

MINOCYCLINE HYDROCHLORIDE- minocycline hydrochloride tablet, film coated, extended release
Amneal Pharmaceuticals of New York, LLC

HIGHLIGHTS OF PRESCRIBING INFORMATION

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

Minocycline HCl Extended Release Tablets for oral use
Initial U.S. Approval: 1971

INDICATIONS AND USAGE

Minocycline HCl 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 Minocycline HCl is approximately 1 mg/kg once daily for 12 weeks. (2)

DOSAGE FORMS AND STRENGTHS

Extended release tablets: 65 and 115 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 Minocycline HCl 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 Minocycline HCl. (5.2)
- If liver injury is suspected, discontinue Minocycline HCl. (5.3)
- If renal impairment exists, Minocycline HCl 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 Minocycline HCl if symptoms occur. (5.6)
- Minocycline has been associated with autoimmune syndromes; discontinue Minocycline HCl immediately if symptoms occur. (5.7)
- Minocycline has been associated with anaphylaxis, serious skin reactions, erythema multiforme, and DRESS syndrome. Discontinue Minocycline HCl immediately if symptoms occur. (5.9)

ADVERSE REACTIONS

The most commonly observed adverse reactions (incidence $\geq 5\%$) are headache, fatigue, dizziness, and pruritus. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Amneal Pharmaceuticals at 1-877-835-5472 or FDA at 1-800-FDA-1088 or 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.

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Indication

Minocycline HCl 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

Minocycline HCl did not demonstrate any effect on non-inflammatory acne lesions. Safety of Minocycline HCl 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, Minocycline HCl should be used only as indicated [see *Warnings and Precautions (5.11)*].

2 DOSAGE AND ADMINISTRATION

The recommended dosage of Minocycline HCl 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 Minocycline HCl

Patient's Weight (lbs)	Patient's Weight (kg)	Tablet Strength (mg)	Actual Dose (mg/kg)
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

* No longer distributed or sold.

† Not distributed by Amneal.

Minocycline HCl Tablets may be taken with or without food [see *Clinical Pharmacology (12.3)*]. Ingestion of food along with Minocycline HCl 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

- 65 mg extended release tablets: blue, unscored, coated, and debossed with "DYN-065" on one side.
- 115 mg extended release tablets: green, unscored, coated, and debossed with "DYN-115" 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

1. 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.

Minocycline HCl should not be used during pregnancy or by individuals of either gender who are attempting to conceive a child [see *Use in Specific Populations (8.1) and Nonclinical Toxicology (13.1)*].

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

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

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

Results of animal studies indicate that tetracyclines cross the placenta, are found in fetal tissues, and can cause retardation of skeletal development on the developing fetus. Evidence of embryotoxicity has been noted in animals treated early in pregnancy [see *Use in Specific Populations (8.1)*].

5.2 Pseudomembranous Colitis

Clostridium difficile-associated diarrhea (CDAD) has been reported with nearly all antibacterial agents, including minocycline, and may range in severity from mild diarrhea to fatal colitis.

Treatment with antibacterial agents alters the normal flora of the colon leading to overgrowth of *C. difficile*.

C. difficile produces toxins A and B which contribute to the development of CDAD. Hypertoxin-producing strains of *C. difficile* cause increased morbidity and mortality, as these infections can be refractory to antimicrobial therapy and may require colectomy. CDAD must be considered in all patients who present with diarrhea following antibiotic use. Careful medical history is necessary since CDAD has been reported to occur over 2 months after the administration of antibacterial agents.

If CDAD is suspected or confirmed, ongoing antibiotic use not directed against *C. difficile* may need to be discontinued. Appropriate fluid and electrolyte management, protein supplementation, antibiotic treatment of *C. difficile*, and surgical evaluation should be instituted as clinically indicated.

5.3 Hepatotoxicity

Postmarketing 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 blood urea nitrogen (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 fontanels 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 (e.g., 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 (i.e, rash or exfoliative dermatitis), eosinophilia, and one or more of the following visceral complications: 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 (e.g., 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 tetracyclines may develop in patients using Minocycline HCl, 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 Minocycline HCl, it should be used only as indicated.

5.12 Superinfection

As with other antibiotic preparations, use of Minocycline HCl may result in overgrowth of nonsusceptible organisms, including fungi. If superinfection occurs, Minocycline HCl 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 Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials cannot be directly compared to rates in the clinical trials of another drug, and 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 Minocycline HCl.

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

Adverse Reactions	Minocycline HCl (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 fontanels 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 multicenter study to evaluate the effect of Minocycline HCl on low-dose oral contraceptives, hormone levels over one menstrual cycle with and without Minocycline HCl 1 mg/kg once daily were measured. Based on the results of this trial, minocycline-related changes in estradiol, progestinic hormone, FSH and LH plasma levels, of breakthrough bleeding, or of contraceptive failure, cannot 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)]

Minocycline HCl 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 postmarketing experience. Only limited information is available regarding these reports; therefore, no conclusion on causal association can be established.

Minocycline-induced skeletal malformations (i.e., 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 three times and two times, respectively, the systemic exposure to minocycline observed in patients as a result of use of Minocycline HCl. 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 Minocycline HCl.

Minocycline was assessed for effects on peri- and postnatal 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 Minocycline HCl. 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 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

Minocycline HCl 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 Minocycline HCl 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 α ,4a α ,5a α ,12a α)]-4,7-Bis(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide monohydrochloride. The structural formula is represented below:

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

When Minocycline HCl 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—In a carcinogenicity study in which minocycline HCl was orally administered to male and female rats once daily for up to 104 weeks at dosages up to 200 mg/kg/day, minocycline HCl was associated in both genders with follicular cell tumors of the thyroid gland, including increased incidences of adenomas, carcinomas and the combined incidence of adenomas and carcinomas in males, and adenomas and the combined incidence of adenomas and carcinomas in females. In a carcinogenicity study in which minocycline HCl was orally administered to male and female mice once daily for up to 104 weeks at dosages up to 150 mg/kg/day, exposure to minocycline HCl did not result in a significantly increased incidence of neoplasms in either males or females.

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 Minocycline HCl. 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 Minocycline HCl, 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.

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

14 CLINICAL STUDIES

The safety and efficacy of Minocycline HCl in the treatment of inflammatory lesions of non-nodular moderate to severe acne vulgaris was assessed in two 12-week, multicenter, randomized, double-blind, placebo-controlled trials 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 Minocycline HCl 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 Tablet Strength (mg)	Actual Dose (mg/kg)
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

	Trial 1		Trial 2	
	Minocycline HCl (1 mg/kg) N = 300	Placebo N = 151	Minocycline HCl (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

Minocycline HCl did not demonstrate any effect on non-inflammatory lesions (benefit or worsening).

16 HOW SUPPLIED/STORAGE AND HANDLING

How Supplied

Minocycline HCl, USP Extended Release Tablets are supplied as aqueous film-coated tablets containing minocycline hydrochloride equivalent to 65 mg or 115 mg minocycline, as follows.

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 0115-9935-08

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 0115-9936-08

Bottle of 30

Storage

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

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

Advise the patient to read the FDA-approved patient labeling (Patient Information).

Patients taking Minocycline HCl, USP Extended Release Tablets should receive the following information and instructions:

- Minocycline HCl should not be used by pregnant women or women attempting to conceive a child [see *Use in Specific Populations (8.1) and Nonclinical Toxicology (13.1)*].
- It is recommended that Minocycline HCl 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 (i.e., 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.
- Minocycline HCl 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 Minocycline HCl Tablets whole and not to chew, crush, or split the tablets.

Distributed by:

Amneal Pharmaceuticals LLC
Bridgewater, NJ 08807

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Patient Information

Minocycline HCl Extended Release Tablets

Read this Patient Information leaflet that comes with Minocycline HCl 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 Minocycline HCl?

Minocycline HCl is a tetracycline-class drug. Minocycline HCl is a 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. Minocycline HCl is not effective for acne that is not red-looking (this means acne that is not inflammatory).

It is not known if Minocycline HCl 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 Minocycline HCl?

Do not take Minocycline HCl 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 Minocycline HCl?

Before you take Minocycline HCl, 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 Minocycline HCl.
- are pregnant or plan to become pregnant. Minocycline HCl may harm your unborn baby. Taking Minocycline HCl 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 Minocycline HCl if you plan to become pregnant **or** if you are already taking Minocycline HCl and plan to become pregnant. Stop taking Minocycline HCl and call your doctor right away if you become pregnant while taking Minocycline HCl.
- are breastfeeding or plan to breastfeed. Minocycline HCl passes into your milk and may harm your baby. You and your doctor should decide if you will take Minocycline HCl 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. Minocycline HCl may affect the way other medicines work, and other medicines may affect how Minocycline HCl works.

Especially tell your doctor if you take:

- **birth control pills.** Minocycline HCl may make your birth control pills less effective. You could become pregnant. You should use a second form of birth control while taking Minocycline HCl.
- **a blood thinner medicine.**
- **a penicillin antibiotic medicine.** Minocycline HCl 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). Minocycline HCl 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 Minocycline HCl?

- Take Minocycline HCl exactly as your doctor tells you.
- Skipping doses or not taking all doses of Minocycline HCl may:
 - make the treatment not work as well.
 - increase the chance that the bacteria will become resistant to Minocycline HCl.
- **Minocycline HCl can be taken with or without food.** Taking Minocycline HCl 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 Minocycline HCl Tablets whole. Do not chew, crush, or split the tablets.**

If you take too much Minocycline HCl, call your doctor or poison control center right away. Your doctor may do blood tests to check you for side effects during treatment with Minocycline HCl.

What should I avoid while taking Minocycline HCl?

- Avoid sunlight, sunlamps, and tanning beds. Minocycline HCl 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 Minocycline HCl affects you. Minocycline HCl may cause you to feel dizzy or light-headed, or have a spinning feeling (vertigo).

What are possible side effects of Minocycline HCl?

Minocycline HCl may cause serious side effects, including:

- **Harm to an unborn baby.** See "**What should I tell my doctor before taking Minocycline HCl?**"
- **Permanent teeth discoloration.** Minocycline HCl may permanently turn a baby's or child's teeth yellow-grey-brown during tooth development. Minocycline HCl 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 Minocycline HCl?**"
- **Intestine infection** (pseudomembranous colitis). Pseudomembranous colitis can happen with most antibiotics, including Minocycline HCl. Call your doctor right away if you get watery diarrhea, diarrhea that does not go away, or bloody stools.
- **Serious liver problems.** Stop taking Minocycline HCl 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 Minocycline HCl?**" Central nervous system effects such as light-headedness, dizziness, and a spinning feeling (vertigo) may go away during your treatment with Minocycline HCl 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 Minocycline HCl 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 Minocycline HCl 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.** Minocycline HCl 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 Minocycline HCl 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 Minocycline HCl 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 Minocycline HCl.

These are not all the side effects with Minocycline HCl. 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 Amneal Pharmaceuticals at 1-877-835-5472.

How should I store Minocycline HCl?

- Store Minocycline HCl between 59° to 86°F (15° to 30°C).
- Keep Minocycline HCl Tablets in the container that it comes in and keep the container tightly closed.
- Keep Minocycline HCl Tablets dry.

Keep Minocycline HCl and all medicines out of the reach of children.

General information about Minocycline HCl

Medicines are sometimes prescribed for purposes other than those listed in the Patient Information leaflet. Do not use Minocycline HCl for a condition for which it was not prescribed. Do not give Minocycline HCl 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 Minocycline HCl. If you would like more information, talk to your doctor. You can ask your doctor or pharmacist for information about Minocycline HCl that is written for health professionals.

For more information, call 1-877-835-5472.

What are the ingredients in Minocycline HCl?

Active ingredient: minocycline HCl.

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

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 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, and FD&C Blue #2.

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

Distributed by:

Amneal Pharmaceuticals LLC
Bridgewater, NJ 08807

U.S. Patent Numbers: 7,790,705; 7,919,483; 8,252,776; 8,268,804; 8,722,650 and 9,192,615

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Rev. 04/2019-00

9680800 N0122B

PRINCIPAL DISPLAY PANEL - 65 mg Bottle Label

NDC 0115-9935-08

**Minocycline HCl, USP
Extended Release
Tablets
65 mg***

**Rx only
30 Tablets**

amneal

NDC 0115-9935-08

**Minocycline HCl, USP
Extended Release
Tablets**

65 mg*

**Rx only
30 Tablets**

amneal®

*Each tablet contains: minocycline hydrochloride equivalent to 65 mg minocycline.
USUAL DOSAGE: Take one tablet daily.
Keep this and all medications out of reach of children.
Dispense in tight, light-resistant containers as defined in the USP. Protect from light, moisture, and excessive heat.
Store at 25°C (77°F); excursions are permitted to 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature].
Distributed by: **Amneal Pharmaceuticals LLC**
Bridgewater, NJ 08807

Product of Canada Rev. 04-2019-00
9680600 L0121A

01159935084

Package/Label Display Panel - 115mg label

NDC 0115-9936-08

**Minocycline HCl, USP
Extended Release
Tablets
115 mg***

**Rx only
30 Tablets**

amneal

NDC 0115-9936-08

**Minocycline HCl, USP
Extended Release
Tablets**

115 mg*

**Rx only
30 Tablets**



*Each tablet contains: minocycline hydrochloride equivalent to 115 mg minocycline.

USUAL DOSAGE: Take one tablet daily.

Keep this and all medications out of reach of children.

Dispense in tight, light-resistant containers as defined in the USP. Protect from light, moisture, and excessive heat.

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

Distributed by: **Amneal Pharmaceuticals LLC**
Bridgewater, NJ 08807

Product of Canada
9680700

Rev. 04-2019-00
L0122A



N 3

MINOCYCLINE HYDROCHLORIDE

minocycline hydrochloride tablet, film coated, extended release

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	Item Code (Source)	NDC:0115-9935
Route of Administration	ORAL		

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
minocycline hydrochloride (UNII: 0020414E5U) (minocycline - UNII:FYY3R43WGO)	minocycline	65 mg

Inactive Ingredients

Ingredient Name	Strength
HYPROMELLOSE 2910 (50 MPA.S) (UNII: 1IVH67816N)	
lactose monohydrate (UNII: EWQ57Q8I5X)	
FD&C Blue No. 1 (UNII: H3R47K3TBD)	
polyethylene glycol 3350 (UNII: G2M7P15E5P)	
FD&C Blue No. 2 (UNII: L06K8R7DQK)	
titanium dioxide (UNII: 15FIX9V2JP)	
triacetin (UNII: XHX3C3X673)	
D&C Yellow No. 10 (UNII: 35SW5USQ3G)	

Product Characteristics

Color	BLUE	Score	no score
Shape	OVAL	Size	16mm
Flavor		Imprint Code	DYN;065
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:0115-9935-08	1 in 1 CARTON	07/23/2009	
1		30 in 1 BOTTLE; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA authorized generic	NDA050808	07/23/2009	

MINOCYCLINE HYDROCHLORIDE

minocycline hydrochloride tablet, film coated, extended release

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	Item Code (Source)	NDC:0115-9936
Route of Administration	ORAL		

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
minocycline hydrochloride (UNII: 0020414E5U) (minocycline - UNII:FYY3R43WGO)	minocycline	115 mg

Inactive Ingredients

Ingredient Name	Strength
HYPROMELLOSE 2910 (50 MPA.S) (UNII: 1IVH67816N)	
lactose monohydrate (UNII: EWQ57Q8I5X)	
D&C Yellow No. 10 (UNII: 35S5USQ3G)	
triacetin (UNII: XHX3C3X673)	
FD&C Blue No. 1 (UNII: H3R47K3TBD)	
titanium dioxide (UNII: 15FIX9V2JP)	
FD&C Blue No. 2 (UNII: L06K8R7DQK)	

Product Characteristics

Color	GREEN	Score	no score
Shape	OVAL	Size	16mm
Flavor		Imprint Code	DYN;115
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:0115-9936-08	1 in 1 CARTON	07/23/2009	
1		30 in 1 BOTTLE; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA authorized generic	NDA050808	07/23/2009	

Labeler - Amneal Pharmaceuticals of New York, LLC (123797875)

Establishment

Name	Address	ID/FEI	Business Operations
Alcami Carolinas Corporation		832395235	MANUFACTURE(0115-9935, 0115-9936)

Revised: 12/2021

Amneal Pharmaceuticals of New York, LLC