A closer look at...

ACNE
For the first-line treatment of inflammatory and comedonal acne

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The only, once-daily adapalene/benzoyl peroxide combination—in a patient-preferred PUMP.

- 78% of acne patients preferred the PUMP over the tube
- 92% of acne patients reported satisfaction with the PUMP

Measured dose for consistent delivery.

*Survey of 291 patients 12 to 35 years of age who completed a randomized study of Epiduo® Gel tube vs pump after 1 week of treatment with each dispenser.

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Please see brief summary of Prescribing Information on next page.
ADVERSE REACTIONS
Observed local adverse reactions in patients treated with EPIDUO Gel were erythema, scaling, dryness, stinging, and burning. Other most commonly reported adverse events (≥1%) in patients treated with EPIDUO Gel were dry skin, contact dermatitis, application site burning, application site irritation, skin irritation.

DRUG INTERACTIONS
Exercise caution in using preparations containing sulfur, resorcinol, or salicylic acid, medicated or abrasive soaps and cleansers and products with high concentrations of alcohol or astringents in combination with EPIDUO Gel. Concomitant use of topical products with a strong drying effect can increase irritation. Use with caution.

Pregnancy
Pregnancy Category C. There are no well-controlled trials in pregnant women treated with EPIDUO Gel. Animal reproduction studies have not been conducted with the combination gel or benzoyl peroxide. Furthermore, such studies are not always predictive of human response; therefore, EPIDUO Gel should be used during pregnancy only if the potential benefit justifies the risk to the fetus. No teratogenic effects were observed in rats treated with oral doses of 0.15 to 5.0 mg adapalene/kg/day, up to 25 times (mg/m²/day) the maximum recommended human dose (MRHD) of 2 grams of EPIDUO Gel. However, teratogenic changes were observed in rats and rabbits when treated with oral doses of a 25 mg adapalene/kg/day representing 123 and 246 times MRHD, respectively. Findings included cleft palate, microphthalmia, encephalocele and skeletal abnormalities in rats; and umbilical hernia, exophthalmos and kidney and skeletal abnormalities in rabbits. Dermal teratology studies conducted in rats and rabbits at doses of 0.6-6.0 mg adapalene/kg/day (25-59 times (mg/m²)) the MRHD exhibited no fetotoxicity and only minimal increases in supernumerary ribs in both species and delayed ossification in rabbits.

Nursing Mothers
It is not known whether adapalene or benzoyl peroxide is excreted in human milk following use of EPIDUO Gel. Because many drugs are excreted in human milk, caution should be exercised when EPIDUO Gel is administered to a nursing woman.

Pediatric Use
Safety and effectiveness of EPIDUO Gel in pediatric patients under the age of 12 have not been established.

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

Carcinogenesis, Mutagenesis, Impairment of Fertility
No carcinogenicity, photocarcinogenicity, genotoxicity, or fertility studies were conducted with EPIDUO Gel.

Carcinogenicity studies with adapalene have been conducted in mice at topical doses of 0.4, 1.3, and 4.0 mg/kg/day (1.2, 3.9, and 12 mg/m²/day), and in rats at oral doses of 0.15, 0.5, and 1.5 mg/kg/day (0.9, 3.0, and 9.0 mg/m²/day). In terms of body surface area, the highest dose levels are 9.8 (mice) and 7.4 times (rats) the MRHD of 2 grams of EPIDUO Gel. In the rat study, an increased incidence of benign and malignant pheochromocytomas in the adrenal medulla of male rats was observed. No significant increase in tumor formation was observed in rodents topically treated with 15-25% benzoyl peroxide carbopol gel (6-10 times the concentration of benzoyl peroxide in EPIDUO Gel) for two years. Rats received maximum daily applications of 136 (males) and 205 (females) mg benzoyl peroxide/kg. In terms of body surface area, these levels are 27-40 times the MRHD. Similar results were obtained in mice topically treated with 25% benzoyl peroxide carbopol gel for 56 weeks followed by intermittent treatment with 15% benzoyl peroxide carbopol gel for rest of the 2 years study period, and in mice topically treated with 5% benzoyl peroxide carbopol gel for two years.

The role of benzoyl peroxide as a tumor promoter has been well established in several animal species. However, the significance of this finding in humans is unknown. In a photocarcinogenicity study conducted with 5% benzoyl peroxide carbopol gel, no increase in UV-induced tumor formation was observed in hairless mice topically treated for 40 weeks. No photocarcinogenicity studies were conducted with adapalene. However, animal studies have shown an increased tumorigenic risk with the use of pharmacologically similar drugs (e.g., retinoids) when exposed to UV irradiation in the laboratory or sunlight. Although the significance of these findings to humans is not clear, patients should be advised to avoid or minimize exposure to either sunlight or artificial irradiation sources. Adapalene did not exhibit mutagenic or genotoxic effects in vitro (Ames test, Chinese hamster ovary cell assay, mouse lymphoma TK assay) or in vivo (mouse micronucleus test). Bacterial mutagenicity assays (Ames test) with benzoyl peroxide has provided mixed results, mutagenic potential was observed in a few but not in a majority of investigations. Benzoyl peroxide has been shown to produce single-strand DNA breaks in human bronchial epithelial and mouse epidermal cells, it has caused DNA-protein cross-links in the human cells, and has also induced a dose-dependent increase in sister chromatid exchanges in Chinese hamster ovary cells. In rat oral studies, 20 mg adapalene/kg/day (120 mg/m²/day; 98 times the MRHD based on mg/m²/day comparison) did not affect the reproductive performance and fertility of F1 males and females, or growth, development and reproductive function of F1 offspring. No fertility studies were conducted with benzoyl peroxide.

PATIENT COUNSELING INFORMATION
– Advise patients to cleanse the area to be treated with a mild or soapless cleanser; pat dry. Apply EPIDUO Gel as a thin layer, avoiding the eyes, lips and mucous membranes.
– Advise patients to use more than the recommended amount and not to apply more than once daily. The recommended amount is usually sufficient for the entire face and neck. If more is needed, apply to larger areas of the face and neck.
– Advise patients to minimize exposure to sunlight, including sunlamps. Recommend the use of sunscreen products and protective apparel, (e.g., hat) when exposure cannot be avoided.
– Advise patients to avoid exposure to sunlight, including sunlamps. Recommend the use of sunscreen products and protective apparel, (e.g., hat) when exposure cannot be avoided.
– EPIDUO Gel may bleach hair and colored fabric.

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Fort Worth, Texas 76177 USA
Manufactured by: G Production Inc.
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References:

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For Topical Use Only
Not For Ophthalmic, Oral, or Intravaginal Use.

BRIEF SUMMARY
INDICATIONS AND USAGE
EPIDUO Gel is a combination of adapalene, a retinoid, and benzoyl peroxide, and is indicated for the topical treatment of acne vulgaris in patients 12 years of age and older.

CONTRAINDICATIONS
None.

WARNINGS AND PRECAUTIONS
Ultraviolet Light and Environmental Exposure: Avoid exposure to sunlight and sunlamps. Wear sunscreen when sun exposure cannot be avoided. Erythema, scaling, dryness, and stinging/burning may occur with use of EPIDUO Gel.

Erythema, scaling, dryness, and stinging/burning may occur with use of EPIDUO Gel.

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Hormonal therapies serve as key adjunct acne treatment

Dermatologists have known for years that hormonal therapies, such as oral contraceptives (OCs), are an effective treatment for acne, particularly for resistant acne in adult women. Despite that, they are not a first line of therapy and are commonly used in combination with traditional treatments. Other hormonal therapies, namely spironolactone, are increasingly being used to treat this subset of acne patients, as well.

For nearly 50 years, birth control pills have been used off-label to treat largely resistant acne in adult women, noted Alan Shalita, MD, distinguished teaching professor and chair of the department of dermatology at the SUNY Downstate Medical Center in Brooklyn. Oral contraceptives containing both estrogen and progestin decrease ovulatory-related ovarian androgen production and free testosterone, the latter of which drives the sebaceous glands, while increasing sex hormone-binding globulin (SHBG). Estrogen may play a more extensive role, he added, noting it is possible that androgen receptors are in the follicle wall. Using a different mechanism of action, spironolactone is an antiandrogen and aldosterone antagonist that competes with 5-α dihydrotestosterone for androgen receptors in the skin. Thus, spironolactone inhibits testosterone and 5-α dihydrotestosterone binding and also increases SHBG.

In the past decade, the use of OCs has most likely increased, particularly among dermatologists, as a result of the Food and Drug Administration’s approval of four OCs for acne treatment. But as Julie Harper, MD, clinical associate professor at the University of Alabama in Birmingham, points out, the use of all combination estrogen and progestin OCs results in an increase in SHBG and a resultant decrease in free testosterone.
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Some of the newer OCs contain drospirenone (DRSP), which differs from the classic progestins in its derivation from spironolactone, noted Aleksandar L. Krunic, MD, PhD, associate professor of dermatology and director of dermatologic surgery at the University of Illinois College of Medicine, adjunct associate professor of dermatology at Northwestern University’s Feinberg School of Medicine in Chicago, and one of the authors of a study on DRSP and spironolactone (J Am Acad Dermatol 2008;58:602-2). These DRSP-containing OCs exhibit partial antiandrogenic activity, but lack androgenic effect, he explained. They regulate the menstrual cycle and result in lighter, less painful periods as well as reduced sebum production and hair growth, and often improve acne by the third cycle. (On April 11, the FDA announced additional warnings for some DRSP-containing OCs because a review indicated they have three times the risk of other OCs of causing blood clots.)

SUBSET OF PATIENTS
Candidates for hormonal therapy are women beyond menarche with evidence of hormone-related acne, late-onset acne, and/or menstrual flares. Those who are unresponsive to conventional therapies and need oral contraception for gynecologic/birth control reasons also are good candidates.

“...the first line of therapy unless they have signs of androgen-related acne right away and they need contraception...”

The classic example of hormonal acne is a concentration of lesions along the chin, jawline, lower face, and neck, according to Diane Berson, MD, assistant clinical professor on faculty at the Weill Medical College of Cornell University at New York Presbyterian Hospital. These women tend to have premenstrual breakouts with or without menstrual irregularities and hirsutism.

Jim Leyden, MD, emeritus professor of dermatology at the University of Pennsylvania’s School of Medicine, prescribes OCs more freely in women with hormone-related acne in their late teens and 20s. But if a younger teenager is not responding to the traditional therapies, he will consider it an option. The same is true of spironolactone. Prescribing the latter is an easy way of offering hormonal treatment without getting into dicey questions about “the pill” with mothers and daughters, he said. Dr. Krunic said he will prescribe hormonal therapy for 12 to 24 menstrual cycles, then slowly start to wean patients off the treatment — unless the patient desires to continue birth control pills for contraception, in which case he refers them to their gynecologist for further prescriptions and follow-up.

Women with endocrine disorders, such as polycystic ovarian syndrome (PCOS) and congenital adrenal hyperplasia (CAH), may benefit from hormonal therapies, as well.

Patients who frequently skip menstrual cycles, with or without hirsutism, may have an abnormal hormonal status or PCOS, Dr. Leyden said. When taking a history, instead of asking the patient if her menstrual cycle is regular, he said it’s better to ask how often she gets a period, pointing out that

PASSING THE TEST
Dermatologists treating patients for acne who suspect hormonal abnormalities should test them to rule out other conditions. Julie Harper, MD, clinical associate professor at the University of Alabama in Birmingham, recommends following the steps below.

Test for testosterone, DHEAS, and LH/FSH

NORMAL

proceed with treatment for acne

ABNORMAL

testosterone level

significantly higher levels

consider ovarian tumor

mildly increased testosterone levels or LH/FSH ratio higher than 2:3

consider PCOS

with increased DHEAS

consider CAH, test for 17-hydroxyprogesterone

Evaluate the 17-hydroxyprogesterone results to confirm/rule out CAH
“being regular” is not the same as having a normal cycle. Even if the patient lacks facial hair, he said, ask about it because most women have excess hair removed. Depending on the patient’s age, you may want to ask about pregnancies and their outcomes, Dr. Harper added. Asking about her response to previous acne treatments may also be helpful. “If a person has been on isotretinoin many times and the acne always comes back that might be an indication there’s an underlying problem that needs to be addressed,” she said.

For patients suspected of having hormonal abnormalities, dermatologists typically test for levels of total and free testosterone, dehydroepiandrosterone sulfate (DHEAS), and luteinizing hormone/follicle stimulating hormone (LH/FSH). If the lab results come back abnormal, Dr. Harper will test for 17 hydroxyprogesterone. In general, a modestly high DHEAS level may indicate CAH, but higher levels should trigger evaluation for an adrenal tumor. Higher total testosterone levels may be seen in ovarian tumors, but mild increases are indicative of PCOS as are LH/FSH ratios greater than two to three. Levels of 17 hydroxyprogesterone have been used to confirm adult-onset CAH. Even when the lab workup is normal, which is most of the time, these patients can still benefit from hormonal treatment, she noted.

**IN COMBINATION, ALONE**

Many dermatologists use spironolactone in conjunction with OCs to minimize its side effects, which commonly include menstrual irregularities and breast tenderness, Dr. Shalita explained. A typical treatment dose of spironolactone is 50 to 100 mg daily. At higher doses, the side effects are more prominent.

The other advantage to combining these hormonal therapies is that they treat acne using two mechanisms of action, essentially doubling the effect, Dr. Berson said. If the acne is not being adequately controlled with OCs, she may add spironolactone.

“Birth control pills can take two to three months to show an effect, but with spironolactone, most patients notice decreased outbreaks and oiliness in a couple of weeks,” Dr. Berson added.

Some dermatologists believe that spironolactone shouldn’t be prescribed in the absence of OCs because it is associated with hypospadias and feminization of the male fetus, Dr. Leyden said.

But as Dr. Harper points out, spironolactone is one of several medications that patients shouldn’t become pregnant while taking. Although she generally prescribes it in combination with OCs to help minimize side effects, Dr. Harper will prescribe spironolactone alone after thoroughly explaining the potentially serious risks of becoming pregnant. Like her counterparts, she also prescribes spironolactone without OCs for patients in whom the use of estrogen is contraindicated, or in post-menopausal women or those who have had a hysterectomy, or smokers.

Moreover, patients are not candidates for combined therapy with OCs if they have risk factors such as obesity, high blood pressure, stroke, deep vein thrombosis (DVT), migraines, or a family history of breast/endometrial cancer, Dr. Krunic noted.

**USED WITH TRADITIONAL THERAPIES**

Hormonal therapies are typically used in combination with traditional acne therapies, including topical or systemic retinoids, topical benzoyl peroxide, and topical or systemic antibiotics. As Dr. Shalita points out, the consensus of the Global Alliance for Improving Outcomes in Acne is that a topical retinoid should be used to treat all but the most severe forms of acne.

As the patient responds to treatment, Dr. Berson may stop the oral antibiotics or topical antimicrobials while continuing the hormonal therapy. “But even when the patient is clear, I tend to keep her on retinoids because they treat existing acne and help prevent future breakouts,” she said.

Dr. Harper frequently overlaps hormonal and traditional therapies because she gets faster results that way. She may use both for two to three months and then discontinue the traditional therapy. “When hormone therapy is effective, patients are on them for a long time,” she noted.

Dr. Krunic has found that most of these patients are just partially responsive to retinoids. In addition, their skin is often more sensitive to the drying effect of topical retinoids or irritation from benzoyl peroxide. As a result, he commonly combines antiandrogen therapy with systemic antibiotics, often in the beta-lactam or cephalosporin group. Topically, he prefers lotions or water-based vehicles like cleansing cloths containing sodium sulfacetamide and sulfur.

Dr. Leyden has a slightly different approach. For patients who are unresponsive to several conventional therapies, he will stop all of them and prescribe spironolactone, and assess their progress in six weeks. “Many times, spironolactone is enough,” Dr. Leyden said. But for a teenager with blackheads, non-inflammatory lesions, pustules, and papules, he will use a topical antibiotic and retinoid and add spironolactone. Assuming the patient comes under control fairly quickly, he will slowly stop the antibiotics, but will continue the retinoids because of the blackheads.

“Many times, you can get away without oral antibiotics,” he noted.

**RISKS, CONCERNS**

Using OCs is associated with an increased risk of DVT, stroke, and myocardial infarction, among others. But Dr. Berson points out that there is a decreased risk and fewer side effects associated with today’s OCs due to the smaller amounts of estrogen in them. Newer OCs contain 20 to 35 mcg of estrogen compared with 100 mcg in the first-generation OCs. She informs her patients about the signs of DVT, that it can be pains and cramping in both the legs and/or arms, and tells them to contact her if they develop any symptoms. Dr. Berson also recommends that they stay active and drink a lot of water as immobility and dehydration will increase one’s potential to develop DVT.

Stroke, myocardial infarction, and DVT are also very strongly linked to other risk factors, such as smoking. Dr. Harper noted. Although a slight increased risk of developing breast cancer has been raised, she questions that. Regarding the FDA’s investigation of DRSP-containing OCs, she said two studies suggest that these birth control pills are associated with twice the risk of developing DVT than those containing levonorgestrel. “When the lay population hears that there is a double risk, it sounds frightening,” she said. “But when you look at the absolute risk, it increases from six out of 10,000 events to 10 out of 10,000 events. It’s really
Hormonal therapies serve as key adjunct acne treatment

important that dermatologists understand those numbers because we’re the ones our patients will ask.”

In addition, an increased risk of hyperkalemia when DRSP-containing OCs are combined with spironolactone was not demonstrated in recent studies, Dr. Krunic noted. Despite the hyperkalemia warning, physicians are using OCs containing DRSP with spironolactone preferentially and they are not following the recommended potassium monitoring requirements, he said.

There is, however, some concern regarding the use of OCs hindering bone density in young adolescents. The body relies on estrogen for bone development, much of which occurs within four years after menarche. By the late teens and early 20s, however, peak bone mass is formed. “When you give someone the birth control pill, you’re choosing how much estrogen that person will have because you’re suppressing the amount the body will make,” Dr. Harper said. “The concern is that estrogen levels in the pill are too low to support enough bone formation to prevent osteoporosis and bone fractures later in life. After reviewing the literature, I’m not sure that we know the answer to that.” There is evidence showing that the combination OCs with 30 mcg of ethinyl estradiol are adequate to ensure sufficient bone accrual during adolescence and normal bone health into adulthood. Still, Dr. Harper cautions dermatologists to be aware that lower levels of estrogen may not always be better, especially for young adolescents.

Regarding antibiotics decreasing the effectiveness of OCs, Dr. Harper said that there is no evidence to support that with the antibiotics used to treat acne. The hypothesis is that antibiotics decrease the gut flora needed to further degrade inactive metabolites of the OCs to active drug during enterohepatic recirculation. Dr. Berson points out that the failure rate of OCs is 3 percent, which remains the same with antibiotic use. Moreover, it takes one month for birth control pills to take effect, the same amount of time it takes the gut flora to normalize, she said. Women are told to use appropriate precautions to prevent pregnancy during that time.

They may not be the first line of therapy, but hormonal therapies are an effective secondary adjunctive treatment that will, no doubt, continue to grow in popularity. “Women are asking for it by name,” Dr. Leyden said. “They want the pill that doesn’t make them break out.”

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DERMATOLOGISTS PRESCRIBING MORE OCS, BUT NUMBERS STILL LOW

Oral contraceptives (OCs) are rarely prescribed for acne despite their efficacy for treating it, according to a study presented by Steven Feldman, MD, PhD, of Wake Forest University, at the AAD’s recent Annual Meeting in San Diego.

Overall, physicians prescribed OCs at 2.58 percent of acne visits, with dermatologists prescribing them at 2.03 percent of visits. In recent years, such prescriptions increased by 0.9 percentage points among dermatologists. Dr. Feldman suggested that the low rate of OC prescriptions among dermatologists is likely due to their lack of experience with birth control pills in routine practice.

Some dermatologists may be reluctant to prescribe OCs because they tend to think of them as falling under the purview of a gynecologist. Part of that could be that dermatologists have the mistaken impression that patients going on the birth control pill must get a pap smear, Dr. Shalita said. But several years ago, the American Congress of Obstetricians and Gynecologists came out with a report saying that women who are not sexually active don’t need to see a gynecologist for a year after being on the birth control pill, he said. If they are sexually active, they should be getting a routine pap smear anyway.

Then there is the awkward conversation that can ensue when discussing OCs for teenagers. “I never use the words ‘birth control pill’ with mothers,” Dr. Leyden said. “I always talk about estrogen therapy, which if you take it every day will help prevent you from getting pregnant.” Dr. Berson similarly discusses hormone treatment, especially when speaking with a 16-year-old girl who is there with her mom. “You don’t want to say we’re putting your daughter on the birth control pill because it can open a Pandora’s Box,” she said.

Younger dermatologists are probably more comfortable than older ones prescribing OCs, Dr. Harper said. She speculates that this is because they are coming out of residency training learning about them. In addition, FDA approval has had an impact. "Oral contraceptives were being used off-label. But now that the FDA has approved them for the treatment of acne, more dermatologists can feel comfortable with prescribing them," Dr. Berson said. When she first started prescribing OCs, Dr. Berson always recommended that patients go to the gynecologist, but that is unnecessary unless the patient has an underlying endocrinopathy or is at risk of complication. Nowadays, she gives patients a three-month prescription and recommends that they see a gynecologist annually because the assumption is that a patient on OCs is more likely to be sexually active, which puts them at risk for sexually transmitted diseases.

"Oral contraceptives and spironolactone have been very helpful additions to our therapeutic armamentarium for acne," Dr. Berson said. "Dermatologists are getting more comfortable with giving women this form of treatment as an adjunct to traditional treatments."

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Indication and Important Safety Information

Acanya Gel is indicated for the topical treatment of acne vulgaris in patients 12 years of age or older. Acanya Gel is contraindicated in patients with a history of regional enteritis, ulcerative colitis, or antibiotic-associated colitis. Discontinuation is recommended if significant diarrhea, bloody diarrhea, severe abdominal cramping, or colitis (including pseudomembranous colitis) develops. Clindamycin taken orally or through IV may result in severe colitis, which may result in death. Anaphylaxis, as well as other allergic reactions leading to hospitalizations, has been reported in postmarketing use of products containing clindamycin/benzoyl peroxide. If a patient develops symptoms of an allergic reaction such as swelling or shortness of breath, they should be instructed to discontinue use and contact a physician immediately. Patients should be advised to avoid contact with the eyes or mucous membranes and to minimize sun exposure following the application of Acanya Gel.

To learn more, please visit www.AcanyaGel.com

Please see brief summary of 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.

*Individual results may vary.


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**Acana**
(clindamycin phosphate and benzoyl peroxide) Gel, 1.2%/2.5%
Ready-to-Use 50g Pump

**INDICATIONS AND USAGE**
Acana Gel is indicated for the topical treatment of acne vulgaris in patients 12 years of age or older.

The safety and efficacy of this product in the treatment of any other disorders have not been evaluated.

**DOSEAGE AND ADMINISTRATION**
Apply a pea-sized amount of ACANYA Gel to the face once daily. Use of ACANYA Gel beyond 12 weeks has not been evaluated.

ACANYA Gel is not for oral, ophthalmic, or intravaginal use.

**CONTRAINDICATIONS**
ACANYA Gel is contraindicated in patients with a history of regional enteritis, ulcerative colitis, or antibiotic-associated colitis.

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

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

Studies indicate toxin(s) produced by Clostridium is one primary cause of antibiotic-associated colitis. The colitis is usually characterized by severe persistent diarrhea occurring, ACANYA Gel should be discontinued.

**ADVERSE REACTIONS**
**Clinical Studies Experience**
Because clinical trials are conducted under prescribed conditions, adverse reaction rates observed in the clinical trial may not reflect the rates observed in practice. Because clinical trials are also conducted under widely varying conditions, adverse reactions observed in the clinical trials of a drug cannot always be directly compared to rates in the clinical trials of another drug. The adverse reaction information from clinical trials does, however, provide a basis for identifying the adverse reactions that appear to be related to drug use and for approximating rates.

The following selected adverse reactions occurred in less than 0.2% of patients treated with ACANYA Gel: application site pain (0.1%); application site exfoliation (0.1%); and application site irritation (0.1%).

During clinical trials, patients were assessed for local cutaneous signs and symptoms of erythema, scaling, itching, burning, and stinging. Most local skin reactions increased and peaked around week 4 and continually decreased over time reaching near baseline levels by week 12. The percentage of patients that had symptoms present before treatment, the maximum value recorded during treatment, and the percent with symptoms present at week 12 are shown below.

**DRUG INTERACTIONS**
**Erythromycin**
ACANYA Gel should not be used in combination with topical or oral erythromycin-containing products due to its clindamycin component. In vitro studies have shown antagonism between erythromycin and clindamycin. The clinical significance of this in vivo antagonism is not known.

**Concomitant Topical Medications**
Concomitant topical acne treatment should be used with caution because a possible cumulative irritant effect may occur, especially with the use of peeling, desquamating, or abrasive agents.

**Neuromuscular Blocking Agents**
Clindamycin has been shown to have neuromuscular blocking properties that may enhance the action of other neuromuscular blocking agents. Therefore, ACANYA Gel should be used with caution in patients receiving such agents.

**USE IN SPECIFIC POPULATIONS**
**Pregnancy Category C**
There are no well-controlled trials in pregnant women treated with ACANYA Gel. It also is not known whether ACANYA Gel can cause fetal harm when administered to a pregnant woman. ACANYA Gel should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Animal reproductive/developmental toxicity studies have not been conducted with ACANYA Gel or benzoyl peroxide. Developmental toxicity studies of clindamycin performed in rats and mice using oral doses of up to 600 mg/kg/day (240 and 120 times the amount of clindamycin in the highest recommended adult human dose of 900 mg/m²/day, respectively) or subcutaneous doses of up to 200 mg/kg/day (80 and 40 times the amount of clindamycin in the highest recommended adult human dose based on mg/m²) respectively revealed no evidence of teratogenicity in mice. However, topical treatment with a different gel formulation containing 1% clindamycin and 5% benzoyl peroxide at doses of 100, 500, and 2000 mg/kg/day caused a dose-dependent increase in the incidence of keratoacanthoma at the treated skin site of male rats in a 2-year dermal carcinogenicity study in rats. In an oral (gavage) carcinogenicity study in rats, treatment with the gel formulation at doses of 300, 900 and 3000 mg/kg/day (1.2, 3.6, and 12 times amount of clindamycin and 2.4, 7.2, and 24 times amount of benzoyl peroxide in the highest recommended adult human dose of 2.5 g ACANYA Gel based on mg/m², respectively) did not cause any increase in tumors. However, topical treatment with a different gel formulation containing 1% clindamycin and 5% benzoyl peroxide at doses of 100, 500, and 2000 mg/kg/day caused a dose-dependent increase in the incidence of keratoacanthoma at the treated skin site of male rats in a 2-year dermal carcinogenicity study in rats. In an oral (gavage) carcinogenicity study in rats, treatment with the gel formulation at doses of 300, 900 and 3000 mg/kg/day (1.2, 3.6, and 12 times amount of clindamycin and 2.4, 7.2, and 24 times amount of benzoyl peroxide in the highest recommended adult human dose of 2.5 g ACANYA Gel based on mg/m², respectively) did not cause any increase in tumors. In a 52-week dermal photocarcinogenicity study in hairless mice, (40 weeks of treatment followed by 12 weeks of observation), the median time to onset of skin tumor formation decreased and the number of tumors per mouse increased relative to controls following chronic concurrent topical administration of the higher concentration benzoyl peroxide formulation (5000 and 10000 mg/kg/day, 5 days/week) and exposure to ultraviolet radiation.

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

**Fertility studies have not been performed with ACANYA Gel or benzoyl peroxide, but fertility and mating ability have been studied with clindamycin. Fertility studies in rats treated orally with up to 300 mg/kg/day of clindamycin (approximately 120 times the amount of clindamycin in the highest recommended adult human dose of 2.5 g ACANYA Gel, based on mg/m²) revealed no effects on fertility or mating.**

**HOW SUPPLIED**
ACANYA Gel is supplied as a 50 g pump (NDC 13548-132-50).

**Dispensing Instructions for the pharmacist**
Dispense ACANYA Gel with a 10 week expiration date. Specify “Store at room temperature up to 25°C (77°F). Do not freeze.”

**Storage and Handling**
**PHARMACIST:** Prior to dispensing, store in a refrigerator, 2°C to 8°C (36°F to 46°F). **PATIENT:** Store at room temperature at or below 25°C (77°F).

**Protect from freezing.**
Keep out of the reach of children.

**RX Only**
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Role of food remains controversial

BY JAN BOWERS, CONTRIBUTING WRITER

DIET & ACNE

SUPPLEMENT TO DERMATOLOGY WORLD
Diet causes acne. No it doesn’t! But that is what the media will say when they get wind of this report.” In a commentary published in the *Journal of the American Academy of Dermatology* (2008;58:794-5), Guy F. Webster, MD, PhD, clinical professor of dermatology at Jefferson Medical College, articulated a controversy surrounding the role of diet in acne vulgaris that’s as lively as ever, four years later. While Dr. Webster was responding to publication of a specific study linking milk consumption and acne in teenaged boys, the current discussion extends to a range of other potential dietary culprits, including foods with a high glycemic index and chocolate.

While chocolate, fats, and sweets were suspected of aggravating acne as early as the 1930s, two studies published in 1969 and 1971 cast doubt on a link between diet and acne, and diet as a significant factor was relegated to myth status for several decades. In a comprehensive examination of the evidence linking diet and acne, published in *JAAD* (2010;63:124-41), authors Whitney Bowe, MD, Smita S. Joshi, MD, and Alan R. Shalita, MD, noted that despite weakness in the studies’ design, “textbooks were revised to reflect this new academic consensus, and dermatologists took the stance that any mumblings about the association between diet and acne were unscientific.”

Beginning in 2005, a series of studies linking consumption of dairy products with acne jumpstarted the controversy and drew some dermatologists — even those who found the studies seriously flawed — to reconsider the role of diet. “We’re learning more about hormonal influences and other factors, so I think it’s worth taking a second look,” said Diane Thiboutot, MD, professor of dermatology at Penn State University College of Medicine. “At this point I’d have to say there’s not sufficient evidence [pointing to a significant role for diet]. Hopefully, as we move forward, we’ll have more data to be able to evaluate whether there is an association.”

The quality of the evidence goes to the heart of the disagreement between those who are convinced of a link between diet and acne and those who are not. Many dermatologists, including Dr. Webster, admit that existing studies suggest an association, but they insist that without data from more rigorous, controlled studies, the link remains hypothetical. “We’ve got to remember that everything we tell a patient has a consequence,” he said. “The advice you give a patient should be based on real facts, not hypothesis. And we don’t have data that strong yet.” Indeed, in a *Lancet* review of acne vulgaris earlier this year (2012;379:361-72), the authors noted, “no evidence suggests that putting people on restrictive diets reduces acne.”

**THE CASE AGAINST MILK**

A co-author of several studies examining the relationship between dairy products and acne stands by his findings and vigorously recommends a dairy-free and low glycemic load (LGL) diet for teenagers and adults with acne. “In patients who have no genetic background for acne, dairy plays no role whatsoever. It will not give them acne,” said William Danby, MD, adjunct assistant professor of surgery, division of dermatology, at Dartmouth Medical School. “But for those who have a propensity for acne and are susceptible to the effects of dairy, it can make their acne much worse.”

Working with researchers at the Harvard School of Public Health, Dr. Danby examined data from the Nurses Health Study II, in which 47,355 women provided information about their high school diet and whether they had physician-diagnosed severe teenage acne. The acne question was included in the first survey in 1989, when the participants were aged 25 to 42. In 1998, members of the cohort were asked if they would be willing to complete a high school food-frequency questionnaire. The reported prevalence of severe acne according to the intake of total milk was statistically significant; it ranged from 0.06 for one or fewer servings per week to 0.08 for more than three servings per day. Thus, acne was positively associated with the reported quantity of milk ingested, particularly skim milk.

Published in *JAAD* (2005;52(2):207-14), the study has drawn criticism for its methodology but has also served to refocus attention on dairy and acne. “There have been several studies now that have shown a consistent relationship between dairy and acne. Although this effect cannot be ignored, the effect of dairy on acne appears to be incremental,” said Dr. Bowe, who is assistant clinical professor of dermatology at SUNY Downstate College of Medicine. Other weaknesses cited by Dr. Bowe and her co-authors include the study’s retrospective design, and the fact that the women were asked to recall their milk consumption in the distant past.
Dr. Danby emphasized that his group included two Harvard statisticians who work in public health. “The questionnaires have all been validated over the years, this is standard evidence,” he said. “Regarding the numbers, the people who drank two glasses of skim milk per day had a 1.44 risk, or a 44 percent increase. At one end of the spectrum you’d have the people who don’t have the genes for developing acne — they’d be at zero — and at the other end would be people who are at three to five times the risk, but the mean is .44. I worry about those at the top end who have the acne genes and the high dairy load.”

A recent study in Italy, in press with *JAAD* and available online since February (doi:10.1016/j.jaad.2012.02.018), offered more support for the milk hypothesis. The authors enlisted 205 cases and 358 controls and interviewed them about their family history, smoking and alcohol consumption, and medical history. Participants also completed a food frequency questionnaire; the authors used the responses to investigate the relationship between acne and the consumption of pasta and bread; a variety of meats; whole, skim, and low-fat milk; cheese; a variety of sweets, including chocolate; and fruits and vegetables. The study found that the risk of moderate to severe acne “increased with increased milk consumption,” with an odds ratio of 1.78 and a stronger connection seen between skim milk and acne than whole milk. The study results also suggested that fish consumption could provide some protection from acne. Except for milk and fish, the authors noted, “no association emerged between intake of other food items and risk of acne.”

Dr. Danby theorizes that steroid hormones and other components of bovine milk precipitate a complex cascade that acts to overstimulate the pilosebaceous unit. Dr. Webster maintained that this explanation remains a “tantalizing hypothesis” until a controlled study is conducted that assesses the effects of a dairy-free diet on teenagers at risk for acne. “Their study has strong enough evidence to say that there’s an effect of diet on acne, but no study has confirmed any mechanism,” Dr. Webster said.

**HIGH GLYCEMIC LOAD DIET**

The strongest evidence points to a high glycemic load (HGL) diet as a significant factor in acne, Dr. Bowe said. “It began when a group of scientists looked at two hunter-gatherer societies that consumed low glycemic load diets — vegetables, nuts, proteins. No white bread, white potatoes, cookies, cereals — none of the foods most likely to spike blood glucose levels.” The group’s first published study on this topic, which dubbed acne a “disease of Western civilization,” appeared in the *Archives of Dermatology* (2002;138(12):1584-90). Their

### GLYCEMIC INDEX

The glycemic index (GI) ranks the potential of different foods to increase blood glucose levels. The glycemic load takes into account both the quality and quantity of carbohydrates, and is calculated by multiplying the GI of a food by the amount of carbohydrate in grams provided by that food and dividing the total by 100. Dietary glycemic load is the sum of the glycemic loads for all foods consumed in the diet. Low GI foods include peanuts, low-fat yogurt, apples, kidney beans, and most vegetables. High GI foods include white bread, white potatoes, watermelon, doughnuts, and dates.
DIET & ACNE

observations of 1,200 Kitavan Islanders of Papua New Guinea and 115 Aché hunter-gatherers of Paraguay (including a total of 315 subjects aged 15-25) revealed no cases of acne. The lead author, Loren Cordain, developed some interesting theories that were very convincing, based on the basic science,” Dr. Bowe said. “The thinking is that if you have a diet with a high glycemic index, then diet-induced hyperinsulinemia leads to a cascade of endocrine response that includes male hormones, androgen, growth hormones, insulin-like growth factor-1, and the end of that cascade leads to plugging of follicles and actually increases secretion of the sebaceous glands.” (See sidebar for more on the glycemic index.)

In the comprehensive JAAD article, Dr. Bowe and her co-authors noted that Dr. Cordain’s evidence might be stronger if the acne-free subjects had been given a high glycemic load (HGL) diet and had subsequently developed acne. She cites a study by a group of Australian scientists, published in JAAD (2007;57(2):247-56), as providing the best evidence of dietary impact on acne. “This was a well-designed, randomized controlled trial that showed a significant reduction in acne in subjects who basically cut the high glycemic index foods out of their diet,” Dr. Bowe said. “They were able to measure blood levels of IGF and free androgen as well as insulin sensitivity, and found that patients on the LGL diet became more sensitive to insulin, had less free androgen and less IGF. And that group has done several studies since then that have only bolstered their argument.” One limitation of the 2007 study, noted by the authors and by Dr. Bowe, was that the subjects on the LGL diet lost weight and decreased their body mass index (BMI), and the effects of diet and weight loss could not be separated. When the investigators statistically adjusted the data for changes in BMI, the effect of the LGL diet on several clinical parameters was lost. In addition, the subjects were all male, and the results could not be generalized to female adolescents.

Drs. Webster and Thiboutot also singled out the Australian study as the strongest evidence to date that diet can affect acne, but both warned against jumping to conclusions. “The study was very encouraging, but it was done with a small number of patients,” said Dr. Thiboutot. “I think more research is needed, and hopefully there are more studies underway that will put this in perspective. A lot of this data is theoretical linkages and possible associations, but not really a cause and effect.” Dr. Webster noted that a low-carbohydrate, high-protein diet is expensive and could impose a burden on low-income patients. “They’ve shown there’s a signal between diet and acne, so then you’ve got to do a study that lets you say how important it is,” he said. “The reason is that you don’t want to give your patients ridiculous recommendations, or recommendations that cost them money and don’t do anything.”

CHOCOLATE COMES FULL CIRCLE

Once a prime suspect in the hunt for a dietary villain, chocolate has again come under scrutiny. A recent letter to the editor of Clinics in Dermatology (2011;29:459-460) pointed out a variety of flaws in the 1969 Journal of the American Medical Association paper, “Effect of Chocolate on Acne Vulgaris,” on which the idea that chocolate does not affect acne is often based. After addressing concerns about how the subjects of the JAMA study were sorted, the methods of stratification used, and the fact that the study was supported by a chocolate manufacturers’ association, the letter authors wrote, “Clinicians cannot be unequivocal in their advice to acne sufferers on the inclusion or exclusion of dietary chocolate until a well-designed randomized controlled clinical trial is conducted.”

That day has not arrived, but a team at the University of Miami Miller School of Medicine is working on it. “Patients often swear that chocolate causes their acne. The notion that chocolate and acne are not related is based on previous studies which did not assess the effect of pure chocolate on acne. That had never been done,” said Samantha Block, a third-year medical student working on a team headed by Brian Berman, MD, PhD, professor of dermatology and cutaneous surgery. “Dr. Berman and the other team members felt strongly that we needed to reassess the effect of 100 percent cocoa on acne.” The study team also included Whitney Valins, MD, Caroline Caperton, MD, Martha Viera, MD, and Sadegh Amini, MD.

The team recruited 10 healthy male subjects, aged 13 to 35, with one to four acneiform lesions. The subjects were not using any prescription or over-the-counter medications. “We had them binge on chocolate that was 100 percent, unsweetened cocoa in a single sitting,” Block said. The researchers counted the number of acneiform lesions on day four and day seven following the chocolate consumption. Their results, presented in poster form at the American Academy of Dermatology’s
Optimized for efficacy with minimal irritation

- 36% mean reduction in inflammatory lesions at 12 weeks*†
- 41% mean reduction in noninflammatory lesions at 12 weeks*‡
- Low irritation profile†
- Moisturizing and hydrating agents†,‡,§

*Combined results of two 12-week, prospective, multicenter, randomized, vehicle-controlled studies of patients with mild to moderate acne vulgaris of the face.
†The contribution of individual components to efficacy has not been evaluated.

**Indication and Important Safety Information:** Atralin Gel is indicated for the treatment of acne vulgaris. The most common adverse reaction was mild to moderate irritation of the skin (i.e., dry skin, skin burning, erythema, and exfoliative dermatitis), which occurred during the first few weeks of treatment with Atralin Gel. To prevent aggravating the skin, protect it from sun, tanning lights, extreme wind or cold, and harsh skincare products. Use of sunscreen products of at least SPF 15 and protective clothing over treated areas are recommended when exposure cannot be avoided. Atralin Gel should not be used on eczematous or sunburned skin due to potential for severe irritation.

Contraindications
The safety and efficacy of the use of this product in the treatment of any other disorders have not been evaluated.

Important Limitations of Use
The safety and efficacy of this drug have not been established in children and adolescents.

Adverse Reactions

Skin Irritation

Fish Allergies

Weather extremes, such as wind or cold, also may be irritating to patients under treatment with tretinoin.

Table 1. Number of Subjects with Selected Adverse Reactions (Occurring in At Least 1% of Subjects)

<table>
<thead>
<tr>
<th>Event</th>
<th>Atralin Gel</th>
<th>Vehicle Gel</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>% (n=60)</td>
<td>% (n=467)</td>
</tr>
<tr>
<td>Dry Skin</td>
<td>53 (31)</td>
<td>6 (1.3%)</td>
</tr>
<tr>
<td>Tight Skin</td>
<td>38 (24)</td>
<td>2 (0.4%)</td>
</tr>
<tr>
<td>Skin Burning</td>
<td>1 (0.2%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Pain of Skin</td>
<td>17 (11%)</td>
<td>7 (1.5%)</td>
</tr>
<tr>
<td>Surfaces</td>
<td>1 (0.2%)</td>
<td>0 (0%)</td>
</tr>
</tbody>
</table>

Pregnancy

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

Nursing Mothers

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Atralin Gel is administered to a nursing woman.

Pediatric Use

Atralin Gel was not evaluated in children below the age of 10 years. It is not known whether this drug is safe and effective in children and adolescents.

Geriatric Use

Atralin Gel was not evaluated in the elderly. It is not known whether this drug is safe and effective in elderly patients.

Drug Interactions

When treating with Atralin Gel, caution should be exercised with the use of concomitant topical medication, medicated or abrasive soaps and cleansers, products that have a strong drying effect, and products with high concentrations of alcohol, astringents, spices, or lime. Particular caution should be exercised with the concomitant use of topical over-the-counter acne preparations containing benzoyl peroxide, sulfur, salicylic acid, or nicotinic acid. Allow the effects of such preparations to subside before use of Atralin Gel is begun.

Use in Specific Populations

Pediatric Use

Safety and effectiveness in children below the age of 10 have not been established.

Table 1. Efficacy Profile of Oral Tretinoin in the Treatment of Acne

<table>
<thead>
<tr>
<th>Event</th>
<th>Oral Tretinoin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Improvement in Total Lesions</td>
<td>44%</td>
</tr>
<tr>
<td>Improvement in Inflammatory</td>
<td>35%</td>
</tr>
<tr>
<td>Improvement in Nodular Lesions</td>
<td>26%</td>
</tr>
</tbody>
</table>

Long-term treatment with tretinoin has led Dr. Thiboutot to pursue her own investigation because she is unconvinced by the existing epidemiologic studies. “We’re working with nutritionists at our medical center to sort of get a feel for the amount of dairy products that patients with acne are consuming, compared to patients without acne,” she said. “At this point, I haven’t altered my practice to make recommendations regarding diet. There may be an association, but I just don’t think we have enough evidence to support the recommendation that all patients with acne need to be on modified diets.”

Although he said he is thoroughly convinced that both dairy and an HGL diet adversely affect acne, Dr. Danby doesn’t rely on diet modification as stand-alone therapy. “Patients with acne want to get better. Depending on what degree of activity they have, we’re now recruiting patients for a follow-up study to assess whether or not acne improved, placebo-controlled manner with more subjects. We recognize that the number of subjects was one limitation of this first study.”

What to Tell Patients

The controversy surrounding the possible milk-acne connection has led Dr. Thiboutot to pursue her own investigation because she is unconvinced by the existing epidemiologic studies. “We’re working with nutritionists at our medical center to sort of get a feel for the amount of dairy products that patients with acne are consuming, compared to patients without acne,” she said. “At this point, I haven’t altered my practice to make recommendations regarding diet. There may be an association, but I just don’t think we have enough evidence to support the recommendation that all patients with acne need to be on modified diets.”

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2011 Annual Meeting and in a subsequent letter to the editor published in JAAD (2011;65(4):e114-e115), showed a statistically significant increase in the mean number of total lesions and a dose-dependent relationship between the amount of chocolate consumed and the number of lesions on days four and seven.

An audience member at the AAD presentation noted that microcomedo formation is thought to occur over six to eight weeks, and questioned how the chocolate could have impacted formation so quickly. Dr. Berman replied that the subjects may have had microscopic microcomedones at baseline, and the chocolate may have hastened their development. “That is something that will have to be investigated,” of course,” Block said. “We’re now recruiting patients for a follow-up study to assess chocolate and acne in a double-blind, placebo-controlled manner with more subjects. We recognize that the number of subjects was one limitation of this first study.”

Editor’s note: This article is an updated version of one that appeared in the September 2011 issue of Dermatology World. www.aad.org
The use and regulation of isotretinoin has been a significant issue in dermatology since the strong link between the drug and birth defects came to light, and ramped up further when the media took to the issue in the early 2000s. Women of childbearing age taking oral isotretinoin were said to have a fetal exposure risk of up to one in every 300-450 courses of therapy, according to the CDC. After a 250 percent increase in isotretinoin prescriptions from 1992 to 2000, widespread fear of perceived risks led to a decline in prescriptions of 23 percent between 2002 and 2003. >>
As a result, the FDA began efforts to ensure safe use in patients of childbearing age while still protecting patient access to the vital drug. Following the widely perceived failure of the FDA’s original System to Manage Accutane-Related Teratogenicity (SMART) program, the FDA instituted the iPLEDGE program in March 2006. Under the program, patients and their physicians and pharmacists were required to register on the FDA’s iPLEDGE website and follow a set of regulations designed to minimize the risk of fetal exposure. More than six years after the program’s implementation, dermatologists say the program has set a number of good prescribing practices while paradoxically failing to significantly decrease the annual number of fetal exposures.

**iPLEDGE AND PATIENT REGISTRATION**

Controversial at the outset, the iPLEDGE program, with its strict prescribing windows, blackout periods, and mandatory registration for both female and male patients, has been called “a logistical nightmare” with loopholes “sealed with a wall of bureaucratic red tape,” by Danbury, Conn., physician Graeme Lipper, MD, in an isotretinoin column published on MedScape. Yet over the years, some of the program’s rougher edges have been smoothed away thanks to physician and patient advocacy. According to dermatologist Mary Maloney, MD, who chairs the American Academy of Dermatology Association’s Regulatory Policy Committee, there is still room for the program to improve, becoming more consumer-friendly, though it’s doubtful that this will happen soon.

“One of the things that I question is the validity of continuing to register men. And I think that there is absolutely no question about the fact that there’s no

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**ISOTRETINOIN AND IBD**

During isotretinoin’s prolonged term in the public eye, some in medicine and the media began to question whether there was a link between the drug and the development or exacerbation of inflammatory bowel disease (IBD). After Roche Holding ceased production of Accutane in 2009, a Los Angeles Times headline read “New study may deal final blow to acne drug Accutane.” Yet a number of dermatologists and researchers found no link with IBD following population-based case control studies.

Researchers at the University of Manitoba found that isotretinoin use was neither more nor less prevalent in patients suffering from IBD than in the general population. A June 2011 article by Catalin Mihai Popescu, MD, PhD, and Raluca Popescu, MD, PhD, in Archives of Dermatology (2011:147(6);724-729) concluded that there was insufficient evidence to confirm or refute a causal association between isotretinoin and IBD.

Dermatologist Elliot Mostow, MD, who prescribes isotretinoin to patients, and who offered comment on the Archives article (2011:147(6);729-730), said that he makes patients aware of all the issues linked to the drug, and stresses that the benefits outweigh the potential side effects.

“\"I have a discussion with my patients who are contemplating isotretinoin that goes beyond iPLEDGE to try to include as many potential areas of side effects that they might read about elsewhere as possible,\" Dr. Mostow said. \"I want them to know that I am aware of the issues, some that can be proven, some that cannot, and am still willing to prescribe the medication because I believe that the benefits outweigh the risks.\"

Dr. Mostow acknowledges that especially in patients with a family history of IBD, it can be an especially difficult decision to accept isotretinoin treatment.

It’s a great drug. We need to have it available for the patients that need it.
indication for the registration of men. It doesn’t provide us any detail on the epidemiology of the use of isotretinoin, they’re at no risk of getting pregnant, and whether or not we register them, they can still give their medicine away if they want to,” Dr. Maloney said. “Some of the logic was letting men know that they couldn’t give their medicine to their girlfriend, for example. But it has significant costs to the health care system to register men, so I think that’s an area where we should continue to work and see if we can somehow eliminate some of those costs.”

Former Academy President Stephen P. Stone, MD, who co-authored an editorial on iPLEDGE with Dr. Maloney in the *Journal of the American Academy of Dermatology* (2011;65:418-9), said that at present, the iPLEDGE program is running with relative smoothness, especially compared to the furor that met its launch during his presidential year. From the perspective of those in charge of the program, he said, it may not prove worthwhile to significantly alter it at present.

“I think there are still some dermatologists who feel it should be changed and liberalized a great deal,” Dr. Stone said. “But I’m not sure that it will be done. There is certainly a vested interest on the part of people who participate in the program to maintain it running smoothly. And I think that quite frankly there is a concern if we change too much, it will increase the risk of pregnancies. Another question is how much it will cost to make these changes. Still, it makes no sense to include males in the program at this point.”

**MEASURABLE RESULTS**

While many aspects of iPLEDGE and isotretinoin are hotly debated, one fact that remains at the center of the debate is that the program has not been able to significantly decrease the number of fetal exposures per year. This, according to Dr. Maloney, implies that the program has reached something approaching a baseline minimum.

“The failures are failures of compliance, either with taking birth control pills, or with using two barrier methods,” Dr. Maloney said. “We just haven’t seen that number budge significantly through all of the FDA’s programs. It’s always been 120 plus or minus five, seven, two — and we can’t seem to break that number.”

While the fetal exposure numbers may not have changed, Dr. Stone said, there is a visible difference.

“I reference the article by Popescu in the *Archives of Dermatology* (and my own comment there), that a critical number is the ‘number needed to treat’ of 2977 (I say 2900 generally), meaning we need to treat 2977 people to get one case of ulcerative colitis,” Dr. Mostow said. “I use a line I borrowed from the epidemiologist David Savitz, PhD, stating that the one thing we know for sure is that this product will not prevent or cure any of the side effects that are reported in the literature. It can be a tough decision, and I acknowledge that with parents and patients. All of this being said, most people appreciate the honest approach and many decide to proceed.”

Aware of the litigious nature of isotretinoin treatment, Dr. Mostow has patients or their parents sign an additional form outlining each of the potential side effects that he discusses with patients, and takes extra time to address each of the concerns that patients may have. In all, Dr. Mostow said, the vast majority of patients are thankful that isotretinoin is available as a means of treatment. That, he said, is the most consistent side effect of isotretinoin in his office.
in physician attitudes toward exposure and risk management.

“People who continued to prescribe the drug have developed a significant understanding of the rationale for the REMS [Risk Evaluation and Mitigation Strategies]. It clearly is important that these drugs that can cause such terrible, avoidable side effects be carefully handled,” Dr. Stone said. “I remember years ago I was talking to a dermatologist who said that he wasn’t going to do pregnancy tests on his patients back before it was compulsory. He said ‘I’m from a small town, I know these kids, I know they’re not sexually active.’ Well lo and behold, that’s exactly the kind of patient that risks exposure. So I think we’ve developed a healthier awareness that you really do have to at least follow some rules and take more than a common sense approach to the issue.”

Despite appearing to reach something of a plateau, Dr. Maloney said that as the chair of the Academy’s relevant committee, she has not received any feedback from the FDA indicating that a more strict REMS system is in the works.

“I can’t speak for the FDA, but personally, I haven’t felt pressure from them that we need to have a stricter program,” she said. “I haven’t felt that as a practitioner or as part of the Regulatory Policy Committee, which I think is reasonable. I think that we have a very tough REMS program at present.”

To truly decrease the number to zero, Dr. Maloney said, isotretinoin would likely have to be completely withdrawn, which she does not advocate.

“I think it’s a great drug. We need to have it available for the patients that need it, and a lot of them do. I think that because we deal with human beings, we have a program that we probably can’t make a lot better,” Dr. Maloney said.

In terms of issue visibility, Dr. Stone said, patients and physicians are much more aware of the risks associated with isotretinoin and the proper precautions for treatment than before the media, Congress, and the FDA took up the issue.

“I think that we’ve also learned that in spite of the best we can do, there are a small number of patients who, even when we play the game exactly as we should, will get pregnant,” Dr. Stone said. “But certainly it seems that something like iPLEDGE — involving the compulsory regulation of the patient, the forced reminding with each prescription refill of the serious risk of pregnancy — gets the point across that would not be gotten across if we just had to put a sticker on the prescription pad.”
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shine in the treatment of acne scars, but lag behind conventional therapy for active disease
In the battle against acne vulgaris and the distressing scars it can leave in its wake, lasers and other light-based therapies are showing great promise in the treatment of scars but somewhat uneven results as therapy for acne flares. Refinements to existing technologies for ablative and non-ablative fractional resurfacing have allowed dermatologists to smooth scars of various shapes and degrees of severity. Photodynamic therapy (PDT) is gaining visibility as an alternative to isotretinoin for patients who have failed conventional topical and systemic treatments, although significant drawbacks for patients and physicians remain. And newer light-emitting devices, including one cleared by the U.S. Food and Drug Administration for home use, are helping to boost the effectiveness of conventional treatments for ongoing disease.

**FRACTIONAL LASERS MINIMIZE SCARS**

The array of lasers used to treat acne scarring is growing as new devices come on the market, including a system that offers a number of different handpieces for different wavelengths. Dermatologists with expertise in using lasers vary in their preference for ablative vs. non-ablative treatment, but there is general agreement that fractional photothermolysis, a technology introduced less than 10 years ago, has led to dramatic advances. Fractional resurfacing uses energy to treat microscopic columns of skin in regularly spaced arrays, leaving intervening areas of skin untouched (one newer device creates a grooved line injury pattern rather than columns). Non-ablative fractional lasers heat and coagulate the tissue, while ablative fractional lasers vaporize tissue. Both stimulate the growth of new collagen. >>
Lasers “have revolutionized the treatment of acne [scars],” said Jeffrey S. Dover, MD, associate clinical professor of dermatology at Yale University School of Medicine and co-founder of SkinCare Physicians in Chestnut Hill, Mass. “We have been overwhelmed with the success of fractional non-ablative lasers for improving acne scarring, particularly for rolling scars and superficial boxcar scars. We used to believe that the more aggressive the treatment, the better the result, but we’ve had a 180-degree turn in our belief, based on very extensive numbers of treatments.” Dr. Dover pointed out that non-ablative treatment is also gentler, better tolerated by the patient, and more easily administered by the dermatologist. “But you need to do a series of a minimum of six treatments to get really nice results, whereas with the ablative devices you can do one single treatment to get improvement,” he added.

Dr. Dover uses erbium fractionated non-ablative lasers in three wavelengths: 1440, 1540, or 1550 nm. He normally administers one treatment per month for six months, and noted that the most significant improvement occurs in the later months of treatment. He called non-ablative laser treatment of acne scarring “one of the most gratifying things I do in my practice because these are people who have tremendous psychological burden, and they are the happiest patients in our entire practice because their condition is dramatically improved.”

Roy G. Geronemus, MD, clinical professor of dermatology at NYU School of Medicine and director of the Laser and Skin Surgery Center of New York, said that, although both ablative and non-ablative fractional lasers work well, he sees a slightly better response with ablative devices. “But it becomes the patient’s decision, because many people cannot afford the downtime that’s required for ablative procedures,” he pointed out. “Also, for darker skin types, we might prefer a non-ablative treatment because it is less likely to result in pigment change.” Another factor affecting the choice of laser is the type of scarring the patient has. “For the deeper scars, I think you’re better off with the more ablative treatment,” Dr. Geronemus said. “But for overall rolling scars or some of the pitted scars, I think both devices can work quite nicely. Large pores do a little better with one of the superficial non-ablative treatments, and that’s done with the thulium 1927 nm laser. So we’ll often combine different types of lasers depending on the condition the patient has.”

Because patients with moderate to severe acne are typically afflicted with a variety of scars, combination therapy with different lasers or lasers plus another modality may lead to the best results, said Arielle N.B. Kauvar, MD, clinical professor of dermatology at NYU School of Medicine and director of New York Laser and Skin Care. “I believe there has been a shift away from ablative lasers toward repetitive, non-ablative fractional laser treatment for acne scars,” she said. “The optimal treatment often requires combining laser treatment with minimally invasive surgical techniques and fillers. If a patient has complicated scars such as deep boxcar scars or large areas of fibrosis, the combination of non-ablative fractional laser treatment and subcision will provide improved results over laser treatment alone.”

In addition to fractional lasers, Dr. Kauvar said she uses a pulsed dye laser or KTP laser to treat the red scars that can persist after inflammatory acne lesions have resolved. “Another laser that’s very useful for both acne scarring and acne treatment is the 1450 nm diode laser, a near-infrared laser that heats and stimulates collagen, but only superficially,” she remarked. “In my practice, I commonly treat mild adolescent or adult acne with a combination of pulsed dye laser and diode laser to treat both the ongoing acne as well as the red and superficial scars that are already present.”

Bruce E. Katz, MD, clinical professor of dermatology at Mt. Sinai School of Medicine and director of the Juva Skin and Laser Center, said he uses both the fractional CO2 ablative laser and fractional radiofrequency. “Fractional radiofrequency is a newer technology, and we’ve been getting very nice results with minimal downtime,” he noted. “It works very similarly to fractional CO2 in terms of stimulating collagen and smoothing out irregularities. We use fractional CO2 in fairer skin and fractional radiofrequency in darker skin types.”

PDT, NEWER DEVICES EFFECTIVE AGAINST ACNE FLARES

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some advances yet to come. I personally think these results have been a little disappointing,” Dr. Dover said. “The results are variable, it’s an out-of-pocket expense not covered by insurance, and I think that for the most part, these selections are being made through frustration of the patients and perhaps physicians.”

A device that combines broadband light (400 to 1,200 nm) with a vacuum, Isolaz, is gaining support for its use particularly in the treatment of comedonal acne. “It’s inexpensive, safe, and well-tolerated,” said Dr. Dover, who has served as an investigator for Solta Medical, which makes Isolaz. “A series of four or five treatments has helped many of our patients — mostly teenagers, but also some women in their 30s and 40s — in conjunction with traditional treatments.” Dr. Geronemus, who also serves as an investigator for Solta and said he uses a wide variety of devices for active acne, remarked that in his experience, “the vacuum is nice for patients with comedonal acne, and the broadband helps with the inflammatory acne.”

Home treatment with a device that emits blue light was also cited as a possible adjunct to oral and topical therapy. Noting that most home devices are underpowered, Dr. Dover singled out the TRIA Skin Perfecting Blue Light as “a highly powered blue light source that has some nicely done studies in peer-reviewed journals that show it’s pretty effective.” Dr. Geronemus, who tested the TRIA device in his practice and reported encouraging results in a poster presentation (J Amer Acad Dermatol, 2012;66(4):AB14), said home devices are “a growing source that has some nicely done studies in peer-reviewed journals that show it’s pretty effective.” Dr. Geronemus, who tested the TRIA device in his practice and reported encouraging results in a poster presentation (J Amer Acad Dermatol, 2012;66(4):AB14), said home devices are “a growing source that has some nicely done studies in peer-reviewed journals that show it’s pretty effective.”

As researchers continue to investigate PDT for patients with acne recalcitrant to conventional therapy, fundamental questions remain regarding its effectiveness and the optimal treatment parameters. Sally Ibbotson, MD, clinical senior lecturer in the Photobiology Unit of the University of Dundee in Scotland, examined the medical literature and published an editorial on the topic in Photodiagnosis and Photodynamic Therapy (2012;9:2-4). In a separate communication, Dr. Ibbotson said that “in my own experience and based on the literature, cystic and comedonal acne generally doesn’t do well with PDT. The consensus is that PDT could be considered for inflammatory acne if other conventional therapies prove ineffective or are contraindicated/not tolerated. The literature is most in support of photosensitizer pro-drug combined with red light but the jury is still out as to the optimal emission spectrum of source, dose, irradiance, and PDT regime to use.”

Although the approach of one PDT expert may prove the axiom “no pain, no gain,” he maintained that for properly selected patients, PDT consistently yields results comparable to treatment with isotretinoin with far less risk. Cmdr. Nathan S. Uebelhoer, DO, head of the dermatologic surgery and laser division at Naval Medical Center San Diego, cautioned that “to do it right takes a lot of time and there’s not a lot of reimbursement, but I love PDT. It works very, very well.” He presented on the topic at the Controversies in Cosmetic and Laser Surgery meeting in 2009 and 2010.

In contrast, Dr. Uebelhoer insisted that patient selection is critical to the success of PDT. “Inflammatory acne, including papular, pustular, and nodular acne, those patients do respond. I have treated patients with cystic acne, and as with isotretinoin, they respond modestly but they often need more than the normal regimen.” Patients with skin types III and IV must be advised that they will experience transient hyperpigmentation for about three months. And because treatments are painful, and patients must avoid sunlight for 36 hours post-treatment, young adults tend to be better candidates than teenagers.

Dr. Uebelhoer based his treatment regimen on the more classic approach of R. Rox Anderson, MD, the Harvard-based dermatologist who leads a team of researchers at the Wellman Center for Photomedicine. “One of Rox Anderson’s techniques is the long application of topical 5-Aminolevulinic acid (ALA),” he explained. “I leave it on for two or three hours. Then I’ll treat with somewhere between 100 and 200 joules of continuous wave LED red light, 630 to 635 nm. I wait two to four weeks (or shorter for type I or II skin) and I treat them again. I will usually treat patients four times, though I’ve done some five times and some twice.” After the first 36 hours, when peeling starts to occur, patients must wear sun protection outside, Dr. Uebelhoer said. “Peeling goes on for five to seven days post-op, then after seven days they’re bright red, and after 10 days they’re presentable in public.” Patients whose acne has affected their quality of life for years tell him that the downtime required by the regimen is a small price to pay, Dr. Uebelhoer said.

Dr. Uebelhoer admitted that “just like with oral retinoids, there’s going to be some level of recurrence” of acne after PDT. “Further treatment may require oral antibiotics or simple topicals or topical retinoids.” Citing Dr. Uebelhoer’s “exquisite results” with PDT, Dr. Dover nonetheless maintained that “he’s able to do things our patients just won’t tolerate.” Both physicians predicted that the results and the tolerability of PDT will improve as more dermatologists begin using it and refining the treatment parameters. dw
IMPORTANT INFORMATION ABOUT
DIFERIN® Gel
(adapalene) Gel, 0.3%

BRIEF SUMMARY
This summary contains important information about DIFERIN [Dif-er-in] Gel, 0.3%. It is not meant to take the place of your doctor’s instructions. Read this information carefully before you start using DIFERIN Gel, 0.3%. Ask your doctor or pharmacist if you do not understand any of this information or if you want to know more about DIFERIN Gel, 0.3%. For full Prescribing Information and Patient Information please see the package insert.

WHAT IS DIFERIN GEL, 0.3%?
DIFERIN (adapalene) Gel, 0.3% is a prescription medicine known as a retinoid and is indicated for the topical (skin use only) treatment of acne vulgaris in people 12 years of age and older.

WHO IS DIFERIN GEL, 0.3% FOR?
DIFERIN Gel, 0.3% is for patients age 12 and older. You should not use DIFERIN Gel, 0.3% if you are allergic to adapalene or any of the ingredients in DIFERIN Gel, 0.3%. For a complete listing of ingredients, please see the full prescribing information.

WHAT SHOULD I TELL MY DOCTOR BEFORE USING DIFERIN GEL, 0.3%?
Tell your doctor about all your health conditions, especially if you
• have other skin problems, including cuts or sunburn.
• have any other medical conditions.
• are pregnant or planning to become pregnant. It is not known if DIFERIN Gel, 0.3% can harm your unborn baby.
• are breastfeeding or plan to breastfeed. It is not known if DIFERIN Gel, 0.3% passes into your breast milk and if it can harm your baby.
• are using any other prescription or non-prescription medications, including vitamins and herbal supplements.
• Especially tell your doctor if you are using any other medication for acne. Using DIFERIN Gel, 0.3% with topical medicines that contain sulfur, resorcinol or salicylic acid may cause skin irritation.

WHAT SHOULD I AVOID WHILE USING DIFERIN GEL, 0.3%?
• You should avoid spending time in sunlight or artificial sunlight, such as tanning beds or sunlamps. DIFERIN Gel, 0.3% can make your skin sensitive to sun and the light from tanning beds and sunlamps. Use sunscreen and wear a hat and clothes that cover the areas treated by DIFERIN Gel, 0.3% if you have to be in sunlight.
• Weather extremes, such as cold or wind, may irritate the skin of patients using DIFERIN Gel, 0.3%.
• Products containing alpha hydroxy or glycolic acids should be avoided.
• This medication should not be applied to cuts, abrasions, eczematous or sunburned skin.
• Do not wax the treatment area while using DIFERIN Gel, 0.3%. It could damage the treated skin.
• Limit use of the following while using DIFERIN Gel, 0.3% as they may cause irritation:
  • harsh soaps
  • astringents
  • cosmetics that have strong skin drying effects
  • products with high concentrations of alcohol
  • preparations containing sulphur, resorcinol or salicylic acid
  • products containing alpha hydroxy or glycolic acid.

WHAT ARE THE MOST COMMON SIDE EFFECTS OF DIFERIN GEL, 0.3%?
The most common side effects associated with use of DIFERIN Gel, 0.3% are skin pain, skin peeling, and sunburn.
Other local skin reactions that are most likely to happen during the first 4 weeks of treatment and lessen with continued use of DIFERIN Gel, 0.3% include dryness, redness, burning/stinging, and scaling.
Moisturizers may be used if necessary.
If you experience any of the following symptoms of a potential allergic reaction while taking DIFERIN Gel, 0.3%, you should stop using the medication and consult a doctor.
• skin rash, itching or hives
• trouble breathing or chest pain
• swelling of your face, eyes, lips, tongue or throat
These are not all of the possible side effects of DIFERIN Gel, 0.3%. For more information, ask your doctor or pharmacist.
You are encouraged to report negative side effects of prescription drugs to the FDA at www.fda.gov/medwatch or call 1-800-FDA-1088. You may also contact GALDERMA LABORATORIES, L.P. AT 1-866-735-4137.

HOW SHOULD I USE DIFERIN GEL, 0.3%?
• Use DIFERIN Gel, 0.3% exactly as prescribed by your doctor.
• Unless you have been instructed otherwise, apply a thin film of DIFERIN Gel, 0.3% once daily to entire face or affected area(s) after washing gently with a non-medicated soap and patting the area dry.
• DIFERIN Gel, 0.3% is for skin use only. It is not for use in or on your mouth, eyes or vagina.
• Do not use more than the recommended amount daily as this will not produce faster results, but may increase irritation.

WHERE SHOULD I GO FOR MORE INFORMATION ABOUT DIFERIN GEL, 0.3%?
• Talk to your doctor or pharmacist
• Go to www.differin.com or call 1-866-735-4137

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*A phase 3b, 12-week, noninferiority, multicenter, investigator-blinded, controlled clinical study of patients 12 to 35 years of age with acne vulgaris (N=172).

*At the end of 12 weeks, neither product was found to be inferior. 160 patients participated in the satisfaction survey.

*A single-center, randomized, investigator-blinded, bilateral (split-face) comparison of healthy subjects ≥18 years of age (N=30). Subjects received Differin® Gel, 0.3% on one-half of the face and tretinoin gel microsphere, 0.04% on the other half for 21 days. Tolerability parameters (erythema, dryness, burning/stinging, and scaling) were assessed in healthy subjects.

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

Please see brief summary of Prescribing Information on adjacent page.

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