

# Topical Imiquimod, 5-FU Useful as Mohs Adjuncts

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MONTEREY, CALIF. — Pretreatment with topical imiquimod or 5-fluorouracil appears to improve surgical results in both basal cell and squamous cell carcinoma, Dr. Abel Torres reported at the annual meeting of the Pacific Dermatologic Association.

Published and unpublished studies by Dr. Torres, chief of the division of der-

matology at Loma Linda (Calif.) University and his colleagues indicate that these adjunctive treatments can be tissue sparing in Mohs surgery. Furthermore, adjunctive use of imiquimod cream appears to have an immunologic component that may be especially helpful for immunocompromised patients.

These adjunctive uses of 5-fluorouracil (5-FU) and imiquimod are off label, although both agents are labeled for the treatment of actinic keratoses and for su-

perfic basal cell carcinoma (BCC), he noted.

In an open-label series of 40 cases of squamous cell carcinoma (SCC), pretreatment with 5-FU 5% cream twice a day for 3 weeks, followed by Aquaphor for 3 weeks, appeared to be tissue sparing in the subsequent Mohs surgery. In addition, Dr. Torres' reported his clinical impression that there was no greater recurrence rate seen with this pretreatment than he would have expected without it.

The rationale for this treatment is that SCCs often have a superficial component that can be ill defined and difficult to distinguish from actinic keratoses. If one can remove the superficial component prior to surgery, the surgeon can maximize tissue preservation while still ensuring tumor removal.

Dr. Torres said it's important to wait at least 2 weeks after treatment with 5-FU before conducting the surgery. Otherwise, inflammation at histology is likely.

He cautioned that the results of randomized, double-blind, vehicle-controlled studies, which are in the planning stage, will be necessary before it will be possible to recommend this treatment without reservation.

One of the outstanding questions is whether the pretreatment will create "skip areas," essentially turning a unifocal lesion into a multifocal one. Until control data become available, patients should be advised of the innovative nature of this treatment.

Dr. Torres has already published a controlled study of imiquimod 5% cream as an adjunct to Mohs surgery in the treatment of basal cell carcinoma (BCC). Seventy-two patients with superficial or nevoid BCC were randomized to receive either vehicle or imiquimod cream five times a week for 2, 4, or 6 weeks before they underwent Mohs surgery (Dermatol. Surg. 2004;30:1462-9).

Only 6% of the patients receiving placebo showed evidence of histologic clearance. In contrast, two-thirds of patients using imiquimod had histologic clearance at 4 weeks or 6 weeks, a significant difference. The use of imiquimod also was associated with significant reductions in the size of the tumor and the size of the post-surgical defect.

There was only one skip area among the imiquimod patients, compared with five among placebo patients, a nonsignificant difference.

There was some indication of an immunologic aspect to the imiquimod treatment. For example, Dr. Torres observed that all five of one patient's lesions cleared, although only two were treated, indicating some kind of regional effect.

Dr. Torres concluded that using an immune modulator before surgery may improve outcome by eliminating the need for surgery in some individuals and by reducing the morbidity of the surgery and its cost by decreasing the size of the defect and the complexity of its repair.

The observation that imiquimod may be stimulating a regional immune response suggests that this adjunctive treatment may be especially useful in improving the efficacy of Mohs surgery in immune-compromised patients.

## BRIEF SUMMARY

(see package insert for full prescribing information)

**SOLODYN™**  
(MINOCYCLINE HCl, USP) EXTENDED RELEASE TABLETS

**Rx Only**  
**KEEP OUT OF REACH OF CHILDREN**

## INDICATIONS AND USAGE

SOLODYN™ is indicated to treat only inflammatory lesions of non-nodular moderate to severe acne vulgaris in patients 12 years of age and older. SOLODYN™ did not demonstrate any effect on non-inflammatory lesions. Safety of SOLODYN™ has not been established beyond 12 weeks of use.

This formulation of minocycline has not been evaluated in the treatment of infections.

To reduce the development of drug-resistant bacteria as well as to maintain the effectiveness of other antibacterial drugs, SOLODYN™ should be used only as indicated.

## CONTRAINDICATIONS

This drug is contraindicated in persons who have shown hypersensitivity to any of the tetracyclines.

## WARNINGS

### Teratogenic effects

1) MINOCYCLINE, LIKE OTHER TETRACYCLINE-CLASS ANTIBIOTICS, CAN CAUSE FETAL HARM WHEN ADMINISTERED TO A PREGNANT WOMAN. IF ANY TETRACYCLINE IS USED DURING PREGNANCY OR IF THE PATIENT BECOMES PREGNANT WHILE TAKING THESE DRUGS, THE PATIENT SHOULD BE APPRISED OF THE POTENTIAL HAZARD TO THE FETUS.

SOLODYN™ should not be used during pregnancy nor by individuals of either gender who are attempting to conceive a child (see PRECAUTIONS: Impairment of Fertility & Pregnancy).

2) THE USE OF DRUGS OF THE TETRACYCLINE CLASS DURING TOOTH DEVELOPMENT (LAST HALF OF PREGNANCY, INFANCY, AND CHILDHOOD UP TO THE AGE OF 8 YEARS) MAY CAUSE PERMANENT DISCOLORATION OF THE TEETH (YELLOW-GRAY-BROWN).

This adverse reaction is more common during long-term use of the drug but has been observed following repeated short-term courses. Enamel hypoplasia has also been reported. TETRACYCLINE DRUGS, THEREFORE, SHOULD NOT BE USED DURING TOOTH DEVELOPMENT.

3) All tetracyclines form a stable calcium complex in any bone-forming tissue. A decrease in fibula growth rate has been observed in premature human infants given oral tetracycline in doses of 25 mg/kg every 6 hours. This reaction was shown to be reversible when the drug was discontinued.

Results of animal studies indicate that tetracyclines cross the placenta, are found in fetal tissues, and can cause retardation of skeletal development on the developing fetus.

Evidence of embryotoxicity has been noted in animals treated early in pregnancy (see PRECAUTIONS: Pregnancy section).

### Gastro-intestinal effects

1. Pseudomembranous colitis has been reported with nearly all antibacterial agents and may range from mild to life-threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhea subsequent to the administration of antibacterial agents.

Treatment with antibacterial agents alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by *Clostridium difficile* is a primary cause of "antibiotic-associated colitis".

After the diagnosis of pseudomembranous colitis has been established, therapeutic measures should be initiated. Mild cases of pseudomembranous colitis usually respond to discontinuation of the drug alone. In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation, and treatment with an antibacterial drug clinically effective against *Clostridium difficile* colitis.

2. Hepatotoxicity — Post-marketing cases of serious liver injury, including irreversible drug-induced hepatitis and fulminant hepatic failure (sometimes fatal) have been reported with minocycline use in the treatment of acne.

### Metabolic effects

The anti-anabolic action of the tetracyclines may cause an increase in BUN. While this is not a problem in those with normal renal function, in patients with significantly impaired function, higher serum levels of tetracycline-class antibiotics may lead to azotemia, hyperphosphatemia, and acidosis. If renal impairment exists, even usual oral or

parenteral doses may lead to excessive systemic accumulations of the drug and possible liver toxicity. Under such conditions, lower than usual total doses are indicated, and if therapy is prolonged, serum level determinations of the drug may be advisable.

### Central nervous system effects

1. Central nervous system side effects including light-headedness, dizziness or vertigo have been reported with minocycline therapy. Patients who experience these symptoms should be cautioned about driving vehicles or using hazardous machinery while on minocycline therapy. These symptoms may disappear during therapy and usually rapidly disappear when the drug is discontinued.

2. Pseudotumor cerebri (benign intracranial hypertension) in adults and adolescents has been associated with the use of tetracyclines. Minocycline has been reported to cause or precipitate pseudotumor cerebri, the hallmark of which is papilledema. Clinical manifestations include headache and blurred vision. Bulging fontanelles have been associated with the use of tetracyclines in infants. Although signs and symptoms of pseudotumor cerebri resolve after discontinuation of treatment, the possibility for permanent sequelae such as visual loss that may be permanent or severe exists. Patients should be questioned for visual disturbances prior to initiation of treatment with tetracyclines and should be routinely checked for papilledema while on treatment.

Concomitant use of isotretinoin and minocycline should be avoided because isotretinoin, a systemic retinoid, is also known to cause pseudotumor cerebri.

### Photosensitivity

Photosensitivity manifested by an exaggerated sunburn reaction has been observed in some individuals taking tetracyclines. This has been reported rarely with minocycline. Patients should minimize or avoid exposure to natural or artificial sunlight (tanning beds or UVA/B treatment) while using minocycline. If patients need to be outdoors while using minocycline, they should wear loose-fitting clothes that protect skin from sun exposure and discuss other sun protection measures with their physician.

### PRECAUTIONS

#### General

Safety of SOLODYN™ beyond 12 weeks of use has not been established.

As with other antibiotic preparations, use of SOLODYN™ may result in overgrowth of non-susceptible organisms, including fungi. If superinfection occurs, the antibiotic should be discontinued and appropriate therapy instituted.

Bacterial resistance to the tetracyclines may develop in patients using SOLODYN™, therefore the susceptibility of bacteria associated with infection should be considered in selecting antimicrobial therapy. Because of the potential for drug-resistant bacteria to develop during the use of SOLODYN™, it should be used only as indicated.

#### Autoimmune Syndromes

Tetracyclines have been associated with the development of autoimmune syndromes. The long-term use of minocycline in the treatment of acne has been associated with drug-induced lupus-like syndrome, autoimmune hepatitis and vasculitis. Sporadic cases of serum sickness have presented shortly after minocycline use. Symptoms may be manifested by fever, rash, arthralgia, and malaise. In symptomatic patients, liver function tests, ANA, CBC, and other appropriate tests should be performed to evaluate the patients. Use of all tetracycline-class drugs should be discontinued immediately.

**Serious Skin/Hypersensitivity Reaction**  
Post-marketing cases of anaphylaxis and serious skin reactions such as Stevens Johnson syndrome and erythema multiforme have been reported with minocycline use in treatment of acne.

#### Tissue Hyperpigmentation

Tetracycline class antibiotics are known to cause hyperpigmentation. Tetracycline therapy may induce hyperpigmentation in many organs, including nails, bone, skin, eyes, thyroid, visceral tissue, oral cavity (teeth, mucosa, alveolar bone), sclerae and heart valves. Skin and oral pigmentation has been reported to occur independently of time or amount of drug administration, whereas other tissue pigmentation has been reported to occur upon prolonged administration. Skin pigmentation includes diffuse pigmentation as well as over sites of scars or injury.

#### Information for Patients

(See Patient Package Insert that accompanies this Package Insert for additional information to give patients)

1. Photosensitivity manifested by an exaggerated sunburn reaction has been observed in some individuals taking tetracyclines, including minocycline. Patients should minimize or avoid exposure to natural or artificial sunlight (tanning beds or UVA/B treatment) while using minocycline. If patients need to be outdoors while using minocycline, they should wear loose-fitting clothes that protect skin from sun exposure and discuss other sun protection measures with their physician.

2. Patients who experience central nervous system symptoms (see WARNINGS) should be cautioned about driving vehicles or using hazardous machinery while on minocycline therapy. Patients should also be cautioned about seeking medical help for headaches or blurred vision.

3. Concurrent use of tetracycline may render oral contraceptives less effective (See Drug Interactions).

4. Autoimmune syndromes, including drug-induced lupus-like syndrome, autoimmune hepatitis, vasculitis and serum sickness have been observed with tetracycline-class antibiotics, including minocycline. Symptoms may be manifested by arthralgia, fever, rash and malaise. Patients who experience such symptoms should be cautioned to stop the drug immediately and seek medical help.

5. Patients should be counseled about discoloration of skin, scars, teeth or gums that can arise from minocycline therapy.

6. Take SOLODYN™ exactly as directed. Skipping doses or not completing the full course of therapy may decrease the effectiveness of the current treatment course and increase the likelihood that bacteria will develop resistance and will not be treatable by other antibacterial drugs in the future.

7. SOLODYN™ should not be used by pregnant women or women attempting to conceive a child (See Pregnancy, Carcinogenesis and Mutagenesis sections).

8. It is recommended that SOLODYN™ not be used by men who are attempting to father a child (See Impairment of Fertility section).

9. SOLODYN™ should not be used by pregnant women or women attempting to conceive a child (See Pregnancy, Carcinogenesis and Mutagenesis sections).

10. It is recommended that SOLODYN™ not be used by men who are attempting to father a child (See Impairment of Fertility section).

**Laboratory Tests**  
Periodic laboratory evaluations of organ systems, including hematopoietic, renal and hepatic systems should be performed. Appropriate tests for autoimmune syndromes should be performed as indicated.

**Drug Interactions**  
1. Because tetracyclines have been shown to depress plasma prothrombin activity, patients who are on anticoagulant therapy may require downward adjustment of their anticoagulant dosage.

2. Since bacteriostatic drugs may interfere with the bactericidal action of penicillin, it is advisable to avoid giving tetracycline-class drugs in conjunction with penicillin.

3. The concurrent use of tetracycline and methoxyflurane has been reported to result in fatal renal toxicity.

4. Absorption of tetracyclines is impaired by antacids containing aluminum, calcium or magnesium and iron-containing preparations.

5. In a multi-center study to evaluate the effect of SOLODYN™ on low dose oral contraceptives, hormone levels over one menstrual cycle with and without SOLODYN™ 1 mg/kg once-daily were measured.

Based on the results of this trial, minocycline-related changes in estradiol, progesterone, FSH and LH plasma levels, of breakthrough bleeding, or of contraceptive failure, can not be ruled out. To avoid contraceptive failure, female patients are advised to use a second form of contraceptive during treatment with minocycline.

**Drug/Laboratory Test Interactions**  
False elevations of urinary catecholamine levels may occur due to interference with the fluorescence test.

**Carcinogenesis, Mutagenesis & Impairment of Fertility**  
**Carcinogenesis** — Long-term animal studies have not been performed to evaluate the carcinogenic potential of minocycline. A structurally related compound, oxytetracycline, was found to produce adrenal and pituitary tumors in rats.

**Mutagenesis** — Minocycline was not mutagenic *in vitro* in a bacterial reverse mutation assay (Ames test) or CHO/HGPRT mammalian cell assay in the presence or absence of metabolic activation. Minocycline was not clastogenic *in vitro* using human peripheral blood lymphocytes or *in vivo* in a mouse micronucleus test.

**Impairment of Fertility** — Male and female reproductive performance in rats was unaffected by oral doses of minocycline of up to 300 mg/kg/day (which resulted in up to approximately 40 times the level of systemic exposure to minocycline observed in patients as a result of use of SOLODYN™). However, oral administration of 100 or 300 mg/kg/day of minocycline to male rats (resulting in approximately 15 to 40 times the level of systemic exposure to minocycline observed in patients as a result of use of SOLODYN™) adversely affected spermatogenesis. Effects observed at 300 mg/kg/day included a reduced number of sperm cells per gram of epididymis, an apparent reduction in the percentage of sperm that were motile, and (at 100 and 300 mg/kg/day) increased numbers of morphologically abnormal sperm cells. Morphological abnormalities observed in sperm samples included absent heads, misshapen heads, and abnormal flagella.

Limited human studies suggest that minocycline may have a deleterious effect on spermatogenesis.

SOLODYN™ should not be used by individuals of either gender who are attempting to conceive a child.

**Pregnancy — Teratogenic Effects: Pregnancy category D (See WARNINGS)**  
All pregnancies have a background risk of birth defects, loss, or other adverse outcome regardless of drug exposure. There are no adequate and well-controlled studies on the use of minocycline in pregnant women.

Minocycline, like other tetracycline-class antibiotics, crosses the placenta and may cause fetal harm when administered to a pregnant woman. Rare spontaneous reports of congenital anomalies including limb reduction have been reported with minocycline use in pregnancy in post-marketing experience. Only limited information is available regarding these reports; therefore, no conclusion on causal association can be established.

Minocycline induced skeletal malformations (bent limb bones) in fetuses when administered to pregnant rats and rabbits in doses of 30 mg/kg/day and 100 mg/kg/day, respectively, (resulting in approximately 3 times and 2 times, respectively, the systemic exposure to minocycline observed in patients as a result of use of SOLODYN™). Reduced mean fetal body weight was observed in studies in which minocycline was administered to pregnant rats at a dose of 10 mg/kg/day (which resulted in approximately the same level of systemic exposure to minocycline as that observed in patients who use SOLODYN™).

SOLODYN™ should not be used during pregnancy. If the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus and stop treatment immediately.

**Nursing Mothers**  
Tetracycline-class antibiotics are excreted in human milk. Because of the potential for serious adverse effects on bone and tooth development in nursing infants from the tetracycline-class antibiotics, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother (see WARNINGS).

**Pediatric Use**  
SOLODYN™ is indicated to treat only inflammatory lesions of non-nodular moderate to severe acne vulgaris in patients 12 years and older. Safety and effectiveness in pediatric patients below the age of 12 has not been established.

Use of tetracycline-class antibiotics below the age of 8 is not recommended due to the potential for tooth discoloration (see WARNINGS).

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

**ADVERSE REACTIONS**  
Because clinical trials are conducted under prescribed conditions, adverse reaction rates observed in the clinical trial may not reflect the rates observed in practice. However, adverse reaction information from clinical trials provides a basis for identifying the adverse events that appear to be related to drug use.

Adverse events reported in clinical trials for SOLODYN™ are described below in Table 2.

**Table 2 — Selected Treatment-Emergent Adverse Events in at least 1% of Clinical Trial Subjects**

Adverse Event	SOLODYN™ (1 mg/kg) N=674 (%)	PLACEBO N=364 (%)
At least one treatment-emergent event	379 (56)	197 (54)
Headache	152 (23)	83 (23)
Fatigue	62 (9)	24 (7)
Dizziness	59 (9)	17 (5)
Pruritus	31 (5)	16 (4)
Malaise	26 (4)	9 (3)
Mood alteration	17 (3)	9 (3)
Somnolence	13 (2)	3 (1)
Urticaria	10 (2)	1 (0)
Timinitis	10 (2)	5 (1)
Arthralgia	9 (1)	2 (0)
Vertigo	8 (1)	3 (1)
Dry mouth	7 (1)	5 (1)
Myalgia	7 (1)	4 (1)

Adverse reactions not observed in the clinical trials, but that have been reported with minocycline hydrochloride use in a variety of indications include:

**Skin and hypersensitivity reactions:** fixed drug eruptions, balanitis, erythema multiforme, Stevens-Johnson syndrome, anaphylactoid purpura, photosensitivity, pigmentation of skin and mucous membranes, hypersensitivity reactions, angioneurotic edema, anaphylaxis.

**Autoimmune conditions:** polyarthralgia, pericarditis, exacerbation of systemic lupus, pulmonary infiltrates with eosinophilia, transient lupus-like syndrome.

**Central nervous system:** pseudotumor cerebri, bulging fontanelles in infants, decreased hearing.

**Endocrine:** thyroid discoloration, abnormal thyroid function.

**Oncology:** papillary thyroid cancer.

**Oral:** glossitis, dysphagia, tooth discoloration.

**Gastrointestinal:** enterocolitis, pancreatitis, hepatitis, liver failure.

**Renal:** reversible acute renal failure.

**Hematology:** hemolytic anemia, thrombocytopenia, eosinophilia.

Preliminary studies suggest that use of minocycline may have deleterious effects on human spermatogenesis (see Carcinogenesis, Mutagenesis, Impairment of Fertility section).

## OVERDOSAGE

In case of overdosage, discontinue medication, treat symptomatically and institute supportive measures. Minocycline is not removed in significant quantities by hemodialysis or peritoneal dialysis.

## DOSE AND ADMINISTRATION

See the full package insert for complete Dosage and Administration information.

## HOW SUPPLIED

SOLODYN™ (MINOCYCLINE HCl, USP) Extended Release Tablets are supplied as aqueous film coated tablets containing minocycline hydrochloride equivalent to 45 mg, 90 mg or 135 mg minocycline.

The 45 mg extended release tablets are gray, unscored, coated, and debossed with "DYN-045" on one side. Each tablet contains minocycline hydrochloride equivalent to 45 mg minocycline, supplied as follows:

NDC 99207-460-10 Bottle of 100  
NDC 99207-460-11 Bottle of 1000

The 90 mg extended release tablets are yellow, unscored, coated, and debossed with "DYN-090" on one side. Each tablet contains minocycline hydrochloride equivalent to 90 mg minocycline, supplied as follows:

NDC 99207-461-10 Bottle of 100  
NDC 99207-461-11 Bottle of 1000

The 135 mg extended release tablets are pink (orange-brown), unscored, coated, and debossed with "DYN-135" on one side. Each tablet contains minocycline hydrochloride equivalent to 135 mg minocycline, supplied as follows:

NDC 99207-462-10 Bottle of 100  
NDC 99207-462-11 Bottle of 1000

Store at 25°C (77°F); excursions are permitted to 15°-30°C (59°-86°F) [See USP Controlled Room Temperature].

Protect from light, moisture, and excessive heat. Dispense in tight, light-resistant container with child-resistant closure.

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