

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**Approval Package for:**

***APPLICATION NUMBER:***

**NDA 50-808/S-014**

***Trade Name:*** Solodyn

***Generic Name:*** minocycline HCl

***Sponsor:*** Medicis Pharmaceutical Corporation

***Approval Date:*** March 18, 2011

***Indications:*** A tetracycline-class drug indicated to treat only inflammatory lesions of non-nodular moderate to severe acne vulgaris in patients 12 years of age and older.

# CENTER FOR DRUG EVALUATION AND RESEARCH

*APPLICATION NUMBER:*  
**NDA 50-808/S-014**

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*APPLICATION NUMBER:*  
**NDA 50-808/S-014**

**APPROVAL LETTER**



NDA 050808/S-014

**SUPPLEMENT APPROVAL**

Medicis Pharmaceutical Corporation  
Attention: Ann Seaback, RAC  
Manager, Regulatory Affairs  
7720 North Dobson Road  
Scottsdale, AZ 85256

Dear Ms. Seaback:

Please refer to your Supplemental New Drug Application (sNDA) dated September 29, 2010, received September 29, 2010, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Solodyn® (minocycline HC1) Extended Release Tablets, 45, 55, 65, 80, 90, 105, 115, and 135 mg.

We acknowledge receipt of your amendments dated October 29, 2010, February 22, March 4 and 14, 2011.

This "Prior Approval" supplemental new drug application proposes changes in the Warnings and Precautions and Adverse Reactions sections of the label. Additionally, the supplement provides for revisions to the Patient Package Insert.

We have completed our review of this supplemental application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text.

**CONTENT OF LABELING**

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Content of labeling must be identical to the enclosed labeling (text for the package insert and text for the patient package insert), with the addition of any labeling changes in pending "Changes Being Effected" (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

Information on submitting SPL files using eLIST may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As" at <http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf>.

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in MS Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes and annotate each change. To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

### **LETTERS TO HEALTH CARE PROFESSIONALS**

If you decide to issue a letter communicating important safety-related information about this drug product (i.e., a “Dear Health Care Professional” letter), we request that you submit, at least 24 hours prior to issuing the letter, an electronic copy of the letter to this NDA to the following address:

MedWatch Program  
Office of Special Health Issues  
Food and Drug Administration  
10903 New Hampshire Ave  
Building 32, Mail Stop 5353  
Silver Spring, MD 20993

### **PROMOTIONAL MATERIALS**

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit the following, in triplicate, (1) a cover letter requesting advisory comments, (2) the proposed materials in draft or mock-up form with annotated references, and (3) the package insert(s) to:

Food and Drug Administration  
Center for Drug Evaluation and Research  
Division of Drug Marketing, Advertising, and Communications  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

You must submit final promotional materials and package insert(s), accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at <http://www.fda.gov/opacom/morechoices/fdaforms/cder.html>; instructions are provided on page 2 of the form. For more information about submission of promotional materials to the Division of Drug Marketing, Advertising, and Communications (DDMAC), see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>.

All promotional materials that include representations about your drug product must be promptly revised to be consistent with the labeling changes approved in this supplement, including any

new safety information [21 CFR 314.70(a)(4)]. The revisions in your promotional materials should include prominent disclosure of the important new safety information that appears in the revised package labeling. Within 7 days of receipt of this letter, submit your statement of intent to comply with 21 CFR 314.70(a)(4) to the address above or by fax to 301-847-8444.

**REPORTING REQUIREMENTS**

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Cristina Attinello, Regulatory Project Manager, at (301) 796-3986.

Sincerely,

*{See appended electronic signature page}*

Tatiana Oussova, M.D., M.P.H.  
Deputy Director for Safety  
Division of Dermatology and Dental Products  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research

ENCLOSURE:  
Content of Labeling

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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TATIANA OUSSOVA  
03/18/2011

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**NDA 50-808/S-014**

**LABELING**

**HIGHLIGHTS OF PRESCRIBING INFORMATION**

These highlights do not include all the information needed to use SOLODYN<sup>®</sup> safely and effectively. See full prescribing information for SOLODYN<sup>®</sup>.

**SOLODYN<sup>®</sup>**  
**(minocycline HCl) Extended Release Tablets for oral use**  
**Initial U.S. Approval: 1971**

**INDICATIONS AND USAGE**  
 SOLODYN<sup>®</sup> is a tetracycline-class drug indicated to treat only inflammatory lesions of non-nodular moderate to severe acne vulgaris in patients 12 years of age and older. (1)

**DOSAGE AND ADMINISTRATION**  
 The recommended dosage of SOLODYN<sup>®</sup> is approximately 1 mg/kg once daily for 12 weeks. (2)

**DOSAGE FORMS AND STRENGTHS**  
 Extended release tablets: 45, 55, 65, 80, 90, 105, 115, and 135 mg (3)

**CONTRAINDICATIONS**  
 This drug is contraindicated in persons who have shown hypersensitivity to any of the tetracyclines. (4)

**WARNINGS AND PRECAUTIONS**

- The use of SOLODYN 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). (5.1)
- If pseudomembranous colitis occurs, discontinue SOLODYN. (5.2)
- If liver injury is suspected, discontinue SOLODYN. (5.3)
- If renal impairment exists, SOLODYN doses may need to be adjusted to avoid excessive systemic accumulations of the drug and possible liver toxicity. (5.4)
- Minocycline may cause central nervous system side effects including light-headedness, dizziness, or vertigo. Advise patients. (5.5)

- Minocycline may cause pseudotumor cerebri (benign intracranial hypertension) in adults and adolescents. Discontinue SOLODYN if symptoms occur. (5.6)
- Minocycline has been associated with autoimmune syndromes; discontinue SOLODYN immediately if symptoms occur. (5.7)
- Minocycline has been associated with anaphylaxis, serious skin reactions, erythema multiforme, and DRESS syndrome. Discontinue SOLODYN<sup>®</sup> immediately if symptoms occur. (5.9)

**ADVERSE REACTIONS**  
 The most commonly observed adverse reactions (incidence ≥ 5%) are headache, fatigue, dizziness, and pruritus. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Medicus, The Dermatology Company at 1-800-900-6389 or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch).

- DRUG INTERACTIONS**
- Patients who are on anticoagulant therapy may require downward adjustment of their anticoagulant dosage. (7.1)
  - The concurrent use of tetracycline and methoxyflurane has been reported to result in fatal renal toxicity. (7.3)
  - To avoid contraceptive failure, female patients are advised to use a second form of contraceptive during treatment with minocycline. (7.5)

- USE IN SPECIFIC POPULATIONS**
- Minocycline like other tetracycline-class drugs can cause fetal harm when administered to a pregnant woman (5.1, 8.1)
  - The use of drugs of the tetracycline class during tooth development may cause permanent discoloration of teeth (5.1, 8.4)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 03/2011

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**FULL PRESCRIBING INFORMATION****1 INDICATIONS AND USAGE****1.1 Indication**

SOLODYN<sup>®</sup> is indicated to treat only inflammatory lesions of non-nodular moderate to severe acne vulgaris in patients 12 years of age and older.

**1.2 Limitations of Use**

SOLODYN<sup>®</sup> did not demonstrate any effect on non-inflammatory acne lesions. Safety of SOLODYN<sup>®</sup> has not been established beyond 12 weeks of use. This formulation of minocycline has not been evaluated in the treatment of infections [see *Clinical Studies* (14)].

To reduce the development of drug-resistant bacteria as well as to maintain the effectiveness of other antibacterial drugs, SOLODYN<sup>®</sup> should be used only as indicated [see *Warnings and Precautions* (5.11)].

**2 DOSAGE AND ADMINISTRATION**

The recommended dosage of SOLODYN<sup>®</sup> is approximately 1 mg/kg once daily for 12 weeks. Higher doses have not shown to be of additional benefit in the treatment of inflammatory lesions of acne, and may be associated with more acute vestibular side effects.

The following table shows tablet strength and body weight to achieve approximately 1 mg/kg.

**Table 1: Dosing Table for SOLODYN<sup>®</sup>**

Patient's Weight (lbs.)	Patient's Weight (kg)	Tablet Strength (mg)	Actual mg/kg Dose
99 – 109	45 – 49	45	1 – 0.92
110 – 131	50 – 59	55	1.10 – 0.93
132 – 157	60 – 71	65	1.08 – 0.92
158 – 186	72 – 84	80	1.11 – 0.95
187 – 212	85 – 96	90	1.06 – 0.94
213 – 243	97 – 110	105	1.08 – 0.95
244 – 276	111 – 125	115	1.04 – 0.92
277 – 300	126 – 136	135	1.07 – 0.99

SOLODYN<sup>®</sup> Tablets may be taken with or without food [see *Clinical Pharmacology* (12)]. Ingestion of food along with SOLODYN<sup>®</sup> may help reduce the risk of esophageal irritation and ulceration.

In patients with renal impairment, the total dosage should be decreased by either reducing the recommended individual doses and/or by extending the time intervals between doses [see *Warnings and Precautions* (5.4)].

**3 DOSAGE FORMS AND STRENGTHS**

- 45 mg extended release tablets: gray, unscored, coated, and debossed with "DYN-045" on one side.
- 55 mg extended release tablets: pink, unscored, coated, and debossed with "DYN-055" on one side.
- 65 mg extended release tablets: blue, unscored, coated, and debossed with "DYN-065" on one side.
- 80 mg extended release tablets: gray, unscored, coated, and debossed with "DYN-080" on one side.
- 90 mg extended release tablets: yellow, unscored, coated, and debossed with "DYN-090" on one side.
- 105 mg extended release tablets: purple, unscored, coated, and debossed with "DYN-105" on one side.
- 115 mg extended release tablets: green, unscored, coated, and debossed with "DYN-115" on one side.
- 135 mg extended release tablets: pink (orange-brown), unscored, coated, and debossed with "DYN-135" on one side.

**4 CONTRAINDICATIONS**

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

**5 WARNINGS AND PRECAUTIONS****5.1 Teratogenic Effects**

- A. MINOCYCLINE, LIKE OTHER TETRACYCLINE-CLASS DRUGS, 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<sup>®</sup> should not be used during pregnancy or by individuals of either gender who are attempting to conceive a child [see *Nonclinical Toxicology* (13.1) & *Use in Specific Populations* (8.1)].

- B. 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.

- C. 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 *Use in Specific Populations* (8.1)].

**5.2 Pseudomembranous Colitis**

**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.

**5.3 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.

**5.4 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 drugs 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.

## 5.5 Central Nervous System Effects

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.

## 5.6 Benign Intracranial Hypertension

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. If visual disturbance occurs during treatment, patients should be checked for papilledema. Concomitant use of isotretinoin and minocycline should be avoided because isotretinoin, a systemic retinoid, is also known to cause pseudotumor cerebri.

## 5.7 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.

## 5.8 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.

## 5.9 Serious Skin/Hypersensitivity Reaction

Cases of anaphylaxis, serious skin reactions (e.g. Stevens Johnson syndrome), erythema multiforme, and drug rash with eosinophilia and systemic symptoms (DRESS) syndrome have been reported postmarketing with minocycline use in patients with acne. DRESS syndrome consists of cutaneous reaction (such as rash or exfoliative dermatitis), eosinophilia, and one or more of the following visceral complications such as: hepatitis, pneumonitis, nephritis, myocarditis, and pericarditis. Fever and lymphadenopathy may be present. In some cases, death has been reported. If this syndrome is recognized, the drug should be discontinued immediately.

## 5.10 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.

## 5.11 Development of Drug Resistant Bacteria

Bacterial resistance to the tetracyclines may develop in patients using SOLODYN<sup>®</sup>, 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<sup>®</sup>, it should be used only as indicated.

## 5.12 Superinfection

As with other antibiotic preparations, use of SOLODYN<sup>®</sup> may result in overgrowth of nonsusceptible organisms, including fungi. If superinfection occurs, SOLODYN<sup>®</sup> should be discontinued and appropriate therapy instituted.

## 5.13 Laboratory Monitoring

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

## 6 ADVERSE REACTIONS

### 6.1 Clinical Trial 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.

The following table summarizes selected adverse reactions reported in clinical trials at a rate of  $\geq 1\%$  for SOLODYN<sup>®</sup>.

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

Adverse Reactions	SOLODYN <sup>®</sup> (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)
Tinnitus	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)

### 6.2 Postmarketing Experience

Adverse reactions 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, DRESS syndrome [see *Warnings and Precautions* (5.9)].

*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* brown-black microscopic thyroid discoloration, abnormal thyroid function.

*Oncology* 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 *Nonclinical Toxicology* (13.1)].

## 7 DRUG INTERACTIONS

### 7.1 Anticoagulants

Because tetracyclines have been shown to depress plasma prothrombin activity, patients who are on anticoagulant therapy may require downward

adjustment of their anticoagulant dosage.

## 7.2 Penicillin

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

## 7.3 Methoxyflurane

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

## 7.4 Antacids and Iron Preparations

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

## 7.5 Low Dose Oral Contraceptives

In a multi-center study to evaluate the effect of SOLODYN<sup>®</sup> on low dose oral contraceptives, hormone levels over one menstrual cycle with and without SOLODYN<sup>®</sup> 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.

## 7.6 Drug/Laboratory Test Interactions

False elevations of urinary catecholamine levels may occur due to interference with the fluorescence test.

## 8 USE IN SPECIFIC POPULATIONS

### 8.1 Pregnancy

*Teratogenic Effects* Pregnancy category D [see Warnings and Precautions (5.1)]

SOLODYN<sup>®</sup> 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.

There are no adequate and well-controlled studies on the use of minocycline in pregnant women. Minocycline, like other tetracycline-class drugs, 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<sup>®</sup>). 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<sup>®</sup>).

Minocycline was assessed for effects on peri- and post-natal development of rats in a study that involved oral administration to pregnant rats from day 6 of gestation through the period of lactation (postpartum day 20), at dosages of 5, 10, or 50 mg/kg/day. In this study, body weight gain was significantly reduced in pregnant females that received 50 mg/kg/day (resulting in approximately 2.5 times the systemic exposure to minocycline observed in patients as a result of use of SOLODYN<sup>®</sup>). No effects of treatment on the duration of the gestation period or the number of live pups born per litter were observed. Gross external anomalies observed in F1 pups (offspring of animals that received minocycline) included reduced body size, improperly rotated forelimbs, and reduced size of extremities. No effects were observed on the physical development, behavior, learning ability, or reproduction of F1 pups, and there was no effect on gross appearance of F2 pups (offspring of F1 animals).

### 8.3 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 and Precautions (5.1)].

## 8.4 Pediatric Use

**SOLODYN<sup>®</sup> 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 and Precautions (5.1)].

## 8.5 Geriatric Use

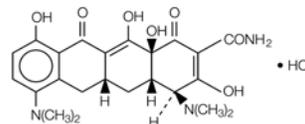
Clinical studies of SOLODYN<sup>®</sup> did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, 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.

## 10 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.

## 11 DESCRIPTION

Minocycline hydrochloride, a semi synthetic derivative of tetracycline, is [4S-(4 $\alpha$ ,4 $\alpha$ ,5 $\alpha$ ,12 $\alpha$ )]-4,7-Bis(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacene-carboxamide mono hydrochloride. The structural formula is represented below:



M. W. 493.95

SOLODYN<sup>®</sup> Tablets for oral administration contain minocycline hydrochloride USP equivalent to 45 mg, 55 mg, 65 mg, 80 mg, 90 mg, 105 mg, 115 mg or 135 mg of minocycline. In addition, 45 mg, 55 mg, 65 mg, 80 mg, 90 mg, 105 mg, 115 mg, and 135 mg tablets contain the following inactive ingredients: lactose monohydrate NF, hypromellose type 2910 USP, magnesium stearate NF, colloidal silicon dioxide NF, and carnauba wax NF. The 45 mg tablets also contain Opadry II Gray which contains: lactose monohydrate NF, hypromellose type 2910 USP, titanium dioxide USP, triacetin USP, and iron oxide black JPE. The 55 mg tablets also contain Opadry II Pink which contains: hypromellose type 2910 USP, titanium dioxide USP, lactose monohydrate NF, polyethylene glycol 3350 NF, triacetin USP, and FD&C Red #40. The 65 mg tablets also contain Opadry II Blue which contains: hypromellose type 2910 USP, lactose monohydrate NF, FD&C Blue #1, polyethylene glycol 3350 NF, FD&C Blue #2, titanium dioxide USP, triacetin USP, and D&C Yellow #10. The 80 mg tablets also contain Opadry II Gray which contains: hypromellose type 2910 USP, lactose monohydrate NF, polyethylene glycol 3350 NF, FD&C Blue #2, FD&C Red #40, titanium dioxide USP, triacetin USP, and FD&C Yellow #6. The 90 mg tablets also contain Opadry II Yellow which contains: hypromellose type 2910 USP, lactose monohydrate NF, titanium dioxide USP, iron oxide yellow NF, polyethylene glycol 3350 NF, and triacetin USP. The 105 mg tablets also contain Opadry II Purple which contains: hypromellose type 2910 USP, lactose monohydrate NF, titanium dioxide USP, D&C Red #27, polyethylene glycol 3350 NF, triacetin USP, and FD&C Blue #1. The 115 mg tablets also contain Opadry II Green which contains: hypromellose type 2910 USP, lactose monohydrate NF, D&C Yellow #10, triacetin USP, FD&C Blue #1, titanium dioxide USP, and FD&C Blue #2. The 135 mg tablets also contain Opadry II Pink which contains: hypromellose type 2910 USP, lactose monohydrate NF, titanium dioxide USP, polyethylene glycol 3350 NF, iron oxide red NF, and triacetin USP.

## 12 CLINICAL PHARMACOLOGY

### 12.1 Mechanism of Action

The mechanism of action of SOLODYN<sup>®</sup> for the treatment of acne is unknown.

### 12.2 Pharmacodynamics

The pharmacodynamics of SOLODYN<sup>®</sup> for the treatment of acne are unknown.

### 12.3 Pharmacokinetics

SOLODYN<sup>®</sup> Tablets are not bioequivalent to non-modified release minocycline products. Based on pharmacokinetic studies in healthy adults, SOLODYN<sup>®</sup> Tablets produce a delayed T<sub>max</sub> at 3.5–4.0 hours as compared to a non-modified release reference minocycline product (T<sub>max</sub> at 2.25–3 hours). At steady-state (Day 6), the mean AUC(0–24) and C<sub>max</sub> were 33.32 µg×hr/mL and 2.63 µg/mL for SOLODYN<sup>®</sup> Tablets and 46.35 µg×hr/mL and 2.92 µg/mL for Minocin<sup>®</sup> capsules, respectively. These parameters are based on dose adjusted to 135 mg per day for both products.

A single-dose, four-way crossover study demonstrated that SOLODYN<sup>®</sup> Tablets used in the study (45 mg, 90 mg, 135 mg) exhibited dose-proportional pharmacokinetics. In another single-dose, five-way crossover pharmacokinetic study, SOLODYN<sup>®</sup> Tablets 55 mg, 80 mg, and 105 mg were shown to be dose-proportional to SOLODYN<sup>®</sup> Tablets 90 mg and 135 mg.

When SOLODYN<sup>®</sup> Tablets were administered concomitantly with a meal that included dairy products, the extent and timing of absorption of minocycline did not differ from that of administration under fasting conditions.

Minocycline is lipid soluble and distributes into the skin and sebum.

## 13 NONCLINICAL TOXICOLOGY

### 13.1 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<sup>®</sup>). 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<sup>®</sup>) 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<sup>®</sup> should not be used by individuals of either gender who are attempting to conceive a child.

## 14 CLINICAL STUDIES

The safety and efficacy of SOLODYN<sup>®</sup> in the treatment of inflammatory lesions of non-nodular moderate to severe acne vulgaris was assessed in two 12-week, multi-center, randomized, double-blind, placebo-controlled, studies in subjects ≥ 12 years. The mean age of subjects was 20 years and subjects were from the following racial groups: White (73%), Hispanic (13%), Black (11%), Asian/Pacific Islander (2%), and Other (2%).

In two efficacy and safety trials, a total of 924 subjects with non-nodular moderate to severe acne vulgaris received SOLODYN<sup>®</sup> or placebo for a total of 12 weeks, according to the following dose assignments.

**Table 3: Clinical Studies Dosing Table**

Subject's Weight (lbs)	Subject's Weight (kg)	Available Caplet Strength (mg)	Actual mg/kg Dose
99 – 131	45 – 59	45	1 – 0.76
132 – 199	60 – 90	90	1.5 – 1
200 – 300	91 – 136	135	1.48 – 0.99

The two primary efficacy endpoints were:

- 1) Mean percent change in inflammatory lesion counts from Baseline to 12 weeks.
- 2) Percentage of subjects with an Evaluator's Global Severity Assessment (EGSA) of clear or almost clear at 12 weeks.

Efficacy results are presented in Table 4.

**Table 4: Efficacy Results at Week 12**

	Study 1		Study 2	
	SOLODYN <sup>®</sup> (1 mg/kg) N = 300	Placebo N = 151	SOLODYN <sup>®</sup> (1 mg/kg) N = 315	Placebo N = 158
Mean Percent Improvement in Inflammatory Lesions	43.1%	31.7%	45.8%	30.8%
No. (%) of Subjects Clear or Almost Clear on the EGSA*	52 (17.3%)	12 (7.9%)	50 (15.9%)	15 (9.5%)

\*Evaluator's Global Severity Assessment

**SOLODYN<sup>®</sup> did not demonstrate any effect on non-inflammatory lesions (benefit or worsening).**

## 16 HOW SUPPLIED/STORAGE AND HANDLING

### 16.1 How Supplied

SOLODYN<sup>®</sup> (minocycline HCl, USP) Extended Release Tablets are supplied as aqueous film coated tablets containing minocycline hydrochloride equivalent to 45 mg, 55 mg, 65 mg, 80 mg, 90 mg, 105 mg, 115 mg or 135 mg minocycline, are supplied as follows.

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 99207-460-30	Bottle of 30
NDC 99207-460-10	Bottle of 100

The 55 mg extended release tablets are pink, unscored, coated, and debossed with "DYN-055" on one side. Each tablet contains minocycline hydrochloride equivalent to 55 mg minocycline, supplied as follows:

NDC 99207-465-30	Bottle of 30
------------------	--------------

The 65 mg extended release tablets are blue, unscored, coated, and debossed with "DYN-065" on one side. Each tablet contains minocycline hydrochloride equivalent to 65 mg minocycline, supplied as follows:

NDC 99207-463-30	Bottle of 30
------------------	--------------

The 80 mg extended release tablets are gray, unscored, coated, and debossed with "DYN-080" on one side. Each tablet contains minocycline hydrochloride equivalent to 80 mg minocycline, supplied as follows:

NDC 99207-466-30	Bottle of 30
------------------	--------------

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 99207-461-30	Bottle of 30
NDC 99207-461-10	Bottle of 100

The 105 mg extended release tablets are purple, unscored, coated, and debossed with "DYN-105" on one side. Each tablet contains minocycline hydrochloride equivalent to 105 mg minocycline, supplied as follows:

NDC 99207-467-30	Bottle of 30
------------------	--------------

The 115 mg extended release tablets are green, unscored, coated, and debossed with “DYN-115” on one side. Each tablet contains minocycline hydrochloride equivalent to 115 mg minocycline, supplied as follows:

NDC 99207-464-30	Bottle of 30
------------------	--------------

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 99207-462-30	Bottle of 30
NDC 99207-462-10	Bottle of 100

## 16.2 Storage

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

## 16.3 Handling

Keep out of reach of children.

Protect from light, moisture, and excessive heat.

Dispense in tight, light-resistant container with child-resistant closure.

## 17 PATIENT COUNSELING INFORMATION

[See FDA-approved patient labeling (Patient Information)]

Patients taking SOLODYN<sup>®</sup> (minocycline HCl, USP) Extended Release Tablets should receive the following information and instructions:

- SOLODYN<sup>®</sup> should not be used by pregnant women or women attempting to conceive a child [see *Use in Specific Populations* (8.1), *Nonclinical Toxicology* (13.1)].
- It is recommended that SOLODYN<sup>®</sup> not be used by men who are attempting to father a child [see *Nonclinical Toxicology* (13.1)].
- Patients should be advised that pseudomembranous colitis can occur with minocycline therapy. If patients develop watery or bloody stools, they should seek medical attention
- Patients should be counseled about the possibility of hepatotoxicity. Patients should seek medical advice if they experience symptoms which can include loss of appetite, tiredness, diarrhea, skin turning yellow, bleeding easily, confusion, and sleepiness.
- Patients who experience central nervous system symptoms [see *Warnings and Precautions* (5.5)] should be cautioned about driving vehicles or using hazardous machinery while on minocycline therapy. Patients should seek medical help for persistent headaches or blurred vision.
- Concurrent use of tetracycline may render oral contraceptives less effective [see *Drug Interactions* (7.5)].
- Autoimmune syndromes, including drug-induced lupus-like syndrome, autoimmune hepatitis, vasculitis and serum sickness have been observed with tetracycline-class drugs, 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.
- Patients should be counseled about discoloration of skin, scars, teeth or gums that can arise from minocycline therapy.
- 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. Treatment should be discontinued at the first evidence of skin erythema.

- SOLODYN<sup>®</sup> should be taken 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.
- Patients should be advised to swallow SOLODYN<sup>®</sup> tablets whole and not to chew, crush, or split the tablets.

Patient Information  
SOLODYN<sup>®</sup> (SO-lo-dīn)  
(minocycline HCl)

**Extended Release Tablets**

Read this Patient Information leaflet that comes with SOLODYN<sup>®</sup> before you start taking it and each time you get a refill. There may be new information. This leaflet does not take the place of talking with your doctor about your condition or treatment.

**What is SOLODYN<sup>®</sup>?**

SOLODYN<sup>®</sup> is a tetracycline class drug. SOLODYN<sup>®</sup> is prescription medicine used to treat pimples and red bumps (non-nodular inflammatory lesions) that happen with moderate to severe acne vulgaris in people 12 years and older. SOLODYN<sup>®</sup> is not effective for acne that is not red-looking (this means acne that is not inflammatory).

It is not known if SOLODYN<sup>®</sup> is:

- safe for use longer than 12 weeks.
- safe and effective for the treatment of infections.
- safe and effective in children under the age of 12 years.

**Who should not take SOLODYN<sup>®</sup>?**

Do not take SOLODYN<sup>®</sup> if you are allergic to tetracycline class drugs. Ask your doctor or pharmacist for a list of these medicines if you are not sure.

**What should I tell my doctor before taking SOLODYN<sup>®</sup>?**

Before you take SOLODYN<sup>®</sup>, tell your doctor if you:

- have kidney problems. Your doctor may prescribe a lower dose of medicine for you.
- have liver problems.
- have diarrhea or watery stools.
- have vision problems.
- plan to have surgery with general anesthesia.
- have any other medical conditions.
- are a male, and you and your female partner are trying to conceive a baby. You should not take SOLODYN<sup>®</sup>.
- are pregnant or plan to become pregnant. SOLODYN<sup>®</sup> may harm your unborn baby. Taking SOLODYN<sup>®</sup> while you are pregnant may cause serious side effects on the growth of bone and teeth of your baby. Talk to your doctor before taking SOLODYN<sup>®</sup> if you plan to become pregnant, or if you are already taking SOLODYN<sup>®</sup> and plan to become pregnant. Stop taking SOLODYN<sup>®</sup> and call your doctor right away if you become pregnant while taking SOLODYN<sup>®</sup>.
- are breastfeeding or plan to breastfeed. SOLODYN<sup>®</sup> passes into your milk and may harm your baby. You and your doctor should decide if you will take SOLODYN<sup>®</sup> or breastfeed. You should not do both.

**Tell your doctor about all the other medicines you take including prescription and nonprescription medicines, vitamins and herbal supplements.** SOLODYN<sup>®</sup> may affect the way other medicines work, and other medicines may affect how SOLODYN<sup>®</sup> works.

Especially tell your doctor if you take:

- **birth control pills.** SOLODYN<sup>®</sup> may make your birth control pills less effective. You could become pregnant. You should use a second form of birth control while taking SOLODYN<sup>®</sup>.
- **a blood thinner medicine.**
- **a penicillin antibiotic medicine.** SOLODYN<sup>®</sup> and penicillins should not be used together.
- **antacids that contain aluminum, calcium, or magnesium or iron-containing products.**
- an acne medicine that contains **isotretinoin** (Amnesteem, Claravis, Sotret). SOLODYN<sup>®</sup> and isotretinoin should not be used together.

Ask your doctor or pharmacist if you are not sure if your medicine is one that is listed above.

Know the medicines you take. Keep a list of them to show your doctor and pharmacist.

**How should I take SOLODYN<sup>®</sup>?**

- Take SOLODYN<sup>®</sup> exactly as your doctor tells you.
- Skipping doses or not taking all doses of SOLODYN<sup>®</sup> may:
  - make the treatment not work as well.
  - increase the chance that the bacteria will become resistant to SOLODYN<sup>®</sup>.
- **SOLODYN<sup>®</sup> can be taken with or without food.** Taking SOLODYN<sup>®</sup> with food may lower your chances of getting irritation or ulcers in your esophagus. Your esophagus is the tube that connects your mouth to your stomach.
- **Swallow SOLODYN<sup>®</sup> Tablets whole. Do not chew, crush, or split the tablets.**

**If you take too much SOLODYN<sup>®</sup>, call your doctor or poison control center right away.** Your doctor may do blood tests to check you for side effects during treatment with SOLODYN<sup>®</sup>.

**What should I avoid while taking SOLODYN<sup>®</sup>?**

- Avoid sunlight, sunlamps, and tanning beds. SOLODYN<sup>®</sup> can make your skin sensitive to the sun and the light from sunlamps and tanning beds. You could get severe sunburn.
- Protect your skin while out in sunlight.
- You should not drive or operate dangerous machinery until you know how SOLODYN<sup>®</sup> affects you. SOLODYN<sup>®</sup> may cause you to feel dizzy or lightheaded, or have a spinning feeling (vertigo).

**What are possible side effects of SOLODYN<sup>®</sup>?**

**SOLODYN<sup>®</sup> may cause serious side effects, including:**

- **Harm to an unborn baby.** See “What should I tell my doctor before taking SOLODYN<sup>®</sup>?”
- **Permanent teeth discoloration.** SOLODYN<sup>®</sup> may permanently turn a baby or child's teeth yellow-grey-brown during tooth development. SOLODYN<sup>®</sup> should not be used during tooth development. Tooth development happens in the last half of pregnancy, and from birth to 8 years of age. See “What should I tell my doctor before taking SOLODYN<sup>®</sup>?”
- **Intestine infection** (pseudomembranous colitis). Pseudomembranous colitis can happen with most antibiotics, including SOLODYN<sup>®</sup>. Call your doctor right away if you get watery diarrhea, diarrhea that does not go away, or bloody stools.
- **Serious liver problems.** Stop taking SOLODYN<sup>®</sup> and call your doctor right away if you get any of the following symptoms of liver problems:
  - loss of appetite
  - tiredness
  - diarrhea
  - yellowing of your skin or the whites of your eyes
  - unexplained bleeding
  - confusion
  - sleepiness
- **Central nervous system effects.** See “What should I avoid while taking SOLODYN<sup>®</sup>?” Central nervous system effects such as light headedness, dizziness, and a spinning feeling (vertigo) may go away during your treatment with SOLODYN<sup>®</sup> or if treatment is stopped.
- **Benign intracranial hypertension, also called pseudotumor cerebri.** This is a condition where there is high pressure in the fluid around the brain. This swelling may lead to vision changes and permanent vision loss. Stop taking SOLODYN<sup>®</sup> and tell your doctor right away if you have blurred vision, vision loss, or unusual headaches.

- **Immune system reactions including a lupus-like syndrome, hepatitis, and inflammation of blood or lymph vessels (vasculitis).** Using SOLODYN<sup>®</sup> for a long time to treat acne may cause immune system reactions. Tell your doctor right away if you get a fever, rash, joint pain, or body weakness. Your doctor may do tests to check your blood for immune system reactions.
- **Serious rash and allergic reactions.** SOLODYN<sup>®</sup> may cause a serious rash and allergic reactions that may affect parts of your body such as your liver, lungs, kidneys and heart. Sometimes these can lead to death.
- Stop taking SOLODYN<sup>®</sup> and get medical help right away if you have any of these symptoms:
  - skin rash, hives, sores in your mouth, or your skin blisters and peels
  - swelling of your face, eyes, lips, tongue, or throat
  - trouble swallowing or breathing
  - blood in your urine
  - fever, yellowing of the skin or the whites of your eyes, dark colored urine
  - pain on the right side of the stomach area (abdominal pain)
  - chest pain or abnormal heartbeats
  - swelling in your legs, ankles and feet
  - darkening of your nails, skin, eyes, scars, teeth, and gums.

**The most common side effects of SOLODYN<sup>®</sup> include:**

- headache
- tiredness
- dizziness or spinning feeling
- itching

Call your doctor if you have a side effect that bothers you or that does not go away. Your doctor may do tests to check you for side effects during treatment with SOLODYN<sup>®</sup>.

These are not all the side effects with SOLODYN<sup>®</sup>. Ask your doctor or pharmacist for more information.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088. You may also report side effects to Medicis at 1-800-900-6389.

**How should I store SOLODYN<sup>®</sup>?**

- Store SOLODYN<sup>®</sup> between 59 F to 86 F (15 C to 30 C).
- Keep SOLODYN<sup>®</sup> Tablets in the container that it comes in and keep the container tightly closed.
- Keep SOLODYN<sup>®</sup> tablets dry.

**Keep SOLODYN<sup>®</sup> and all medicines out of the reach of children.**

**General information about SOLODYN<sup>®</sup>**

Medicines are sometimes prescribed for purposes other than those listed in the Patient Information leaflet. Do not use SOLODYN<sup>®</sup> for a condition for which it was not prescribed. Do not give SOLODYN<sup>®</sup> to other people, even if they have the same symptoms you have. It may harm them.

This Patient Information leaflet summarizes the most important information about SOLODYN<sup>®</sup>. If you would like more information, talk to your doctor. You can ask your doctor or pharmacist for information about SOLODYN<sup>®</sup> that is written for health professionals.

For more information, call 1-800-550-5115.

**What are the ingredients in SOLODYN<sup>®</sup>?**

**Active ingredient:** minocycline HCl.

**Inactive ingredients:** lactose monohydrate, hypromellose type 2910, magnesium stearate, colloidal silicon dioxide, and carnauba wax.

The 45 mg tablets also contain Opadry II Gray which contains: lactose monohydrate, hypromellose type 2910, titanium dioxide, triacetin, and iron oxide black JPE.

The 55 mg tablets also contain Opadry II Pink which contains: hypromellose type 2910, titanium dioxide, lactose monohydrate, polyethylene glycol 3350, triacetin, and FD&C Red #40.

The 65 mg tablets also contain Opadry II Blue which contains: hypromellose type 2910, lactose monohydrate, FD&C Blue #1, polyethylene glycol 3350, FD&C Blue #2, titanium dioxide, triacetin, and D&C Yellow #10.

The 80 mg tablets also contain Opadry II Gray which contains: hypromellose type 2910, lactose monohydrate, polyethylene glycol 3350, FD&C Blue #2, FD&C Red #40, titanium dioxide, triacetin, and FD&C Yellow #6.

The 90 mg tablets also contain Opadry II Yellow which contains: hypromellose type 2910, lactose monohydrate, titanium dioxide, iron oxide yellow, polyethylene glycol 3350, and triacetin.

The 105 mg tablets also contain Opadry II Purple which contains: hypromellose type 2910, lactose monohydrate, titanium dioxide, D&C Red #27, polyethylene glycol 3350, triacetin, and FD&C Blue #1.

The 115 mg tablets also contain Opadry II Green which contains: hypromellose type 2910, lactose monohydrate NF, D&C Yellow #10, triacetin, FD&C Blue #1, titanium dioxide, FD&C Blue #2.

The 135 mg tablets also contain Opadry II Pink which contains: hypromellose type 2910, lactose monohydrate, titanium dioxide, polyethylene glycol 3350, iron oxide red, and triacetin.

SOLODYN<sup>®</sup> is manufactured by WellSpring Pharmaceutical Canada Corp. for Medicis Pharmaceutical Corporation, Scottsdale, Arizona, 85256.

This Patient Information has been approved by the U.S. Food and Drug Administration.

**Revised: 03/2011**

U.S. Patent 5,908,838, U.S. Patent 7,790,705 and Patents Pending\*

\*90 mg is also covered by U.S. Patents 7,541,347 and 7,544,373

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Manufactured for:

**Medicis, The Dermatology Company**

Scottsdale, AZ 85256

Manufactured by:

**WellSpring Pharmaceutical Canada Corp.**

Oakville, Ontario, CANADA L6H 1M5

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**NDA 50-808/S-014**

**MEDICAL REVIEW(S)**

Medical Officer's Review of NDA 50-808  
Supplement 014 (Labeling)

**Supporting Documents:** 114, 115, 117, 118, 119

**Correspondence Dates:** Sept. 29 & Oct. 29, 2010, Feb. 22, March 4, March 14, 2011

- Doc type: labeling supplement and amendments

**CDER Stamp Dates:** Sept. 29 & Oct. 29, 2010, Feb. 22, March 4, March 14, 2011

**Sponsor:** Medicis

**Drug:** Solodyn

**Route of Administration:** oral

**Dosage Form:** extended release tablets

**Active Ingredient(s):** minocycline hydrochloride

**Pharmacologic Category:** acne product

**Proposed Indication:** inflammatory lesions of non-nodular moderate to severe acne vulgaris in patients 12 years and older

**Review start date:** Jan. 28, 2011

**Review completion date:** March 16, 2011

**Team Leader:** Gordana Diglisic

**Clinical Reviewer:** Patricia C. Brown

**Project Manager:** Cristina Attinello

**Background:**

A safety review concerning Drug Rash with Eosinophilia and Systemic Symptoms (DRESS) syndrome, thyroid malignancy and black thyroid was completed June 3, 2010.

On September 1, 2010 the Division sent a supplement request letter to the sponsor requesting the following changes in the labeling be made so as to furnish adequate information for the safe and effective use of the drug:

1. Update the **WARNINGS AND PRECAUTIONS** section to include the following language: Drug rash with eosinophilia and systemic symptoms (DRESS) syndrome has been reported postmarketing with minocycline use. DRESS syndrome consists of cutaneous reaction (such as rash or exfoliative dermatitis), eosinophilia, and one or more of the following visceral complications such as: hepatitis, pneumonitis, nephritis, myocarditis, and pericarditis. Fever and lymphadenopathy may be present. In some cases, death has been reported. If this syndrome is recognized, the drug should be discontinued immediately.
2. Update **ADVERSE REACTIONS** (section 6.2 Postmarketing Experience) as follows:
  - Add DRESS syndrome under the subheading "*Skin and hypersensitivity reactions*". Include a cross reference to DRESS syndrome in **WARNINGS** and **PRECAUTIONS**.
  - Delete the word "papillary" under the subheading "*Oncology*" so that the subheading reads: "*Oncology: thyroid cancer.*"
  - Add the words "brown-black microscopic" under the subheading "*Endocrine*" so that the subheading reads: "*Endocrine: brown-black microscopic thyroid discoloration, abnormal thyroid function.*"

In response, the sponsor, Medicis Pharmaceutical Corporation, submitted a Prior Approval Supplement, dated September 29, 2010, to address revisions to the Solodyn<sup>®</sup> package insert.

The sponsor accepted the FDA requested changes and incorporated changes to the WARNINGS AND PRECAUTIONS and ADVERSE REACTIONS of labeling.

**Review:**

Labeling has been reviewed.

A consultant review (dated January 6, 2011) from the Division of Risk management (DRISK) has been obtained.

**Proposed Labeling from Submission of September 29, 2010:**

(b) (4)

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See 17 for PATIENT COUNSELING INFORMATION and FDA approved-patient labeling.

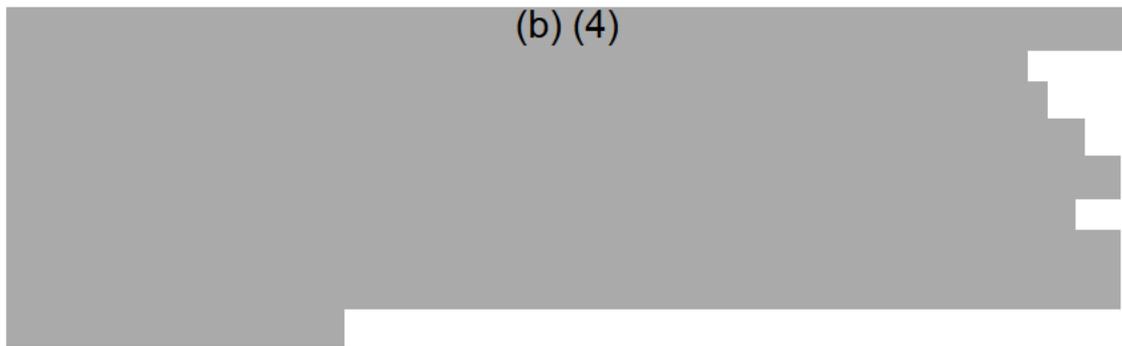
*Reviewer comment: The sponsor has deleted a "the" before FDA and changed the words "approved", "patient", and "labeling" so that they are not capitalized. These changes are acceptable.*

**FULL PRESCRIBING INFORMATION:**

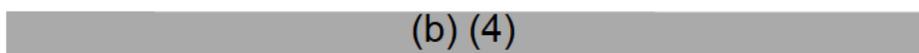
- Section 5, **WARNINGS AND PRECAUTIONS:**  
Subsection 5.9: **Serious Skin/Hypersensitivity Reaction**

**Sponsor** proposed Labeling (additions=underline):

(b) (4)

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(b) (4)

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(b) (4)

- Section 6, **ADVERSE REACTIONS:**  
Subsection 6.2: **Postmarketing Experience**

**Sponsor** proposed Labeling (additions=underline, deletions=~~striketrough~~):

Adverse reactions 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, DRESS syndrome [see WARNINGS and PRECAUTIONS (5.9)].

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

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

*Endocrine:* brown-black microscopic 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.

*Reviewer comment:* Sponsor proposed changes are acceptable.

- Section 17, **PATIENT COUSELING INFORMATION**

(b) (4)

(b) (4)

**Patient Information:**

In response to consultation with DRISK (review dated January 6, 2011), the patient package insert was updated to follow the Med Guide format and to be reflective of information in the Physician Insert.

The above labeling with FDA proposed changes was communicated to the sponsor February 11, 2011. On February 18, 2011, the sponsor responded, accepting some FDA proposed changes and also providing new revisions:

**Sponsor** proposed Labeling (additions=underline, deletions=~~striketrough~~):

**FULL PRESCIBING INFORMATION:**

(b) (4)

**5 WARNINGS AND PRECAUTIONS**

**5.6 Benign Intracranial Hypertension**

...Patients should be questioned for visual disturbances prior to initiation of treatment with tetracyclines ~~and should be routinely checked for papilledema while on treatment.~~ If visual disturbance occurs during treatment, patients should be checked for papilledema.

*Reviewer comment: these changes are acceptable.*

(b) (4)

(b) (4)

**Patient Information:**

**What is SOLODYN<sup>®</sup>?**

(b) (4)

It is not known if SOLODYN<sup>®</sup> is:

- [safe for use longer than 12 weeks.](#)
- safe and effective for the treatment of infections.
- safe and effective in children under the age of 12 years.

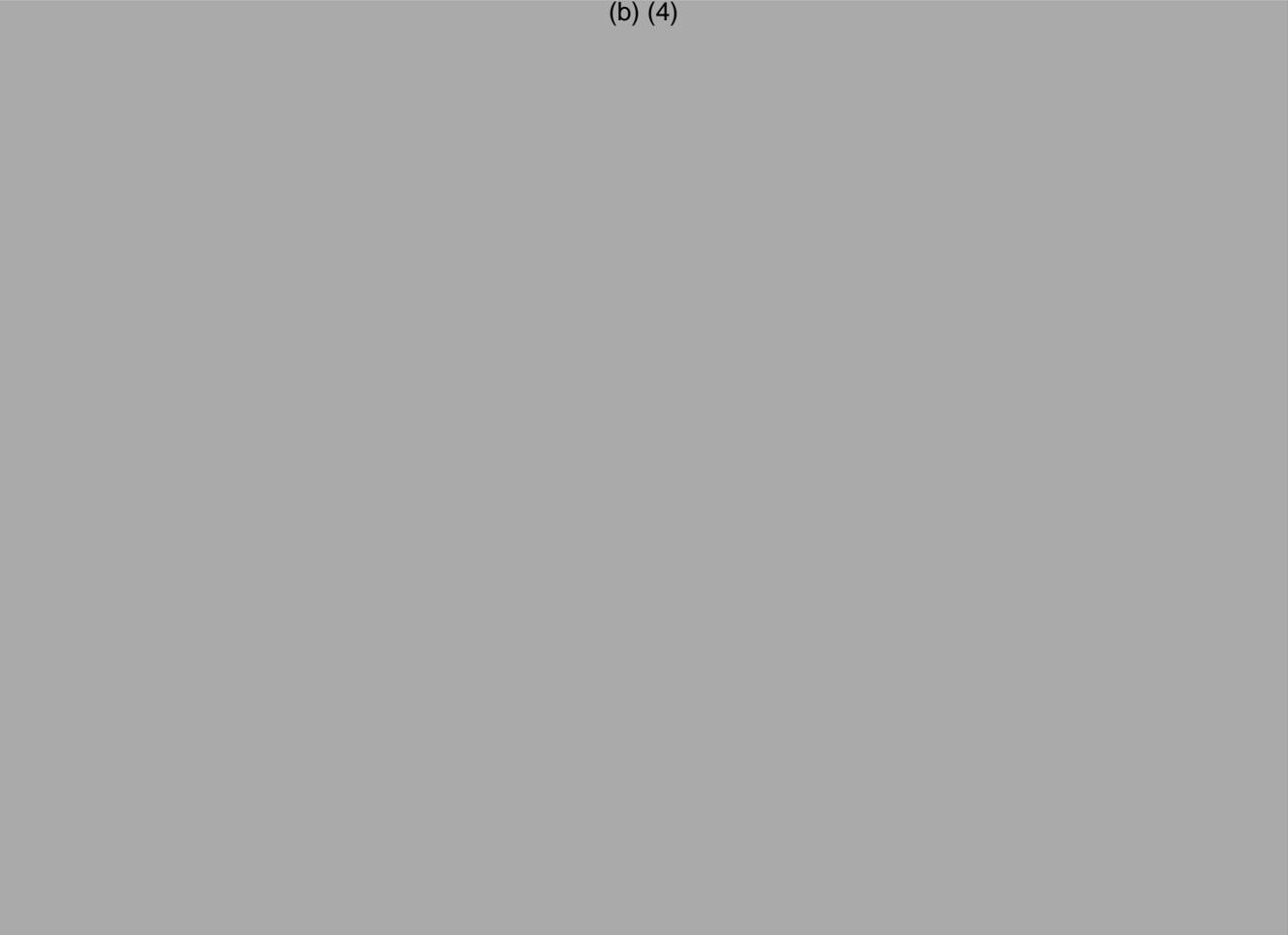
(b) (4)

**Tell your doctor about all the other medicines you take including prescription and nonprescription medicines, vitamins and herbal supplements.** SOLODYN<sup>®</sup> may affect the way other medicines work, and other medicines may affect how SOLODYN<sup>®</sup> works.

Especially tell your doctor if you take:

- **birth control pills.** SOLODYN<sup>®</sup> may make your birth control pills less effective. You could become pregnant. You should use a second form of birth control while taking SOLODYN<sup>®</sup>.
- **a blood thinner medicine.**
- **a penicillin antibiotic medicine.** SOLODYN<sup>®</sup> and penicillins should not be used together.

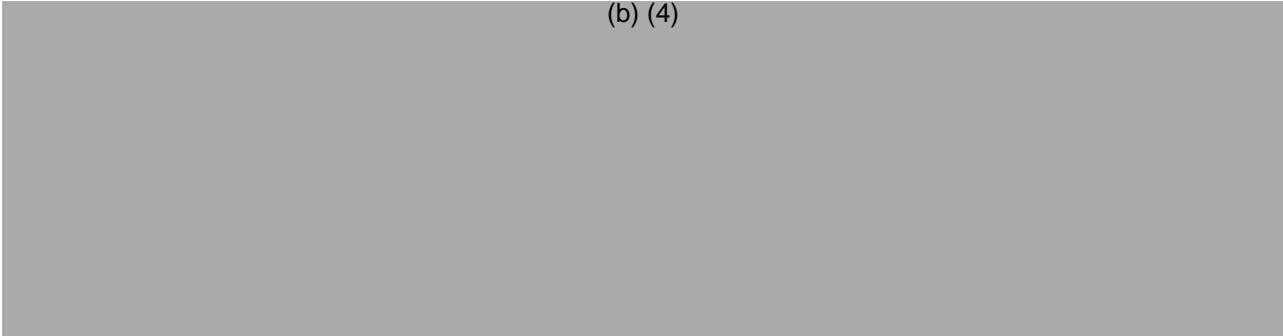
(b) (4)



- **Central nervous system effects.** See “What should I avoid while taking SOLODYN<sup>®</sup>?” Central nervous system effects [such as light headedness, dizziness, and a spinning feeling \(vertigo\)](#) may go away during your treatment with SOLODYN<sup>®</sup> [or if treatment is stopped](#) (b) (4)

*Reviewer comment: These proposed changes are acceptable since they increase clarity.*

(b) (4)



Call your doctor if you have a side effect that bothers you or that does not go away. [Your doctor may do \(b\) \(4\) tests to check you for side effects during treatment with SOLODYN<sup>®</sup>.](#)

*Reviewer comment: These proposed changes are acceptable and include moving the statement in blue above from a location right after the statement; “If you take too much SOLODYN<sup>®</sup>, call your doctor or poison control center right away.”*

(b) (4)

The above labeling with FDA proposed changes was communicated to the sponsor March 1, 2011. On March 4, 2011, the sponsor responded, accepting FDA proposed changes (b) (4)

The FDA also proposed new changes as follows:

FDA proposed labeling (additions=underline, deletions=~~strikethrough~~):

#### **HIGHLIGHTS OF PRESCRIBING INFORMATION:**

##### **WARNINGS AND PRECAUTIONS**

Addition of bulleted item:

- Minocycline has been associated with anaphylaxis, serious skin reactions, erythema multiforme, and DRESS syndrome. Discontinue SOLODYN<sup>®</sup> immediately if symptoms occur. (5.9)

#### **FULL PRESCRIBING INFORMATION:**

Change of tetracycline-class antibiotic to tetracycline-class drug in the following:

### **5 WARNINGS AND PRECAUTIONS**

#### **5.1 Teratogenic Effects**

A. MINOCYCLINE, LIKE OTHER TETRACYCLINE-CLASS DRUGS ANTIBIOTIC, 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.

#### **1.1 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 ~~drugs antibiotic~~ 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.

Deletion of the word “antibiotic” and replacing with “SOLODYN®” in the following:

**5.12 Superinfection**

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

(b) (4)

(b) (4)

The sponsor accepted the above changes on March 11, 2011.

**Conclusion/Recommendation:**

It is recommended that this supplement be approved, as amended with revisions to the labeling as described above and attached below.

A copy of final labeling follows.

**HIGHLIGHTS OF PRESCRIBING INFORMATION**

These highlights do not include all the information needed to use SOLODYN® safely and effectively. See full prescribing information for SOLODYN®.

**SOLODYN®**  
**(minocycline HCl) Extended Release Tablets for oral use**  
**Initial U.S. Approval: 1971**

**INDICATIONS AND USAGE**  
 SOLODYN® is a tetracycline-class drug indicated to treat only inflammatory lesions of non-nodular moderate to severe acne vulgaris in patients 12 years of age and older. (1)

**DOSAGE AND ADMINISTRATION**  
 The recommended dosage of SOLODYN® is approximately 1 mg/kg once daily for 12 weeks. (2)

**DOSAGE FORMS AND STRENGTHS**  
 Extended release tablets: 45, 55, 65, 80, 90, 105, 115, and 135 mg (3)

**CONTRAINDICATIONS**  
 This drug is contraindicated in persons who have shown hypersensitivity to any of the tetracyclines. (4)

**WARNINGS AND PRECAUTIONS**

- The use of SOLODYN 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). (5.1)
- If pseudomembranous colitis occurs, discontinue SOLODYN. (5.2)
- If liver injury is suspected, discontinue SOLODYN. (5.3)
- If renal impairment exists, SOLODYN doses may need to be adjusted to avoid excessive systemic accumulations of the drug and possible liver toxicity. (5.4)
- Minocycline may cause central nervous system side effects including light-headedness, dizziness, or vertigo. Advise patients.(5.5)

- Minocycline may cause pseudotumor cerebri (benign intracranial hypertension) in adults and adolescents. Discontinue SOLODYN if symptoms occur.(5.6)
- Minocycline has been associated with autoimmune syndromes; discontinue SOLODYN immediately if symptoms occur. (5.7)
- Minocycline has been associated with anaphylaxis, serious skin reactions, erythema multiforme, and DRESS syndrome. Discontinue SOLODYN® immediately if symptoms occur. (5.9)

**ADVERSE REACTIONS**  
 The most commonly observed adverse reactions (incidence ≥ 5%) are headache, fatigue, dizziness, and pruritus. (6.1)

**To report SUSPECTED ADVERSE REACTIONS, contact Medicis, The Dermatology Company at 1-800-900-6389 or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch).**

- DRUG INTERACTIONS**
- Patients who are on anticoagulant therapy may require downward adjustment of their anticoagulant dosage. (7.1)
  - The concurrent use of tetracycline and methoxyflurane has been reported to result in fatal renal toxicity. (7.3)
  - To avoid contraceptive failure, female patients are advised to use a second form of contraceptive during treatment with minocycline. (7.5)

- USE IN SPECIFIC POPULATIONS**
- Minocycline like other tetracycline-class drugs can cause fetal harm when administered to a pregnant woman (5.1 , 8.1)
  - The use of drugs of the tetracycline class during tooth development may cause permanent discoloration of teeth (5.1, 8.4)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 03/2011

**FULL PRESCRIBING INFORMATION: CONTENTS\***

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\*Sections or subsections omitted from the full prescribing information are not listed.

**FULL PRESCRIBING INFORMATION****1 INDICATIONS AND USAGE****1.1 Indication**

SOLODYN<sup>®</sup> is indicated to treat only inflammatory lesions of non-nodular moderate to severe acne vulgaris in patients 12 years of age and older.

**1.2 Limitations of Use**

SOLODYN<sup>®</sup> did not demonstrate any effect on non-inflammatory acne lesions. Safety of SOLODYN<sup>®</sup> has not been established beyond 12 weeks of use. This formulation of minocycline has not been evaluated in the treatment of infections [see *Clinical Studies (14)*].

To reduce the development of drug-resistant bacteria as well as to maintain the effectiveness of other antibacterial drugs, SOLODYN<sup>®</sup> should be used only as indicated [see *Warnings and Precautions (5.11)*].

**2 DOSAGE AND ADMINISTRATION**

The recommended dosage of SOLODYN<sup>®</sup> is approximately 1 mg/kg once daily for 12 weeks. Higher doses have not shown to be of additional benefit in the treatment of inflammatory lesions of acne, and may be associated with more acute vestibular side effects.

The following table shows tablet strength and body weight to achieve approximately 1 mg/kg.

**Table 1: Dosing Table for SOLODYN<sup>®</sup>**

Patient's Weight (lbs.)	Patient's Weight (kg)	Tablet Strength (mg)	Actual mg/kg Dose
99 – 109	45 – 49	45	1 – 0.92
110 – 131	50 – 59	55	1.10 – 0.93
132 – 157	60 – 71	65	1.08 – 0.92
158 – 186	72 – 84	80	1.11 – 0.95
187 – 212	85 – 96	90	1.06 – 0.94
213 – 243	97 – 110	105	1.08 – 0.95
244 – 276	111 – 125	115	1.04 – 0.92
277 – 300	126 – 136	135	1.07 – 0.99

SOLODYN<sup>®</sup> Tablets may be taken with or without food [see *Clinical Pharmacology (12)*]. Ingestion of food along with SOLODYN<sup>®</sup> may help reduce the risk of esophageal irritation and ulceration.

In patients with renal impairment, the total dosage should be decreased by either reducing the recommended individual doses and/or by extending the time intervals between doses [see *Warnings and Precautions (5.4)*].

**3 DOSAGE FORMS AND STRENGTHS**

- 45 mg extended release tablets: gray, unscored, coated, and debossed with "DYN-045" on one side.
- 55 mg extended release tablets: pink, unscored, coated, and debossed with "DYN-055" on one side.
- 65 mg extended release tablets: blue, unscored, coated, and debossed with "DYN-065" on one side.
- 80 mg extended release tablets: gray, unscored, coated, and debossed with "DYN-080" on one side.
- 90 mg extended release tablets: yellow, unscored, coated, and debossed with "DYN-090" on one side.
- 105 mg extended release tablets: purple, unscored, coated, and debossed with "DYN-105" on one side.
- 115 mg extended release tablets: green, unscored, coated, and debossed with "DYN-115" on one side.
- 135 mg extended release tablets: pink (orange-brown), unscored, coated, and debossed with "DYN-135" on one side.

**4 CONTRAINDICATIONS**

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

**5 WARNINGS AND PRECAUTIONS****5.1 Teratogenic Effects**

- A. MINOCYCLINE, LIKE OTHER TETRACYCLINE-CLASS DRUGS, 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<sup>®</sup> should not be used during pregnancy or by individuals of either gender who are attempting to conceive a child [see *Nonclinical Toxicology (13.1) & Use in Specific Populations (8.1)*].

- B. 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.

- C. 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 *Use in Specific Populations (8.1)*].

**5.2 Pseudomembranous Colitis**

**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.

**5.3 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.

**5.4 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 drugs 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.

## 5.5 Central Nervous System Effects

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.

## 5.6 Benign Intracranial Hypertension

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. If visual disturbance occurs during treatment, patients should be checked for papilledema. Concomitant use of isotretinoin and minocycline should be avoided because isotretinoin, a systemic retinoid, is also known to cause pseudotumor cerebri.

## 5.7 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.

## 5.8 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.

## 5.9 Serious Skin/Hypersensitivity Reaction

Cases of anaphylaxis, serious skin reactions (e.g. Stevens Johnson syndrome), erythema multiforme, and drug rash with eosinophilia and systemic symptoms (DRESS) syndrome have been reported postmarketing with minocycline use in patients with acne. DRESS syndrome consists of cutaneous reaction (such as rash or exfoliative dermatitis), eosinophilia, and one or more of the following visceral complications such as: hepatitis, pneumonitis, nephritis, myocarditis, and pericarditis. Fever and lymphadenopathy may be present. In some cases, death has been reported. If this syndrome is recognized, the drug should be discontinued immediately.

## 5.10 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.

## 5.11 Development of Drug Resistant Bacteria

Bacterial resistance to the tetracyclines may develop in patients using SOLODYN<sup>®</sup>, 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<sup>®</sup>, it should be used only as indicated.

## 5.12 Superinfection

As with other antibiotic preparations, use of SOLODYN<sup>®</sup> may result in overgrowth of nonsusceptible organisms, including fungi. If superinfection occurs, SOLODYN<sup>®</sup> should be discontinued and appropriate therapy instituted.

## 5.13 Laboratory Monitoring

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

## 6 ADVERSE REACTIONS

### 6.1 Clinical Trial 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.

The following table summarizes selected adverse reactions reported in clinical trials at a rate of  $\geq 1\%$  for SOLODYN<sup>®</sup>.

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

Adverse Reactions	SOLODYN <sup>®</sup> (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)
Tinnitus	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)

### 6.2 Postmarketing Experience

Adverse reactions 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, DRESS syndrome [see *Warnings and Precautions* (5.9)].

*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* brown-black microscopic thyroid discoloration, abnormal thyroid function.

*Oncology* 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 *Nonclinical Toxicology* (13.1)].

## 7 DRUG INTERACTIONS

### 7.1 Anticoagulants

Because tetracyclines have been shown to depress plasma prothrombin activity, patients who are on anticoagulant therapy may require downward

adjustment of their anticoagulant dosage.

## 7.2 Penicillin

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

## 7.3 Methoxyflurane

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

## 7.4 Antacids and Iron Preparations

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

## 7.5 Low Dose Oral Contraceptives

In a multi-center study to evaluate the effect of SOLODYN<sup>®</sup> on low dose oral contraceptives, hormone levels over one menstrual cycle with and without SOLODYN<sup>®</sup> 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.

## 7.6 Drug/Laboratory Test Interactions

False elevations of urinary catecholamine levels may occur due to interference with the fluorescence test.

## 8 USE IN SPECIFIC POPULATIONS

### 8.1 Pregnancy

*Teratogenic Effects* Pregnancy category D [see Warnings and Precautions (5.1)]

SOLODYN<sup>®</sup> 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.

There are no adequate and well-controlled studies on the use of minocycline in pregnant women. Minocycline, like other tetracycline-class drugs, 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<sup>®</sup>). 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<sup>®</sup>).

Minocycline was assessed for effects on peri- and post-natal development of rats in a study that involved oral administration to pregnant rats from day 6 of gestation through the period of lactation (postpartum day 20), at dosages of 5, 10, or 50 mg/kg/day. In this study, body weight gain was significantly reduced in pregnant females that received 50 mg/kg/day (resulting in approximately 2.5 times the systemic exposure to minocycline observed in patients as a result of use of SOLODYN<sup>®</sup>). No effects of treatment on the duration of the gestation period or the number of live pups born per litter were observed. Gross external anomalies observed in F1 pups (offspring of animals that received minocycline) included reduced body size, improperly rotated forelimbs, and reduced size of extremities. No effects were observed on the physical development, behavior, learning ability, or reproduction of F1 pups, and there was no effect on gross appearance of F2 pups (offspring of F1 animals).

### 8.3 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 and Precautions (5.1)].

## 8.4 Pediatric Use

**SOLODYN<sup>®</sup> 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 and Precautions (5.1)].

## 8.5 Geriatric Use

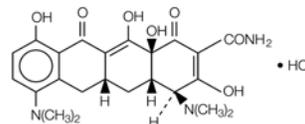
Clinical studies of SOLODYN<sup>®</sup> did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, 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.

## 10 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.

## 11 DESCRIPTION

Minocycline hydrochloride, a semi synthetic derivative of tetracycline, is [4S-(4 $\alpha$ ,4 $\alpha$ ,5 $\alpha$ ,12 $\alpha$ )]-4,7-Bis(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacene-carboxamide mono hydrochloride. The structural formula is represented below:



M. W. 493.95

SOLODYN<sup>®</sup> Tablets for oral administration contain minocycline hydrochloride USP equivalent to 45 mg, 55 mg, 65 mg, 80 mg, 90 mg, 105 mg, 115 mg or 135 mg of minocycline. In addition, 45 mg, 55 mg, 65 mg, 80 mg, 90 mg, 105 mg, 115 mg, and 135 mg tablets contain the following inactive ingredients: lactose monohydrate NF, hypromellose type 2910 USP, magnesium stearate NF, colloidal silicon dioxide NF, and carnauba wax NF. The 45 mg tablets also contain Opadry II Gray which contains: lactose monohydrate NF, hypromellose type 2910 USP, titanium dioxide USP, triacetin USP, and iron oxide black JPE. The 55 mg tablets also contain Opadry II Pink which contains: hypromellose type 2910 USP, titanium dioxide USP, lactose monohydrate NF, polyethylene glycol 3350 NF, triacetin USP, and FD&C Red #40. The 65 mg tablets also contain Opadry II Blue which contains: hypromellose type 2910 USP, lactose monohydrate NF, FD&C Blue #1, polyethylene glycol 3350 NF, FD&C Blue #2, titanium dioxide USP, triacetin USP, and D&C Yellow #10. The 80 mg tablets also contain Opadry II Gray which contains: hypromellose type 2910 USP, lactose monohydrate NF, polyethylene glycol 3350 NF, FD&C Blue #2, FD&C Red #40, titanium dioxide USP, triacetin USP, and FD&C Yellow #6. The 90 mg tablets also contain Opadry II Yellow which contains: hypromellose type 2910 USP, lactose monohydrate NF, titanium dioxide USP, iron oxide yellow NF, polyethylene glycol 3350 NF, and triacetin USP. The 105 mg tablets also contain Opadry II Purple which contains: hypromellose type 2910 USP, lactose monohydrate NF, titanium dioxide USP, D&C Red #27, polyethylene glycol 3350 NF, triacetin USP, and FD&C Blue #1. The 115 mg tablets also contain Opadry II Green which contains: hypromellose type 2910 USP, lactose monohydrate NF, D&C Yellow #10, triacetin USP, FD&C Blue #1, titanium dioxide USP, and FD&C Blue #2. The 135 mg tablets also contain Opadry II Pink which contains: hypromellose type 2910 USP, lactose monohydrate NF, titanium dioxide USP, polyethylene glycol 3350 NF, iron oxide red NF, and triacetin USP.

## 12 CLINICAL PHARMACOLOGY

### 12.1 Mechanism of Action

The mechanism of action of SOLODYN<sup>®</sup> for the treatment of acne is unknown.

### 12.2 Pharmacodynamics

The pharmacodynamics of SOLODYN<sup>®</sup> for the treatment of acne are unknown.

### 12.3 Pharmacokinetics

SOLODYN<sup>®</sup> Tablets are not bioequivalent to non-modified release minocycline products. Based on pharmacokinetic studies in healthy adults, SOLODYN<sup>®</sup> Tablets produce a delayed T<sub>max</sub> at 3.5–4.0 hours as compared to a non-modified release reference minocycline product (T<sub>max</sub> at 2.25–3 hours). At steady-state (Day 6), the mean AUC(0–24) and C<sub>max</sub> were 33.32 µg×hr/mL and 2.63 µg/mL for SOLODYN<sup>®</sup> Tablets and 46.35 µg×hr/mL and 2.92 µg/mL for Minocin<sup>®</sup> capsules, respectively. These parameters are based on dose adjusted to 135 mg per day for both products.

A single-dose, four-way crossover study demonstrated that SOLODYN<sup>®</sup> Tablets used in the study (45 mg, 90 mg, 135 mg) exhibited dose-proportional pharmacokinetics. In another single-dose, five-way crossover pharmacokinetic study, SOLODYN<sup>®</sup> Tablets 55 mg, 80 mg, and 105 mg were shown to be dose-proportional to SOLODYN<sup>®</sup> Tablets 90 mg and 135 mg.

When SOLODYN<sup>®</sup> Tablets were administered concomitantly with a meal that included dairy products, the extent and timing of absorption of minocycline did not differ from that of administration under fasting conditions.

Minocycline is lipid soluble and distributes into the skin and sebum.

## 13 NONCLINICAL TOXICOLOGY

### 13.1 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<sup>®</sup>). 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<sup>®</sup>) 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<sup>®</sup> should not be used by individuals of either gender who are attempting to conceive a child.

## 14 CLINICAL STUDIES

The safety and efficacy of SOLODYN<sup>®</sup> in the treatment of inflammatory lesions of non-nodular moderate to severe acne vulgaris was assessed in two 12-week, multi-center, randomized, double-blind, placebo-controlled, studies in subjects ≥ 12 years. The mean age of subjects was 20 years and subjects were from the following racial groups: White (73%), Hispanic (13%), Black (11%), Asian/Pacific Islander (2%), and Other (2%).

In two efficacy and safety trials, a total of 924 subjects with non-nodular moderate to severe acne vulgaris received SOLODYN<sup>®</sup> or placebo for a total of 12 weeks, according to the following dose assignments.

**Table 3: Clinical Studies Dosing Table**

Subject's Weight (lbs)	Subject's Weight (kg)	Available Caplet Strength (mg)	Actual mg/kg Dose
99 – 131	45 – 59	45	1 – 0.76
132 – 199	60 – 90	90	1.5 – 1
200 – 300	91 – 136	135	1.48 – 0.99

The two primary efficacy endpoints were:

- 1) Mean percent change in inflammatory lesion counts from Baseline to 12 weeks.
- 2) Percentage of subjects with an Evaluator's Global Severity Assessment (EGSA) of clear or almost clear at 12 weeks.

Efficacy results are presented in Table 4.

**Table 4: Efficacy Results at Week 12**

	Study 1		Study 2	
	SOLODYN <sup>®</sup> (1 mg/kg) N = 300	Placebo N = 151	SOLODYN <sup>®</sup> (1 mg/kg) N = 315	Placebo N = 158
Mean Percent Improvement in Inflammatory Lesions	43.1%	31.7%	45.8%	30.8%
No. (%) of Subjects Clear or Almost Clear on the EGSA*	52 (17.3%)	12 (7.9%)	50 (15.9%)	15 (9.5%)

\*Evaluator's Global Severity Assessment

**SOLODYN<sup>®</sup> did not demonstrate any effect on non-inflammatory lesions (benefit or worsening).**

## 16 HOW SUPPLIED/STORAGE AND HANDLING

### 16.1 How Supplied

SOLODYN<sup>®</sup> (minocycline HCl, USP) Extended Release Tablets are supplied as aqueous film coated tablets containing minocycline hydrochloride equivalent to 45 mg, 55 mg, 65 mg, 80 mg, 90 mg, 105 mg, 115 mg or 135 mg minocycline, are supplied as follows.

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 99207-460-30	Bottle of 30
NDC 99207-460-10	Bottle of 100

The 55 mg extended release tablets are pink, unscored, coated, and debossed with "DYN-055" on one side. Each tablet contains minocycline hydrochloride equivalent to 55 mg minocycline, supplied as follows:

NDC 99207-465-30	Bottle of 30
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The 65 mg extended release tablets are blue, unscored, coated, and debossed with "DYN-065" on one side. Each tablet contains minocycline hydrochloride equivalent to 65 mg minocycline, supplied as follows:

NDC 99207-463-30	Bottle of 30
------------------	--------------

The 80 mg extended release tablets are gray, unscored, coated, and debossed with "DYN-080" on one side. Each tablet contains minocycline hydrochloride equivalent to 80 mg minocycline, supplied as follows:

NDC 99207-466-30	Bottle of 30
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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 99207-461-30	Bottle of 30
NDC 99207-461-10	Bottle of 100

The 105 mg extended release tablets are purple, unscored, coated, and debossed with "DYN-105" on one side. Each tablet contains minocycline hydrochloride equivalent to 105 mg minocycline, supplied as follows:

NDC 99207-467-30	Bottle of 30
------------------	--------------

The 115 mg extended release tablets are green, unscored, coated, and debossed with “DYN-115” on one side. Each tablet contains minocycline hydrochloride equivalent to 115 mg minocycline, supplied as follows:

NDC 99207-464-30	Bottle of 30
------------------	--------------

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 99207-462-30	Bottle of 30
NDC 99207-462-10	Bottle of 100

## 16.2 Storage

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

## 16.3 Handling

Keep out of reach of children.

Protect from light, moisture, and excessive heat.

Dispense in tight, light-resistant container with child-resistant closure.

## 17 PATIENT COUNSELING INFORMATION

[See FDA-approved patient labeling (Patient Information)]

Patients taking SOLODYN<sup>®</sup> (minocycline HCl, USP) Extended Release Tablets should receive the following information and instructions:

- SOLODYN<sup>®</sup> should not be used by pregnant women or women attempting to conceive a child [see *Use in Specific Populations (8.1), Nonclinical Toxicology (13.1)*].
- It is recommended that SOLODYN<sup>®</sup> not be used by men who are attempting to father a child [see *Nonclinical Toxicology (13.1)*].
- Patients should be advised that pseudomembranous colitis can occur with minocycline therapy. If patients develop watery or bloody stools, they should seek medical attention
- Patients should be counseled about the possibility of hepatotoxicity. Patients should seek medical advice if they experience symptoms which can include loss of appetite, tiredness, diarrhea, skin turning yellow, bleeding easily, confusion, and sleepiness.
- Patients who experience central nervous system symptoms [see *Warnings and Precautions (5.5)*] should be cautioned about driving vehicles or using hazardous machinery while on minocycline therapy. Patients should seek medical help for persistent headaches or blurred vision.
- Concurrent use of tetracycline may render oral contraceptives less effective [see *Drug Interactions (7.5)*].
- Autoimmune syndromes, including drug-induced lupus-like syndrome, autoimmune hepatitis, vasculitis and serum sickness have been observed with tetracycline-class drugs, 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.
- Patients should be counseled about discoloration of skin, scars, teeth or gums that can arise from minocycline therapy.
- 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. Treatment should be discontinued at the first evidence of skin erythema.

- SOLODYN<sup>®</sup> should be taken 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.
- Patients should be advised to swallow SOLODYN<sup>®</sup> tablets whole and not to chew, crush, or split the tablets.

Patient Information  
SOLODYN<sup>®</sup> (SO-lo-dīn)  
(minocycline HCl)

**Extended Release Tablets**

Read this Patient Information leaflet that comes with SOLODYN<sup>®</sup> before you start taking it and each time you get a refill. There may be new information. This leaflet does not take the place of talking with your doctor about your condition or treatment.

**What is SOLODYN<sup>®</sup>?**

SOLODYN<sup>®</sup> is a tetracycline class drug. SOLODYN<sup>®</sup> is prescription medicine used to treat pimples and red bumps (non-nodular inflammatory lesions) that happen with moderate to severe acne vulgaris in people 12 years and older. SOLODYN<sup>®</sup> is not effective for acne that is not red-looking (this means acne that is not inflammatory).

It is not known if SOLODYN<sup>®</sup> is:

- safe for use longer than 12 weeks.
- safe and effective for the treatment of infections.
- safe and effective in children under the age of 12 years.

**Who should not take SOLODYN<sup>®</sup>?**

Do not take SOLODYN<sup>®</sup> if you are allergic to tetracycline class drugs. Ask your doctor or pharmacist for a list of these medicines if you are not sure.

**What should I tell my doctor before taking SOLODYN<sup>®</sup>?**

Before you take SOLODYN<sup>®</sup>, tell your doctor if you:

- have kidney problems. Your doctor may prescribe a lower dose of medicine for you.
- have liver problems.
- have diarrhea or watery stools.
- have vision problems.
- plan to have surgery with general anesthesia.
- have any other medical conditions.
- are a male, and you and your female partner are trying to conceive a baby. You should not take SOLODYN<sup>®</sup>.
- are pregnant or plan to become pregnant. SOLODYN<sup>®</sup> may harm your unborn baby. Taking SOLODYN<sup>®</sup> while you are pregnant may cause serious side effects on the growth of bone and teeth of your baby. Talk to your doctor before taking SOLODYN<sup>®</sup> if you plan to become pregnant, or if you are already taking SOLODYN<sup>®</sup> and plan to become pregnant. Stop taking SOLODYN<sup>®</sup> and call your doctor right away if you become pregnant while taking SOLODYN<sup>®</sup>.
- are breastfeeding or plan to breastfeed. SOLODYN<sup>®</sup> passes into your milk and may harm your baby. You and your doctor should decide if you will take SOLODYN<sup>®</sup> or breastfeed. You should not do both.

**Tell your doctor about all the other medicines you take including prescription and nonprescription medicines, vitamins and herbal supplements.** SOLODYN<sup>®</sup> may affect the way other medicines work, and other medicines may affect how SOLODYN<sup>®</sup> works.

Especially tell your doctor if you take:

- **birth control pills.** SOLODYN<sup>®</sup> may make your birth control pills less effective. You could become pregnant. You should use a second form of birth control while taking SOLODYN<sup>®</sup>.
- **a blood thinner medicine.**
- **a penicillin antibiotic medicine.** SOLODYN<sup>®</sup> and penicillins should not be used together.
- **antacids that contain aluminum, calcium, or magnesium or iron-containing products.**
- an acne medicine that contains **isotretinoin** (Amnesteem, Claravis, Sotret). SOLODYN<sup>®</sup> and isotretinoin should not be used together.

Ask your doctor or pharmacist if you are not sure if your medicine is one that is listed above.

Know the medicines you take. Keep a list of them to show your doctor and pharmacist.

**How should I take SOLODYN<sup>®</sup>?**

- Take SOLODYN<sup>®</sup> exactly as your doctor tells you.
- Skipping doses or not taking all doses of SOLODYN<sup>®</sup> may:
  - make the treatment not work as well.
  - increase the chance that the bacteria will become resistant to SOLODYN<sup>®</sup>.
- **SOLODYN<sup>®</sup> can be taken with or without food.** Taking SOLODYN<sup>®</sup> with food may lower your chances of getting irritation or ulcers in your esophagus. Your esophagus is the tube that connects your mouth to your stomach.
- **Swallow SOLODYN<sup>®</sup> Tablets whole. Do not chew, crush, or split the tablets.**

**If you take too much SOLODYN<sup>®</sup>, call your doctor or poison control center right away.** Your doctor may do blood tests to check you for side effects during treatment with SOLODYN<sup>®</sup>.

**What should I avoid while taking SOLODYN<sup>®</sup>?**

- Avoid sunlight, sunlamps, and tanning beds. SOLODYN<sup>®</sup> can make your skin sensitive to the sun and the light from sunlamps and tanning beds. You could get severe sunburn.
- Protect your skin while out in sunlight.
- You should not drive or operate dangerous machinery until you know how SOLODYN<sup>®</sup> affects you. SOLODYN<sup>®</sup> may cause you to feel dizzy or lightheaded, or have a spinning feeling (vertigo).

**What are possible side effects of SOLODYN<sup>®</sup>?**

**SOLODYN<sup>®</sup> may cause serious side effects, including:**

- **Harm to an unborn baby.** See “What should I tell my doctor before taking SOLODYN<sup>®</sup>?”
- **Permanent teeth discoloration.** SOLODYN<sup>®</sup> may permanently turn a baby or child's teeth yellow-grey-brown during tooth development. SOLODYN<sup>®</sup> should not be used during tooth development. Tooth development happens in the last half of pregnancy, and from birth to 8 years of age. See “What should I tell my doctor before taking SOLODYN<sup>®</sup>?”
- **Intestine infection** (pseudomembranous colitis). Pseudomembranous colitis can happen with most antibiotics, including SOLODYN<sup>®</sup>. Call your doctor right away if you get watery diarrhea, diarrhea that does not go away, or bloody stools.
- **Serious liver problems.** Stop taking SOLODYN<sup>®</sup> and call your doctor right away if you get any of the following symptoms of liver problems:
  - loss of appetite
  - tiredness
  - diarrhea
  - yellowing of your skin or the whites of your eyes
  - unexplained bleeding
  - confusion
  - sleepiness
- **Central nervous system effects.** See “What should I avoid while taking SOLODYN<sup>®</sup>?” Central nervous system effects such as light headedness, dizziness, and a spinning feeling (vertigo) may go away during your treatment with SOLODYN<sup>®</sup> or if treatment is stopped.
- **Benign intracranial hypertension, also called pseudotumor cerebri.** This is a condition where there is high pressure in the fluid around the brain. This swelling may lead to vision changes and permanent vision loss. Stop taking SOLODYN<sup>®</sup> and tell your doctor right away if you have blurred vision, vision loss, or unusual headaches.

- **Immune system reactions including a lupus-like syndrome, hepatitis, and inflammation of blood or lymph vessels (vasculitis).** Using SOLODYN<sup>®</sup> for a long time to treat acne may cause immune system reactions. Tell your doctor right away if you get a fever, rash, joint pain, or body weakness. Your doctor may do tests to check your blood for immune system reactions.
- **Serious rash and allergic reactions.** SOLODYN<sup>®</sup> may cause a serious rash and allergic reactions that may affect parts of your body such as your liver, lungs, kidneys and heart. Sometimes these can lead to death.
- Stop taking SOLODYN<sup>®</sup> and get medical help right away if you have any of these symptoms:
  - skin rash, hives, sores in your mouth, or your skin blisters and peels
  - swelling of your face, eyes, lips, tongue, or throat
  - trouble swallowing or breathing
  - blood in your urine
  - fever, yellowing of the skin or the whites of your eyes, dark colored urine
  - pain on the right side of the stomach area (abdominal pain)
  - chest pain or abnormal heartbeats
  - swelling in your legs, ankles and feet
  - darkening of your nails, skin, eyes, scars, teeth, and gums.

**The most common side effects of SOLODYN<sup>®</sup> include:**

- headache
- tiredness
- dizziness or spinning feeling
- itching

Call your doctor if you have a side effect that bothers you or that does not go away. Your doctor may do tests to check you for side effects during treatment with SOLODYN<sup>®</sup>.

These are not all the side effects with SOLODYN<sup>®</sup>. Ask your doctor or pharmacist for more information.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088. You may also report side effects to Medicis at 1-800-900-6389.

**How should I store SOLODYN<sup>®</sup>?**

- Store SOLODYN<sup>®</sup> between 59 F to 86 F (15 C to 30 C).
- Keep SOLODYN<sup>®</sup> Tablets in the container that it comes in and keep the container tightly closed.
- Keep SOLODYN<sup>®</sup> tablets dry.

**Keep SOLODYN<sup>®</sup> and all medicines out of the reach of children.**

**General information about SOLODYN<sup>®</sup>**

Medicines are sometimes prescribed for purposes other than those listed in the Patient Information leaflet. Do not use SOLODYN<sup>®</sup> for a condition for which it was not prescribed. Do not give SOLODYN<sup>®</sup> to other people, even if they have the same symptoms you have. It may harm them.

This Patient Information leaflet summarizes the most important information about SOLODYN<sup>®</sup>. If you would like more information, talk to your doctor. You can ask your doctor or pharmacist for information about SOLODYN<sup>®</sup> that is written for health professionals.

For more information, call 1-800-550-5115.

**What are the ingredients in SOLODYN<sup>®</sup>?**

**Active ingredient:** minocycline HCl.

**Inactive ingredients:** lactose monohydrate, hypromellose type 2910, magnesium stearate, colloidal silicon dioxide, and carnauba wax.

The 45 mg tablets also contain Opadry II Gray which contains: lactose monohydrate, hypromellose type 2910, titanium dioxide, triacetin, and iron oxide black JPE.

The 55 mg tablets also contain Opadry II Pink which contains: hypromellose type 2910, titanium dioxide, lactose monohydrate, polyethylene glycol 3350, triacetin, and FD&C Red #40.

The 65 mg tablets also contain Opadry II Blue which contains: hypromellose type 2910, lactose monohydrate, FD&C Blue #1, polyethylene glycol 3350, FD&C Blue #2, titanium dioxide, triacetin, and D&C Yellow #10.

The 80 mg tablets also contain Opadry II Gray which contains: hypromellose type 2910, lactose monohydrate, polyethylene glycol 3350, FD&C Blue #2, FD&C Red #40, titanium dioxide, triacetin, and FD&C Yellow #6.

The 90 mg tablets also contain Opadry II Yellow which contains: hypromellose type 2910, lactose monohydrate, titanium dioxide, iron oxide yellow, polyethylene glycol 3350, and triacetin.

The 105 mg tablets also contain Opadry II Purple which contains: hypromellose type 2910, lactose monohydrate, titanium dioxide, D&C Red #27, polyethylene glycol 3350, triacetin, and FD&C Blue #1.

The 115 mg tablets also contain Opadry II Green which contains: hypromellose type 2910, lactose monohydrate NF, D&C Yellow #10, triacetin, FD&C Blue #1, titanium dioxide, FD&C Blue #2.

The 135 mg tablets also contain Opadry II Pink which contains: hypromellose type 2910, lactose monohydrate, titanium dioxide, polyethylene glycol 3350, iron oxide red, and triacetin.

SOLODYN<sup>®</sup> is manufactured by WellSpring Pharmaceutical Canada Corp. for Medicis Pharmaceutical Corporation, Scottsdale, Arizona, 85256.

This Patient Information has been approved by the U.S. Food and Drug Administration.

**Revised: 03/2011**

U.S. Patent 5,908,838, U.S. Patent 7,790,705 and Patents Pending\*

\*90 mg is also covered by U.S. Patents 7,541,347 and 7,544,373

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Manufactured for:

**Medicis, The Dermatology Company**

Scottsdale, AZ 85256

Manufactured by:

**WellSpring Pharmaceutical Canada Corp.**

Oakville, Ontario, CANADA L6H 1M5

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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PATRICIA C BROWN  
03/16/2011

GORDANA DIGLISIC  
03/16/2011

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**NDA 50-808/S-014**

**OTHER REVIEW(S)**

# **REGULATORY PROJECT MANAGER LABELING REVIEW**

## **Division of Dermatology and Dental Products**

**Application Number:** NDA 050808/S-014

**Name of Drug:** Solodyn (minocycline HCl) extended Release Tablets, 45, 55, 65, 80, 90, 105, 115, and 135 mg

**Applicant:** Medicis Pharmaceutical Corporation

### **Material Reviewed:**

**Submission Date(s):** September 29, 2010

**Receipt Date(s):** September 29, 2010

**Submission Date of Structure Product Labeling (SPL):** September 29, 2010

**Type of Labeling Reviewed:** WORD

### **Background and Summary**

NDA 050808/S-014 for Solodyn (minocycline HCl) extended Release Tablets, 45, 55, 65, 80, 90, 105, 115, and 135 mg was submitted September 29, 2010. This "Prior Approval" supplemental new drug application provides for changes to the Warnings and Precautions and Adverse Reactions sections of the label, regarding DRESS syndrome and thyroid malignancy. A DRISK review was completed January 6, 2011, identifying proposed edits throughout the Patient Package Insert. The proposed edits have been incorporated into the Agency proposed label, agreed upon by the sponsor on March 11, 2011.

### **Review**

The submitted draft labeling, dated September 29, 2010, was compared to the currently approved label, approved on August 27, 2010. Other than the changes proposed in S-014, and revisions to the Patient Package Insert, there are no differences noted between the two labels.

### **Conclusion**

The draft labeling submitted on September 29, 2010, for NDA 050808/S-014 for Solodyn (minocycline HCl) extended Release Tablets, 45, 55, 65, 80, 90, 105, 115, and 135 mg, is acceptable. Other than the changes proposed in S-014 and revisions to the Patient Package Insert, there are no differences noted between the two labels.

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Cristina Attinello  
Regulatory Project Manager

Supervisory Comment/Concurrence:

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Margo Owens  
Team Leader, Project Management Staff

Drafted: CPA/2-17-11, 3-17-11

Revised/Initialed:

Finalized:

Filename: CSO Labeling Review Template (updated 1-16-07).doc

**CSO LABELING REVIEW OF PLR FORMAT**

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/s/  
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CRISTINA Petruccelli Attinello  
03/17/2011

MARGO L OWENS  
03/17/2011

Department of Health and Human Services  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Surveillance and Epidemiology

PATIENT LABELING REVIEW

Date: January 06, 2011

To: Susan Walker, MD, Director  
**Division of Dermatology and Dental Products (DDDP)**

Through: Sharon R. Mills, BSN, RN, CCRP  
Senior Patient Labeling Reviewer  
**Division of Risk Management (DRISK)**

Barbara Fuller, RN, MSN, CWOCN  
Patient Labeling Reviewer  
**Division of Risk Management**

From: Latonia M. Ford, RN, BSN, MBA  
Patient Labeling Reviewer  
**Division of Risk Management**

Subject: DRISK Review of Patient Labeling (Patient Package Insert)

Drug Name (established name): Solodyn (minocycline hydrochloride)

Dosage Form and Route: Extended Release Tablets

Application Type/Number: NDA 50-808  
TSI # 729 and TSI #606

Supplement number S-014

Applicant: Medicis Pharmaceutical Corporation

OSE RCM #: 2010-2656

## 1 INTRODUCTION

This review is written in response to a request by the Division of Dermatology and Dental Products (DDDP) for the Division of Risk Management (DRISK) to review the Applicant's proposed Patient Package Insert for Solodyn (minocycline hydrochloride) Extended Release Tablets.

Solodyn (minocycline hydrochloride) Extended Release Tablets received original approval on May 08, 2006 with the indication to treat only inflammatory lesions of non-nodular moderate to severe acne vulgaris in patients 12 years of age and older.

On September 29, 2010, Medicis Pharmaceutical Corporation submitted a Prior Approval Supplement (PAS) to their New Drug Application, NDA 50-808/S-014 for Solodyn (minocycline hydrochloride) Extended Release Tablets in response to a PAS request letter sent by the DDDP on September 1, 2010. This supplement provides updates to the Warnings and Precautions and Adverse Reactions sections of the Prescribing Information (PI) to include information regarding thyroid malignancy and DRESS (drug rash with eosinophilia and systemic symptoms) Syndrome.

## 2 MATERIAL REVIEWED

- Draft Solodyn (minocycline hydrochloride) Extended Release Tablets, Patient Package Insert (PPI) received on September 29, 2010, and sent by the Review Division to DRISK on December 20, 2010.
- Draft Solodyn (minocycline hydrochloride) Extended Release Tablets, Prescribing Information (PI) received on September 29, 2010, and sent by the Review Division to DRISK on December 20, 2010.

## 3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6<sup>th</sup> to 8<sup>th</sup> grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8<sup>th</sup> grade reading level. In our review of the PPI the target reading level is at or below an 8<sup>th</sup> grade level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We have reformatted the PPI document using the Verdana font, size 11.

In our review of the PPI we have:

- simplified wording and clarified concepts where possible
- ensured that the PPI is consistent with the PI
- removed unnecessary or redundant information
- ensured that the PPI meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

#### **4 CONCLUSIONS**

The PPI is acceptable with our recommended changes.

#### **5 RECOMMENDATIONS**

- Please send these comments to the Applicant and copy DRISK on the correspondence.
- Our annotated versions of the PPI are appended to this memo. Consult DRISK regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the PPI.

Please let us know if you have any questions.

18 pages immediately following withheld for b(4) - Draft Labeling

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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LATONIA M FORD  
01/06/2011

SHARON R MILLS  
01/06/2011  
I concur.

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**NDA 50-808/S-014**

**ADMINISTRATIVE and CORRESPONDENCE**  
**DOCUMENTS**

DEPARTMENT OF HEALTH AND HUMAN SERVICES  
FOOD AND DRUG ADMINISTRATION

Form Approved: OMB No. 0910-0338  
Expiration Date: September 30, 2008  
See OMB Statement on page 2.

**APPLICATION TO MARKET A NEW DRUG, BIOLOGIC,  
OR AN ANTIBIOTIC DRUG FOR HUMAN USE**  
(Title 21, Code of Federal Regulations, Parts 314 & 601)

FOR FDA USE ONLY

APPLICATION NUMBER

**APPLICANT INFORMATION**

NAME OF APPLICANT Medicis Pharmaceutical Corporation	DATE OF SUBMISSION 08/31/2011
TELEPHONE NO. (Include Area Code) 480-291-5611	FACSIMILE (FAX) Number (Include Area Code) 480-291-8611
APPLICANT ADDRESS (Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued): 7720 North Dobson Road Scottsdale, AZ 85256	AUTHORIZED U.S. AGENT NAME & ADDRESS (Number, Street, City, State, ZIP Code, telephone & FAX number) IF APPLICABLE

**PRODUCT DESCRIPTION**

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (If previously issued) 50-808		
ESTABLISHED NAME (e.g., Proper name, USP/USAN name) Minocycline Hydrochloride, USP	PROPRIETARY NAME (trade name) IF ANY SOLODYN®	
CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME (If any) minocycline hydrochloride	CODE NAME (If any)	
DOSAGE FORM: Extended Release Tablets	STRENGTHS: 45, 55, 65, 80, 90, 105, 115, 135 mg	ROUTE OF ADMINISTRATION: Oral
(PROPOSED) INDICATION(S) FOR USE: to treat only inflammatory lesions of non-nodular moderate to severe acne vulgaris		

**APPLICATION DESCRIPTION**

APPLICATION TYPE (check one) <input checked="" type="checkbox"/> NEW DRUG APPLICATION (CDA, 21 CFR 314.50) <input type="checkbox"/> ABBREVIATED NEW DRUG APPLICATION (ANDA, 21 CFR 314.94) <input type="checkbox"/> BIOLOGICS LICENSE APPLICATION (BLA, 21 CFR Part 601)
IF AN NDA, IDENTIFY THE APPROPRIATE TYPE <input checked="" type="checkbox"/> 505 (b)(1) <input type="checkbox"/> 505 (b)(2)
IF AN ANDA, OR 505(b)(2), IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION Name of Drug _____ Holder of Approved Application _____
TYPE OF SUBMISSION (check one) <input type="checkbox"/> PRESUBMISSION <input type="checkbox"/> ORIGINAL APPLICATION <input type="checkbox"/> AMENDMENT TO APENDING APPLICATION <input type="checkbox"/> RESUBMISSION <input type="checkbox"/> ANNUAL REPORT <input type="checkbox"/> ESTABLISHMENT DESCRIPTION SUPPLEMENT <input type="checkbox"/> EFFICACY SUPPLEMENT <input checked="" type="checkbox"/> LABELING SUPPLEMENT <input type="checkbox"/> CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT <input type="checkbox"/> OTHER _____
IF A SUBMISSION OF PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION: _____
IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY <input type="checkbox"/> CBE <input type="checkbox"/> CBE-30 <input type="checkbox"/> Prior Approval (PA)
REASON FOR SUBMISSION Final Printed Container Labels for approved S-015
PROPOSED MARKETING STATUS (check one) <input checked="" type="checkbox"/> PRESCRIPTION PRODUCT (Rx) <input type="checkbox"/> OVER THE COUNTER PRODUCT (OTC)
NUMBER OF VOLUMES SUBMITTED 1 THIS APPLICATION IS <input type="checkbox"/> PAPER <input type="checkbox"/> PAPER AND ELECTRONIC <input checked="" type="checkbox"/> ELECTRONIC

**ESTABLISHMENT INFORMATION (Full establishment information should be provided in the body of the Application.)**  
Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

**Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)**

IND 65,398

This application contains the following items: <i>(Check all that apply)</i>	
<input type="checkbox"/>	1. Index
<input checked="" type="checkbox"/>	2. Labeling <i>(check one)</i> <input type="checkbox"/> Draft Labeling <input checked="" type="checkbox"/> Final Printed Labeling
<input type="checkbox"/>	3. Summary (21 CFR 314.50 (c))
<input type="checkbox"/>	4. Chemistry section
<input type="checkbox"/>	A. Chemistry, manufacturing, and controls information (e.g., 21 CFR 314.50(d)(1); 21 CFR 601.2)
<input type="checkbox"/>	B. Samples (21 CFR 314.50 (e)(1); 21 CFR 601.2 (a)) (Submit only upon FDA's request)
<input type="checkbox"/>	C. Methods validation package (e.g., 21 CFR 314.50(e)(2)(i); 21 CFR 601.2)
<input type="checkbox"/>	5. Nonclinical pharmacology and toxicology section (e.g., 21 CFR 314.50(d)(2); 21 CFR 601.2)
<input type="checkbox"/>	6. Human pharmacokinetics and bioavailability section (e.g., 21 CFR 314.50(d)(3); 21 CFR 601.2)
<input type="checkbox"/>	7. Clinical Microbiology (e.g., 21 CFR 314.50(d)(4))
<input type="checkbox"/>	8. Clinical data section (e.g., 21 CFR 314.50(d)(5); 21 CFR 601.2)
<input type="checkbox"/>	9. Safety update report (e.g., 21 CFR 314.50(d)(5)(vi)(b); 21 CFR 601.2)
<input type="checkbox"/>	10. Statistical section (e.g., 21 CFR 314.50(d)(6); 21 CFR 601.2)
<input type="checkbox"/>	11. Case report tabulations (e.g., 21 CFR 314.50(f)(1); 21 CFR 601.2)
<input type="checkbox"/>	12. Case report forms (e.g., 21 CFR 314.50 (f)(2); 21 CFR 601.2)
<input type="checkbox"/>	13. Patent information on any patent which claims the drug (21 U.S.C. 355(b) or (c))
<input type="checkbox"/>	14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b)(2) or (j)(2)(A))
<input type="checkbox"/>	15. Establishment description (21 CFR Part 600, if applicable)
<input type="checkbox"/>	16. Debarment certification (FD&C Act 306 (k)(1))
<input type="checkbox"/>	17. Field copy certification (21 CFR 314.50 (l)(3))
<input type="checkbox"/>	18. User Fee Cover Sheet (Form FDA 3397)
<input type="checkbox"/>	19. Financial Information (21 CFR Part 54)
<input type="checkbox"/>	20. OTHER <i>(Specify)</i> _____

**CERTIFICATION**

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR Parts 210, 211 or applicable regulations, Parts 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR Parts 201, 606, 610, 660, and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR Part 202.
5. Regulations on making changes in application in FD&C Act section 506A, 21 CFR 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80, and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act, I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.

**Warning:** A willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE Diane Stroehmann, Director, Regulatory Affairs	DATE: 08/31/2011
ADDRESS <i>(Street, City, State, and ZIP Code)</i> 7720 North Dobson Road, Scottsdale, AZ, 85256	Telephone Number 480-291-5611	

**Public reporting burden for this collection of information** is estimated to average 24 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Central Document Room  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

Department of Health and Human Services  
Food and Drug Administration  
Center for Biologics Evaluation and Research (HFM-99)  
1401 Rockville Pike  
Rockville, MD 20852-1448

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

## INSTRUCTIONS FOR FILLING OUT FORM FDA 356h

**APPLICANT INFORMATION** This section should include the name, street address, telephone and facsimile numbers of the legal person or entity submitting the application in the appropriate areas. Note that, in the case of biological products, this is the name of the legal entity or person to whom the license will be issued. The name, street address and telephone number of the legal person or entity authorized to represent a non-U.S. applicant should be entered in the indicated area. Only one person should sign the form.

**PRODUCT DESCRIPTION** This section should include all of the information necessary to identify the product that is the subject of this submission. For new applications, the proposed indication should be given. For supplements to an approved application, please give the approved indications for use.

**APPLICATION INFORMATION** If this submission is an ANDA or 505(b)(2), this section should include the name of the approved drug that is the basis of the application and identify the holder of the approved application in the indicated areas.

**TYPE OF SUBMISSION** should be indicated by checking the appropriate box:

**Original Application** = a complete new application that has never before been submitted;

**Amendment to a Pending Application** = all submissions to pending original applications, or pending supplements to approved applications, including responses to Information Request Letters;

**Resubmission** = a complete response to an action letter, or submission of an application that has been the subject of a withdrawal or a refusal to file action;

**Presubmission** = information submitted prior to the submission of a complete new application;

**Annual Report** = periodic reports for licensed biological products (for NDAs Form FDA-2252 should be used as required in 21 CFR 314.81 (b)(2));

**Establishment Description Supplement** = supplements to the information contained in the Establishment Description section (#15) for biological products;

**Efficacy Supplement** = submissions for such changes as a new indication or dosage regimen for an approved product, a comparative efficacy claim naming another product, or a significant alteration in the patient population; e.g., prescription to Over-The-Counter switch;

**Labeling Supplement** = all label change supplements required under 21 CFR 314.70 and 21 CFR 601.12 that do not qualify as efficacy supplements;

**Chemistry, Manufacturing, and Controls Supplement** = manufacturing change supplement submissions as provided in 21 CFR 314.70, 21 CFR 314.71, 21 CFR 314.72 and 21 CFR 601.12;

**Other** = any submission that does not fit in one of the other categories (e.g., Phase IV response). If this box is checked the type of submission can be explained in the **REASON FOR SUBMISSION** block.

**Submission of Partial Application** Letter date of agreement to partial submission should be provided. Also, provide copy of scheduled plan.

**CBE "Supplement-Changes Being Effected"** supplement submission for certain moderate changes for which distribution can occur when FDA receives the supplement as provided in 21 CFR 314.70 and 21 CFR 601.12.

**CBE-30** "Supplement-Changes Being Effected in 30 Days" supplement submission for certain moderate changes for which FDA receives at least 30 days before the distribution of the product made using the change as provided in 21 CFR 314.70 and 21 CFR 601.12.

**Prior Approval (PA)** "Prior Approval Supplements" supplement submission for a major change for which distribution of the product made using the change cannot occur prior to FDA approval as provided in 21 CFR 314.70 and 21 CFR 601.12.

**REASON FOR SUBMISSION** This section should contain a brief explanation of the submission, e.g., "manufacturing change from roller bottle to cell factory" or "response to Information Request Letter of 1/9/97" or "Pediatric exclusivity determination request" or "to satisfy a subpart H postmarketing commitment".

**NUMBER OF VOLUMES SUBMITTED** Please enter the number of volumes, including and identifying electronic media, contained in the archival copy of this submission.

**This application is**

Paper     Paper and Electronic     Electronic

Please check the appropriate box to indicate whether this submission contains only paper, both paper and electronic media, or only electronic media.

**ESTABLISHMENT INFORMATION** This section should include information on the locations of all manufacturing, packaging and control sites for both drug substance and drug product. If continuation sheets are used, please indicate where in the submission they may be found. For each site please include the name, address, telephone number, registration number (Central File Number), Drug Master File (DMF) number, and the name of a contact at the site. The manufacturing steps and/or type of testing (e.g. final dosage form, stability testing) conducted at the site should also be included. Please indicate whether the site is ready for inspection or, if not, when it will be ready. Please note that, when applicable, the complete establishment description is requested under item 15.

**CROSS REFERENCES** This section should contain a list of all License Applications, Investigational New Drug Applications (INDs), NDAs, Premarket Approval Applications (PMAs), Premarket Notifications (510(k)s), Investigational Device Exemptions (IDEs), Biological Master Files (BMFs) and DMFs that are referenced in the current application.

**Items 1 through 20 on the reverse side of the form** constitute a check list that should be used to indicate the types of information contained within a particular submission. Please check all that apply. The numbering of the items on the checklist is not intended to specify a particular order for the inclusion of those sections into the submission. The applicant may include sections in any order, but the location of those sections within the submission should be clearly indicated in the Index. It is therefore recommended that, particularly for large submissions, the Index immediately follows the Form FDA 356h and, if applicable, the User Fee Cover Sheet (Form FDA 3397).

The CFR references are provided for most items in order to indicate what type of information should be submitted in each section. For further information, the applicant may consult the guidance documents that are available from the Agency.

**Signature** The form must be signed and dated. Ordinarily only one person should sign the form, i.e., the applicant, or the applicant's attorney, agent, or other authorized official. However, if the person signing the application does not reside or have a place of business within the United States, the application should be countersigned by an attorney, agent, or other authorized official who resides or maintains a place of business within the United States.

**From** Attinello, Cristina  
**Sent** Tuesday, March 01, 2011 2:10 PM  
**To** 'Ann Seaback'  
**Cc** 'Diane Stroehmann'; (b) (6) Owens, Margo; Gould, Barbara  
**Subject** RE: Solodyn Labeling Revisions  
**Follow Up Flag** Follow up  
**Flag Status** Red  
**Attachments** Agency-Proposed Label 3-1-11 doc

Good Afternoon,

Attached is a draft copy of the Agency proposed labeling for NDA 050808/S-014 for Solodyn ER Tablets. Please provide your concurrence or any proposed edits in track changes **by the end of business Thursday, March 3, 2011.**

In your response, please reformat FPI: Contents with a consistent numbering scheme (e.g. all numbered headings should either be followed with a period or no period.)

Thank you,

Cristina

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From: Ann Seaback [mailto:aseaback@medicis.com]  
Sent: Friday, February 18, 2011 5:31 PM  
To: Attinello, Cristina  
Cc: Diane Stroehmann; (b) (6)  
Subject: Solodyn Labeling Revisions

Hi Cristina,

As promised, we are replying to you by end of business today regarding the Solodyn physician insert. Please find attached a scanned copy of our official submission to NDA 50-808. Unfortunately, we did not wrap this up early enough today to get the amendment to our eCTD vendor and officially submitted (in eCTD) to the application. Therefore, the electronic submission will not be officially sent to the application until Tuesday due to the holiday. If you have any questions, please give me a call.

Kind regards,

Ann

Ann M. Seaback, RAC  
Manager, Regulatory Affairs  
Medicis Pharmaceutical Corp  
p - 480 291 5535  
f - 480 291 8535

\*\*\*\*\*

The information contained in this email message is proprietary and confidential, and is intended only for the use of the individual or entity named above.

If the reader of this message is not the intended recipient, or the employee or agent responsible to deliver to the intended recipient, you are hereby notified that any dissemination, distribution or copying of this communication is strictly prohibited. If you have received this communication in error, please immediately forward the original message back to the sender and delete your copy of the email.

\*\*\*\*\*

8 pages immediately following withheld for b(4) - Draft Labeling

**From:** Attinello, Cristina  
**Sent:** Friday, February 11, 2011 2:39 PM  
**To:** 'Ann Seaback'; 'Diane Stroehmann'  
**Cc:** Gould, Barbara; Owens, Margo  
**Subject:** Draft Label: NDA 050808/S-014 for Solodyn ER Tablets

**Follow Up Flag:** Follow up  
**Flag Status:** Red

**Attachments:** Agency-Proposed Label 2-11-11.doc

Good Afternoon,

Attached is a draft copy of the Agency proposed labeling for NDA 050808/S-014 for Solodyn ER Tablets. Please provide your concurrence or any proposed edits in track changes by the end of business **Tuesday, February 15, 2011**.



Agency-Proposed  
Label 2-11-11....

Thank you,

**Cristina Petruccelli Attinello, MPH**  
Regulatory Project Manager  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Division of Dermatology & Dental Products  
White Oak, Bldg. 22, Room 5181  
Phone: 301-796-3986  
Fax: 301-796-9895

8 pages immediately following withheld for b(4) - Draft Labeling

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION		<b>REQUEST FOR CONSULTATION</b>		
TO (Division/Office): <b>Janet Anderson, Project Manager</b> <b>Office of Surveillance and Epidemiology (OSE)</b>		FROM: <b>Cristina Attinello, Project Manager</b> <b>Division of Dermatology and Dental Products HFD-540</b>		
DATE 12/16/10	IND NO.	NDA NO. 050808	TYPE OF DOCUMENT	DATE OF DOCUMENT 9/29/10
NAME OF DRUG Solodyn (minocycline HCl)		PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE 1/07/11
NAME OF FIRM: MEDICIS				
<b>REASON FOR REQUEST</b>				
<b>I. GENERAL</b>				
<input type="checkbox"/> NEW PROTOCOL <input type="checkbox"/> PROGRESS REPORT <input type="checkbox"/> NEW CORRESPONDENCE <input type="checkbox"/> DRUG ADVERTISING <input type="checkbox"/> ADVERSE REACTION REPORT <input type="checkbox"/> MANUFACTURING CHANGE/ADDITION <input type="checkbox"/> MEETING PLANNED BY <input type="checkbox"/> PRE--NDA MEETING <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> RESUBMISSION <input type="checkbox"/> SAFETY/EFFICACY <input type="checkbox"/> PAPER NDA <input type="checkbox"/> CONTROL SUPPLEMENT <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER <input type="checkbox"/> FINAL PRINTED LABELING <input type="checkbox"/> LABELING REVISION <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE <input type="checkbox"/> FORMULATIVE REVIEW <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW):				
<b>II. BIOMETRICS</b>				
STATISTICAL EVALUATION BRANCH		STATISTICAL APPLICATION BRANCH		
<input type="checkbox"/> TYPE A OR B NDA REVIEW <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> CONTROLLED STUDIES <input type="checkbox"/> PROTOCOL REVIEW <input type="checkbox"/> OTHER (SPECIFY BELOW):		<input type="checkbox"/> CHEMISTRY REVIEW <input type="checkbox"/> PHARMACOLOGY <input type="checkbox"/> BIOPHARMACEUTICS <input type="checkbox"/> OTHER (SPECIFY BELOW):		
<b>III. BIOPHARMACEUTICS</b>				
<input type="checkbox"/> DISSOLUTION <input type="checkbox"/> BIOAVAILABILITY STUDIES <input type="checkbox"/> PHASE IV STUDIES		<input type="checkbox"/> DEFICIENCY LETTER RESPONSE <input type="checkbox"/> PROTOCOL-BIOPHARMACEUTICS <input type="checkbox"/> IN-VIVO WAIVER REQUEST		
<b>IV. DRUG EXPERIENCE</b>				
<input type="checkbox"/> PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL <input type="checkbox"/> DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below) <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP		<input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE <input type="checkbox"/> POISON RISK ANALYSIS		
<b>V. SCIENTIFIC INVESTIGATIONS</b>				
<input type="checkbox"/> CLINICAL		<input type="checkbox"/> PRECLINICAL		
COMMENTS/SPECIAL INSTRUCTIONS: NDA 050808 Supplement 014 provides for updating the WARNINGS AND PRECAUTIONS and ADVERSE REACTIONS sections of the label with thyroid malignancy and DRESS Syndrome. Please review the PPI and provide any comments or recommendations. The substantially complete PI is attached.  Patricia Brown, Medical Officer Gordana Diglisic, Clinical Team Leader				
SIGNATURE OF REQUESTER Cristina Attinello		METHOD OF DELIVERY (Check one) <input checked="" type="checkbox"/> DARRTS <input type="checkbox"/> HAND		
SIGNATURE OF RECEIVER		SIGNATURE OF DELIVERER Cristina Attinello		

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
-----

CRISTINA Petruccelli Attinello  
12/16/2010



NDA 050808/S-014

**ACKNOWLEDGEMENT --  
PRIOR APPROVAL SUPPLEMENT**

Medicis Pharmaceutical Corporation  
Attention: Ann Seaback, RAC  
Manager, Regulatory Affairs  
7720 North Dobson Road  
Scottsdale, AZ 85256

Dear Ms. Seaback:

We have received your September 29, 2010 Supplemental New Drug Application (sNDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA or the Act) for the following:

**NDA NUMBER:** 050808

**SUPPLEMENT NUMBER:** 014

**PRODUCT NAME:** Solodyn® (minocycline HC1, USP) Extended Release  
Tablets, 45, 55, 65, 80, 90, 105, 115, and 135 mg

**DATE OF SUBMISSION:** September 29, 2010

**DATE OF RECEIPT:** September 29, 2010

This supplemental application proposes changes in the Warnings and Precautions and Adverse Reactions sections of the label.

**SUBMISSION REQUIREMENTS**

Cite the application number listed above at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration  
Center for Drug Evaluation and Research  
Division of Dermatology and Dental Products  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, see <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm>.

If you have questions, call me at (301) 796-3986.

Sincerely,

*{See appended electronic signature page}*

Cristina Attinello, MPH  
Regulatory Health Project Manager  
Division of Dermatology and Dental Products  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research

-----  
**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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CRISTINA Petruccelli Attinello  
12/16/2010