including infections, did not increase with increased duration of study drug exposure or amount of onlinent used. In about 4,400 pediatric patients treated with PROTOPIC Ointment, 24 (0.5%) were reported with eczema expedicum. Since the safety and efficacy of PROTOPIC Dintment have not been established in pediatric patients below 2 years of age, its use in this age group is not recommended.

Geriatric Use

No phototoxicity and no photoallergenicity were detected in clinical studies with 12 and 216 normal volunteers, respectively. One out of 198 normal volunteers showed evidence of sensitization in a contact sensitization study. The following table depicts the adjusted incidence of adverse events pooled across the 3 identically designed 12-week controlled studies for patients in vehicle, PROTOPIC Ointment 0.3%, and PROTOPIC Ointment 0.1% treatment groups. The table also depicts the unadjusted incidence of adverse events in four safety studies, regardless of relationship to study drug.

	12-Week, Randomized, Double-Blind, Phase 3 Studies 12-Week Adjusted Incidence Rate (%)					(up to 3 years) 0.1% and 0.03% Tacrolimus Ointment Incidence Rate (%)		
	Adult			Pediatric		Adult Pediatric Total		
	Vehicle	0.03%	0.1%	Vehicle	0.03%	(0+4682)	(n=4481)	(n=916
	(8×212) %		Tacrolimus Dintment (n=209) %	(n=115) %	Tacrolimus Dintment (n=118) %	%	5	5
Skin Burninat	26	46	58	29	43	28	20	24
Pruritus†	37	46	46	27	41	25	19	22
Flu-like symptoms†	19	23	31	25	28	22	34	28
Allergic Reaction	8	12	6	8	4	9	13	11
Skin Ervthema	20	25	28	13	12	12	7	9
Headachet	11	20	19	- 8	5	13	9	- 11
Skin Infection	11	12	5	14	10	9	16	12
Fever	4	4	1	13	21	2	14	8
Infection	1	1	2	9	7	6	10	8
Cough Increased	2	1	1	14	18	3	10	6
Asthma	4	6	4	6	6	4	13	8
Herpes Simplex	4	4	4	2	0	4	3	3
Eczema Herpeticum	0	1	1	0	2	0	0	0
Pharyngitis	3	3	4	11	6	4	12	8
Accidental Injury	4	3	6	3	6	6	8	7
Pushular Bash	2	3	4	3	2	2	7	5
Folliculitis†	1	6	4	0	2	4	2	3
Rhinitis	4	3	2	2	6	2	4	3
Otitis Media	4	0	1	6	12	2	11	6
Sinusitis†	1	4	2	8	3	6	7	6
Diarrhea	3	3	4	2	5	2	4	3
Urticaria	3	3	6	1	1	3	4	4
Lack of Drug Effect	1	1	0	1	1	6	6	6
Bronchitis	ò	2	2	3	3	4	4	4
Vomiting	0	1	1	7	6	1	4	3
Maculopapular Rash	2	2	2	3	0	2	1	1
Rasht	1	5	2	4	2	2	3	3
Abdominal Pain	3	1	1	2	3	1	3	2
Fungal Dermatitis	0	2	1	3	0	2	4	3
Gastroenteritis	1	2	2	3	Ö	2	4	3
Alcohol Intolerance†	0	3	7	0	0	4	0	2
Acnet	2	4	7	1	ő	3	2	3
Sunhum	1	2	1	0	0	2	1	1
Skin Disorder	2	2	1	1	4	2	2	2
Conjunctivitis	0	2	2	2	1	3	3	3
Pain	1	2	1	0	1	2	1	2
Vesiculobullous Rasht	3	3	2	0	4	2	1	1
Lymphadenopathy	2	2	1	0	3	1	2	1
Nausea	4	3	2	0	1	2	1	2
Skin Tingling†	2	3	8	1	2	2	1	1
Face Edema	2	2	1	2	1	1	1	1
Dyspensia†	1	1	4	0	i	2	2	2

# the Generally "warfs." Other adverse events which occurred at an incidence between 0.2% and less than 1% in clinical studies in the above table include: abnormal vision, abscess, anaphylactoid reaction, anemia, anorexia, axivity, arthritis, arthross, billivubinemia, blenbartis, bone disorder, breast neoplasm benign, burstils, cataract NOS, chest pain, chills, collis, conjunctival delarea, constigation, cramps, cutaneous monillasis, cyslitis, dehydration, dizziness, dry eyes, dry mouth/nose, dyspnea, ear disorder, ecchymosis, ederna, epistaxis, eye pain, hurunculosis, spatintis, gastriointestinal disorder, hamia, hypercholesterolenia, hypetroina, hypothyroidism, joirt disorder, tanyngitis, leukoderma, lung disorder, malaise, migraine, monillasis, motiva ceration, raid disorder, neck pain, neoplasm benign, oral monillasis, ottis externa, skin discoloration, skin hypetrophy, skin ulcer, stomatitis, tendon disorder, thinking abnormal, tooth caries, sweating, syncope, tachypardia, taste perversion, unintended pregnancy, vaginal monillasis, vaginitis, valvular heart disease, vasodilatation, and vertigo. OVERDOSAGE

OVERDOSAGE
PROTOPIC Ointment is not for oral use. Oral ingestion
PROTOPIC Ointment may lead to adverse effects associated v
systemic administration of taronlimus. If oral ingestion occ
medical advice should be sought.

# DOSAGE AND ADMINISTRATION

# PROTOPIC Ointment 0.03% and 0.1%

aduptive initiatius.

The safety of PROTOPIC Ointment under occlusion, which may promote systemic exposure, has not been evaluated. PROTOPIC Ointment should not be used with occlusive dressings.

PEDIATRIC - FOR CHILDREN 2-15 YEARS

# PROTOPIC Ointment 0.03% \*\*PROTOPIC Ointment 0.03%\* Apply a thin layer of PROTOPIC (tacrolimus) Ointment, 0.03% to the affected skin twice daily. The minimum amount should be rubbed in gently and completely to control signs and symptoms of atopic dermatitis. Stop using when signs and symptoms of atopic dermatitis resolve.

- If signs and symptoms (e.g., itch, rash, and redness) do not improve within 6 weeks, patients should be re-examined by their healthcare provider to confirm the diagnosis of
- application strough de limited to areas of involvement win atopic dermatitis.

  The safety of PROTOPIC Dintment under occlusion, which may promote systemic exposure, has not been evaluated. PROTOPIC Dintment should not be used with occlusive dressings.

Astellas Pharma Manufacturing, Inc. Grand Island, NY 14072

PRT24818

# Incidence of Treatment Emergent Adverse Events

# Low-Level Energy Therapy Aids Wound Care

BY KERRI WACHTER

Senior Writer

ORLANDO — Low-level energy is an effective technique for enhancing wound healing, said Dr. Robert F. Jackson, who offered a few postsurgery tips at the annual meeting of the American Academy of Cosmetic Surgery.

Dr. Jackson, a practicing cosmetic surgeon in Marion, Ind., focused on the use of ultrasonic massage, electrical stimulation, and low-level laser therapy.

After liposuction, external ultrasonic massage can correct minor irregularities, decrease edema, and help prevent long-term induration, he said. The therapy also stimulates tissue and wound healing.

Dr. Jackson typically starts this therapy 1 week after surgery and treats patients twice weekly until the induration is gone. He uses a level of  $2\,\mathrm{W/cm^2}$  continuous for 6 minutes per area on the extremities, and 20 minutes for the abdomen and back.

"If you've got induration that you haven't really treated for a long time, you can still treat it, but at that point you'll also have to mechanically stretch the tissue as you use the ultrasonic therapy," Dr. Jackson said.

"It's a very good marketing tool—my patients enjoy it," he said.

When used after cosmetic surgery procedures, electric stimulation improves blood flow, increases wound tensile strength, reduces edema, inhibits bacterial growth, and reduces pain. The primary

Continued from previous page

ry and physical exam; ultrasound imaging should be performed if more than three hemangiomas are present to check for involvement of the liver or spleen, said Dr. Hochman of Charleston, S.C.

Dr. Buckingham warned that hemangiomas on the upper or lower eyelid can endanger vision permanently and deserve referral to a pediatric ophthalmologist.

There is no consensus on treating hemangiomas. Photodynamic therapy (PDT), steroids, and surgery are the main treatment options. Treat superficial or rapidly proliferating hemangiomas every 4-8 weeks with PDT, a safe option with very little risk of scarring, he said.

PDT on the area around an ulcerated hemangioma can help heal the ulcer, data show. Retreat every 4-6 weeks if needed, Dr. Buckingham suggested. PDT also cleans up residual telangiectasias.

For deep hemangiomas, inject steroids into the lesion or try a 10-week course of oral steroids during proliferation; expect a 30%-90% response. Combine steroids and photodynamic therapy for compound lesions. Refer children on oral steroids to an endocrinologist for weekly evaluation.

Reserve surgical debulking for cleanup during involution, or during the proliferative phase for hemangiomas that don't respond to steroids or that threaten vision.

"You don't have to get every bit of tissue out. These are benign tumors in young children, and we have plenty of opportunity in ensuing years to clean things up," Dr. Hochman said.

purpose, however, is to reduce postoperative pain and edema, Dr. Jackson said. Electric stimulation immediately reduces swelling and improves wound healing. And ultimately, the technique improves the end result of the surgery.

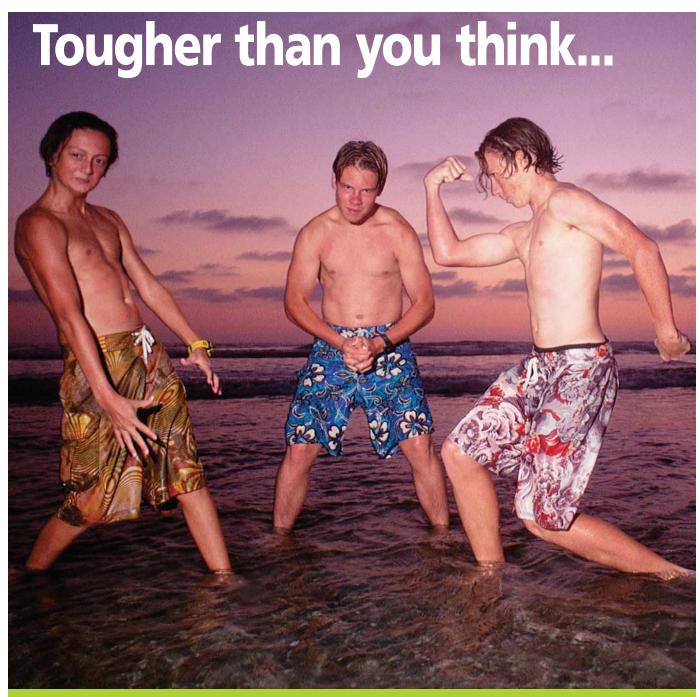
"The Department of Health and Human Services tested all of the adjunctive therapies for pressure sores. ... The only [therapy] they recommended for wound care management was the use of electric stimulation," he said.

Dr. Jackson typically starts this therapy the day after surgery and treats patients twice a week in 20-minute sessions until the wounds are satisfactorily healed. He recommends starting with an intensity of 100 pulses per second and increasing the intensity until the patient can feel the pulsation. Use this intensity for a few minutes and then increase the intensity until it just becomes uncomfortable for the patient. Then reduce the intensity gradually.

Low-level laser therapy is a relatively

new modality that involves the application of low-power monochromatic and coherent light to injuries and lesions. This therapy is believed to promote blood vessel growth. Dr. Jackson uses low-level laser therapy for wound and ulcer healing. The therapy also reduces pain after surgery.

He uses a 635-nm laser for 8 minutes to enhance wound healing. For incision healing, he treats patients once or twice weekly for 3 weeks. Treatments for ulcers continue until healing is complete.



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Although mostly mild, dryness, erythema, burning, or pruritus were experienced by 10% to 52% of patients depending upon formulation. Concomitant use of potentially irritating products or overexposure to sunlight, sunlamps, or extreme wind or cold may increase potential for irritation. Use of sunscreen and protective clothing over treated areas is recommended when exposure cannot be avoided.

Please see next page for brief summary of Prescribing Information.

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