HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use MINOLIRA™ safely and effectively. See full prescribing information for MINOLIRA.
MINOLIRA™ (minocycline hydrochloride) extended-release tablets, for oral use
Initial U.S. Approval: 1971

INDICATIONS AND USAGE

MINOLIRA 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)

Limitations of Use
This formulation of minocycline has not been evaluated in the treatment of infections. To reduce the development of drug-resistant bacteria as well as to maintain the effectiveness of other antibacterial drugs, MINOLIRA should be used only as indicated [see Warnings and Precautions (5.13)].

DOSAGE AND ADMINISTRATION

Recommended dosage: Approximately 1 mg/kg once daily for 12 weeks. (2)

DOSAGE FORMS AND STRENGTHS

Extended- release tablets: 105 mg and 135 mg of minocycline, functionally scored (3)

CONTRAINDICATIONS

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

WARNINGS AND PRECAUTIONS

- The use of MINOLIRA during the second and third trimesters of pregnancy, infancy and childhood up to the age of 8 years may cause permanent discoloration of the teeth (yellow-gray-brown) and reversible inhibition of bone growth. (5.1, 5.2, 5.3, 8.1, 8.4)
- If pseudomembranous colitis occurs, discontinue MINOLIRA. (5.4)
- If liver injury is suspected, discontinue MINOLIRA. (5.5)
- If renal impairment exists, MINOLIRA doses may need to be adjusted to avoid excessive systemic accumulations of the drug and possible liver toxicity. (5.6)
- Minocycline may cause central nervous system side effects including light-headedness, dizziness, or vertigo. (5.7)
- Minocycline may cause intracranial hypertension in adults and adolescents. Discontinue MINOLIRA if symptoms occur. (5.8)
- Minocycline has been associated with autoimmune syndromes; discontinue MINOLIRA immediately if symptoms occur. (5.9)
- Minocycline has been associated with anaphylaxis, serious skin reactions, erythema multiforme, and DRESS syndrome. Discontinue MINOLIRA immediately if symptoms occur. (5.11)

ADVERSE REACTIONS

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

To report SUSPECTED ADVERSE REACTIONS, contact Promius Pharma, LLC at 1-888-966-8766 and www.drreddys.com 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)
- To avoid contraceptive failure, female patients are advised to use a second form of contraception during treatment with minocycline. (7.4)

USE IN SPECIFIC POPULATIONS

- Minocycline like other tetracycline-class drugs can cause fetal harm when administered to a pregnant woman.
- The use of drugs of the tetracycline class during tooth development may cause permanent discoloration of teeth. (5.1, 5.2, 8.1, 8.4)
- Lactation: Breastfeeding is not recommended. (8.2)

See 17 for PATIENT COUNSELING INFORMATION

Revised: 05/2017

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

MINOLIRA is indicated to treat the inflammatory lesions of non-nodular moderate to severe acne vulgaris in patients 12 years of age and older.

Limitations of Use

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

To reduce the development of drug-resistant bacteria as well as to maintain the effectiveness of other antibacterial drugs, MINOLIRA should be used only as indicated *[see Warnings and Precautions (5.13)]*.

2 DOSAGE AND ADMINISTRATION

The recommended dosage of MINOLIRA 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 105 mg and 135 mg tablets may be split on the score line for dosing of patient weight ranges of 45-59 kg and 60-89 kg, respectively (see Table 1).

Table 1: Dosing Table for MINOLIRA

Patient's Weight (kg)	Daily Dose (mg)	Tablet Strength and Size to Administer	Actual Dose (mg/kg)
45 – 59	52.5	half of the 105 mg tablet	1.16 –0.88
60 – 89	67.5	half of the 135 mg tablet	1.13 – 0.76
90 – 125	105	one 105 mg tablet	1.17 – 0.84
126 – 136	135	one 135 mg tablet	1.07 – 0.99

MINOLIRA may be taken with or without food *[see Clinical Pharmacology (12.3)]*. Ingestion of food along with MINOLIRA may help reduce the risk of esophageal irritation and ulceration. MINOLIRA tablets should not be chewed or crushed.

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 (5.6)]*.

3 DOSAGE FORMS AND STRENGTHS

MINOLIRA extended-release tablets are white to off-white, functionally scored, rectangular tablets with brown or gold color speckles and a single score line on both surfaces. MINOLIRA are available in the following two strengths.

- *105 mg extended-release tablets:* ‘M1’debossed on one surface, where ‘M’ and ‘1’ are on either side of the score line. Each tablet contains 105 mg minocycline, equivalent to 113.4 mg of minocycline hydrochloride.
- *135 mg extended-release tablets:* ‘M3’ is debossed on one surface, where ‘M’ and ‘3’ are on either side of the score line. Each tablet contains 135 mg minocycline, equivalent to 145.8 mg of minocycline hydrochloride.

4 CONTRAINDICATIONS

MINOLIRA is contraindicated in patients who have shown hypersensitivity to any of the tetracyclines *[see Serious Skin/Hypersensitivity Reactions (5.11)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Teratogenic Effects

Avoid MINOLIRA use during pregnancy.

MINOLIRA, like other tetracycline-class drugs, can cause fetal harm when administered to a pregnant woman. MINOLIRA, like other tetracycline-class drugs, may cause permanent discoloration of the teeth and inhibit bone growth when administered during pregnancy. Based on animal data, tetracyclines cross the placenta, are found in fetal tissues, and can cause skeletal malformation and retardation of skeletal development on the developing fetus. Evidence of embryotoxicity has been noted in animals treated early in pregnancy. If MINOLIRA is used during pregnancy, advise the patient of the potential risk to the fetus and discontinue treatment *[see Use in Specific Populations (8.1)]*.

5.2 Tooth Discoloration

The use of tetracycline class drugs during tooth development (second and third trimesters 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 tetracycline but has been observed following repeated short-term courses. Enamel hypoplasia has also been reported. Use of tetracycline drugs is not recommended during tooth development.

The safety and effectiveness of MINOLIRA have not been established in pediatric patients less than 12 years of age.

5.3 Inhibition of Bone Growth

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. The safety and effectiveness of MINOLIRA have not been established in patients less than 12 years of age *[see Use in Specific Populations (8.1, 8.4)]*.

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)]*.

5.4 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 two months after the administration of antibacterial agents.

If CDAD is suspected or confirmed, 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.

5.5 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.

5.6 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.

5.7 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.

5.8 Intracranial Hypertension

Intracranial hypertension has been associated with the use of tetracycline-class drugs including MINOLIRA. Clinical manifestations of intracranial hypertension include headache, blurred vision, diplopia and vision loss; papilledema can be found on fundoscopy. Women of childbearing age who are overweight or have a history of IH are at a greater risk for developing intracranial hypertension. Concomitant use of isotretinoin and tetracycline should be avoided because isotretinoin, a systemic retinoid, is also known to cause intracranial hypertension.

Although intracranial hypertension typically resolves after discontinuation of treatment, the possibility for permanent visual loss exists. If visual disturbance occurs during treatment, prompt ophthalmologic evaluation is warranted. Because intracranial pressure can remain elevated for weeks after drug cessation, patients should be monitored until they stabilize.

5.9 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, immediately discontinue the use of all tetracycline-class drugs, including MINOLIRA.

5.10 Photosensitivity

Photosensitivity manifested by an exaggerated sunburn reaction has been observed in some individuals taking tetracyclines; this reaction has been reported less frequently 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

MINOLIRA, they should wear loose-fitting clothes that protect skin from sun exposure and discuss other sun protection measures with their physician.

5.11 Serious Skin/Hypersensitivity Reaction

Cases of anaphylaxis, serious skin reactions (e.g. Stevens Johnson syndrome), erythema multiforme, and drug reaction 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, discontinue MINOLIRA immediately.

5.12 Tissue Hyperpigmentation

Tetracyclines 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 pigmentation over sites of scars or injury.

5.13 Development of Drug-Resistant Bacteria

MINOLIRA has not been evaluated in the treatment of infections.

Bacterial resistance to the tetracyclines may develop in patients using MINOLIRA. Because of the potential for drug-resistant bacteria to develop during the use of MINOLIRA, it should be used only as indicated.

5.14 Superinfection

Use of MINOLIRA may result in overgrowth of nonsusceptible organisms, including fungi. If super infection occurs, discontinue MINOLIRA and institute appropriate therapy.

5.15 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 of a drug 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 ≥1% for minocycline hydrochloride extended release tablets.

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

Adverse Reactions	Minocycline Hydrochloride Extended-Release Tablets (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 (5.11)]*.

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.

Genitourinary: Preliminary studies suggest that use of minocycline may have deleterious effects on human spermatogenesis *[see Nonclinical Toxicology (13.1)]*.

Renal: reversible acute renal failure.

Hematology: hemolytic anemia, thrombocytopenia, eosinophilia.

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

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

7.3 Antacids and Iron Preparations

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

7.4 Low Dose Oral Contraceptives

In a multi-center study to evaluate the effect of minocycline extended release tablets on low dose oral contraceptives, hormone levels over one menstrual cycle with and without minocycline extended release tablets 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 during treatment with minocycline, advise patients of reproductive potential to use a second form of contraception in addition to low-dose oral contraceptives.

7.5 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

Risk Summary

MINOLIRA, like tetracycline class drugs, may cause permanent discoloration of teeth and reversible inhibition of bone growth when administered during pregnancy *[see Warnings and*

Precautions (5.1) and Use in Specific Populations (8.4)]. Post-marketing cases of minocycline use in pregnant women report congenital anomalies such as limb reductions. The limited data are not sufficient to inform a drug-associated risk for birth defects or miscarriage. In animal reproduction studies, minocycline induced skeletal malformations in fetuses when orally administered to pregnant rats and rabbits during the period of organogenesis at systemic exposure of approximately 3 times and 2 times, respectively, the systemic exposure to minocycline observed in patients administered MINOLIRA *(see Data)*. If a patient becomes pregnant while taking this drug, advise the patient of the risk to the fetus and discontinue treatment.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Data

Human Data

The use of tetracycline during tooth development (second and third trimesters of pregnancy) may cause permanent discoloration of deciduous teeth. This adverse reaction is more common during long-term use of the drug but has been observed following repeated short-term courses.

Animal Data

Results of animal studies indicate that tetracyclines cross the placenta, are found in fetal tissues, and can cause retardation of skeletal development of the developing fetus. *[see Warnings and Precautions (5.1)]*.

Minocycline induced skeletal malformations (bent limb bones) in fetuses when administered to pregnant rats and rabbits during the period of organogenesis at 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 administered MINOLIRA). Reduced mean fetal body weight was observed when minocycline was administered to pregnant rats during the period of organogenesis 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 administered MINOLIRA).

Minocycline was assessed for effects on peri- and post-natal development of rats in a study that involved oral administration to pregnant rats during the period of organogenesis through lactation , at doses 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 administered MINOLIRA). 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).

8.2 Lactation

Risk Summary

Tetracycline-class drugs including minocycline are present in breast milk. It is not known whether minocycline has an effect on the breastfed infant or on milk production. Because of the potential for serious adverse effects on bone and tooth development in breastfed infants from the tetracycline-class drugs, advise a woman that breastfeeding is not recommended with MINOLIRA therapy *[see Warnings and Precautions (5.1)]*.

8.3 Females and Males of Reproductive Potential

Contraception

MINOLIRA may reduce the effectiveness of low-dose oral contraceptives. Patients of reproductive potential should not rely on low-dose oral contraceptives as an effective contraceptive method, and should use an additional method of contraception during treatment with MINOLIRA *[see Drug Interactions (7.4)]*.

Infertility

Avoid using MINOLIRA in males who are attempting to conceive a child. Limited human studies suggest that minocycline may have a deleterious effect on spermatogenesis. In a fertility study in rats, minocycline adversely affected spermatogenesis when orally administered to male rats at doses resulting in approximately 15 to 40 times the level of systemic exposure to minocycline observed in patients administered MINOLIRA *[see Nonclinical Toxicology (13.1)]*.

8.4 Pediatric Use

The safety and effectiveness of MINOLIRA have been established in pediatric patients 12 years of age and older for the treatment of inflammatory lesions of non-nodular moderate to severe acne vulgaris *[see Pharmacokinetics (12.3) and Clinical Studies (14)]*. Tooth discoloration and inhibition of bone growth have been observed in pediatric patients *[see Warnings and Precaution (5.2, 5.3)]*. The safety and effectiveness of MINOLIRA have not been established in pediatric patients less than 12 years of age.

8.5 Geriatric Use

Clinical studies of MINOLIRA did not include sufficient numbers of subjects aged 65 years 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.

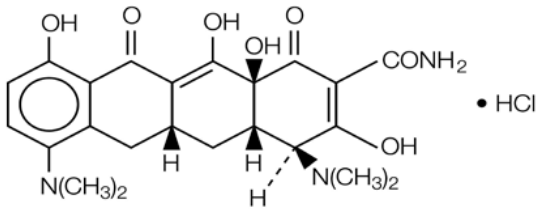
In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and concomitant disease or other drug therapy.

10 OVERDOSAGE

In case of over dosage, 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-(4α,4aα,5aα,12aα)]-4,7-Bis(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide mono hydrochloride. The structural formula is represented below:



$C_{23}H_{27}N_3O_7$•HCl M. W. 493.95

MINOLIRA (minocycline hydrochloride) extended-release tablets for oral administration contain 105 mg or 135 mg of minocycline, equivalent to 113.4 mg or 145.8 mg of minocycline hydrochloride, respectively. MINOLIRA extended-release tablets, 105 mg and 135 mg, contain 25% of minocycline as immediate release beads and 75% of minocycline as extended release beads.

In addition, 105 mg and 135 mg tablets contain the following inactive ingredients: ethyl cellulose NF, hypromellose USP, isopropyl alcohol USP, microcrystalline cellulose NF, polyethylene glycol 400 NF, purified water USP, silicified microcrystalline cellulose NF, sodium stearyl fumarate NF, talc USP, triethyl citrate NF.

Both 105 mg and 135 mg tablets also contain Opadry clear which contains hydroxyl propyl cellulose NF and hypromellose USP.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The mechanism of action of MINOLIRA for the treatment of acne is unknown.

12.2 Pharmacodynamics

The pharmacodynamics of MINOLIRA for the treatment of acne are unknown.

12.3 Pharmacokinetics

The pharmacokinetics of minocycline following oral administration of a single dose of MINOLIRA (135 mg) was investigated in 77 healthy male and female adult subjects under fasting conditions. The pharmacokinetic parameters of minocycline under fasting conditions are presented in Table 3.

Table 3 : Pharmacokinetic Parameters of Minocycline Following Administration of a Single Dose of MINOLIRA (135 mg) under Fasting Conditions (N = 77)

	C_{max} (ng/mL)	T_{max} (hr)*	AUC_{0-t} (ng.hr/mL)	$T_{1/2}$ (hr)
Mean ± SD	700 ± 261	2.0(1.0 – 4.5)	10874 ± 3717	15.6 ± 2.46

*Median (Min-Max)

In a separate trial, a single dose of MINOLIRA (135 mg) was administered orally with a high-fat, high-calorie meal that included dairy products to 36 healthy male and female adult subjects. The estimated calorie content of the meal was 848 Kcal, consisting of 145 Kcal from protein, 250 Kcal from carbohydrates, and 453 Kcal from fat. The pharmacokinetic parameters of minocycline under fed conditions are presented in Table 4.

Table 4 : Pharmacokinetic Parameters of Minocycline Following Administration of a Single Dose of MINOLIRA (135 mg) under Fed Conditions (N = 36)

	C_{max} (ng/mL)	T_{max} (hr)*	AUC_{0-t} (ng.hr/mL)	$T_{1/2}$ (hr)
Mean ± SD	707 ± 190	3.5 (1.5 – 6.0)	12000 ± 2967	17.1 ± 3.03

*Median (Min-Max)

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

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

In a carcinogenicity study in which minocycline hydrochloride was orally administered to male and female rats once daily for up to 104 weeks at dosages up to 200 mg/kg/day, minocycline hydrochloride 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 hydrochloride 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 hydrochloride did not result in a significantly increased incidence of neoplasms in either males or females.

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.

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 administered MINOLIRA). 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 administered MINOLIRA) 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.

14 CLINICAL STUDIES

The safety and efficacy of minocycline hydrochloride extended-release tablets 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, 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 hydrochloride extended-release tablets (approximately 1 mg/kg) or placebo for a total of 12 weeks.

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 5.

Table 5: Efficacy Results at Week 12

	Trial 1		Trial 2	
	Minocycline Hydrochloride Extended Release Tablets (1 mg/kg) N=300	Placebo N=151	Minocycline Hydrochloride Extended Release Tablets (1 mg/kg) N=315	Placebo N=158
Mean Percent Improvement in Inflammatory Lesions	43.1%	31.7%	45.8%	30.8%
Number of subjects clear or almost clear on EGSA*	52 (17.3%)	12 (7.9%)	50 (15.9%)	15 (9.5%)

*Evaluator's Global Severity Assessment

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

16 HOW SUPPLIED/STORAGE AND HANDLING

How Supplied

MINOLIRA is supplied as functionally scored extended-release tablets containing minocycline hydrochloride equivalent to 105 mg and 135 mg of minocycline.

The 105 mg extended-release tablets are white to off-white, rectangular, with brown or gold color speckles. The tablets have a single score line on both surfaces and are debossed with 'M1' on one surface. On the face with debossing, 'M' and '1' are on either side of the score line. Each tablet contains 26.25 mg of minocycline as immediate release beads and 78.75 mg of minocycline as extended release beads. The 105 mg tablets are supplied as follows:

NDC 43598-540-30 Bottle of 30

The 135 mg extended-release tablets are white to off-white, rectangular with brown or gold color speckles. The tablets have a single score line on both surfaces and are debossed with 'M3' on one surface. On the face with debossing, 'M' and '3' are on either side of the score line. Each tablet contains 33.75 mg of minocycline as immediate release beads and 101.25 mg of minocycline as extended release beads. The 135 mg tablets are supplied as follows:

NDC 43598-539-30 Bottle of 30

Storage

Store at 20ºC - 25ºC (68ºF - 77ºF); excursions are permitted to 15ºC-30ºC (59º-86ºF) [see USP Controlled Room Temperature]. Protect from light and moisture.

Handling

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

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information and Instruction for Use).

Advise patients of the following:

Teratogenic effects

- Advise patients to avoid use of MINOLIRA during pregnancy.
- Advise patients that MINOLIRA use during pregnancy may cause inhibition of fetal bone growth.
- Advise patients that MINOLIRA use during pregnancy may cause discoloration of deciduous teeth.
- Advise patients to discontinue MINOLIRA during pregnancy.

Tooth Discoloration

- Advise caregivers of pediatric patients that MINOLIRA use may cause permanent discoloration of deciduous and permanent teeth.

Lactation

- Advise a woman that breast feeding is not recommended during MINOLIRA therapy.

Contraception

- Advise patients of reproductive potential that MINOLIRA may reduce the effectiveness of low-dose oral contraceptives. Advise patients of reproductive potential not rely on low-dose oral contraceptives as an effective contraceptive method and to use an additional method of contraception during treatment with MINOLIRA.

Infertility

- Advise males of reproductive potential that MINOLIRA may impair fertility.

Tissue Hyperpigmentation

- Inform patients that MINOLIRA may cause discoloration of skin, scars, teeth or gums.

Pseudomembranous Colitis

- Advise patients that pseudomembranous colitis can occur with minocycline therapy, including MINOLIRA. Advise patients to seek medical attention if they develop watery or bloody stools.

Hepatotoxicity

- Inform patients about the possibility of hepatotoxicity. Advise patients to seek medical advice if they experience symptoms or signs of hepatotoxicity, including loss of appetite, tiredness, diarrhea, jaundice, increased bleeding tendencies, confusion, and sleepiness.

Central Nervous System Effects

- Inform patients that central nervous system adverse reactions including dizziness or vertigo have been reported with minocycline therapy. Caution patients about driving vehicles or using hazardous machinery if they experience such symptoms while on MINOLIRA.

Intracranial Hypertension

- Inform patients that intracranial hypertension can occur with minocycline therapy. Advise patients to seek medical attention if they develop unusual headache, visual symptoms, such as blurred vision, diplopia, and vision loss.
- Inform patients that 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.
- Advise patients who experience such symptoms to stop the drug immediately and seek medical help.

Photosensitivity

- Inform patients that photosensitivity manifested by an exaggerated sunburn reaction has been observed in some individuals taking tetracyclines, including minocycline.
- Advise patients to minimize or avoid exposure to natural or artificial UV light (tanning beds or UVA/B treatment) while using MINOLIRA.
- Discuss other sun protection measures, if patients need to be outdoors while using MINOLIRA.
- Advise patients to discontinue treatment at the first evidence of sunburn.

Important Administration Instructions

- Inform patients to take MINOLIRA as directed. Missing 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.
- Advise patient not to chew or crush the tablet.
- Advise patients to split MINOLIRA tablet across the score line, if required depending on patient’s body weight.

Manufactured by:

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