40-9286
Rev. K 1/2019

Rx only

Minocycline Hydrochloride Extended-release Tablets

Rx only

40-9286
Rev. K 1/2019

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use MINOCYCLINE HYDROCHLORIDE EXTENDED-RELEASE TABLETS safely and effectively. See full prescribing information for MINOCYCLINE HYDROCHLORIDE EXTENDED-RELEASE TABLETS.

MINOCYCLINE HYDROCHLORIDE extended-release tablets, for oral use
Initial U.S. Approval: 1971

---- INDICATIONS AND USAGE ----

Minocycline Hydrochloride Extended-release Tablets are 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 hydrochloride extended-release tablets is approximately 1 mg/kg once daily for 12 weeks. (2)

-- DOSAGE FORMS AND STRENGTHS --

Extended release tablets: 55, 65, 80, 105 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 hydrochloride extended-release tablets 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 hydrochloride extended-release tablets. (5.2)
- If liver injury is suspected, discontinue minocycline hydrochloride extended-release tablets. (5.3)
- If renal impairment exists, minocycline hydrochloride extended-release tablets 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 hydrochloride extended-release tablets if symptoms occur. (5.6)
- Minocycline has been associated with autoimmune syndromes; discontinue minocycline hydrochloride extended-release tablets immediately if symptoms occur. (5.7)
- Minocycline has been associated with anaphylaxis, serious skin reactions, erythema multiforme, and DRESS syndrome. Discontinue minocycline hydrochloride extended-release tablets 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 Teva Pharmaceuticals USA, Inc. at 1-888-838-2872 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 Hydrochloride Extended-release Tablets are 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 Hydrochloride Extended-release Tablets did not demonstrate any effect on non-inflammatory acne lesions. Safety of minocycline hydrochloride extended-release tablets 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 Hydrochloride Extended-release Tablets should be used only as indicated [*see Warnings and Precautions (5.11)*].

2 DOSAGE AND ADMINISTRATION

The recommended dosage of minocycline hydrochloride extended-release tablets 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 Hydrochloride Extended-release Tablets

Patient's Weight (lbs.)	Patient's Weight (kg)	Tablet Strength (mg)	Actual mg/kg Dose
99 to 109	45 to 49	45	1 to 0.92
110 to 131	50 to 59	55	1.1 to 0.93
132 to 157	60 to 71	65	1.08 to 0.92
158 to 186	72 to 84	80	1.11 to 0.95
187 to 212	85 to 96	90	1.06 to 0.94
213 to 243	97 to 110	105	1.08 to 0.95
244 to 276	111 to 125	115	1.04 to 0.92
277 to 300	126 to 136	135	1.07 to 0.99

Minocycline hydrochloride extended-release tablets may be taken with or without food [*see Clinical Pharmacology (12.3)*]. Ingestion of food along with minocycline hydrochloride extended-release tablets 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

- 55 mg extended-release tablets: pink, capsule-shaped, unscored, film-coated tablets containing minocycline hydrochloride, USP equivalent to 55 mg minocycline and debossed with "TV" on one side and "H1" on the other side.
- 65 mg extended-release tablets: purple, capsule-shaped, unscored, film-coated tablets containing minocycline hydrochloride, USP equivalent to 65 mg minocycline and debossed with "TV" on one side and "2134" on the other side.
- 80 mg extended-release tablets: white, capsule-shaped, unscored, film-coated tablets containing minocycline hydrochloride, USP equivalent to 80 mg minocycline and debossed with "TV" on one side and "H2" on the other side.
- 105 mg extended-release tablets: brown, capsule-shaped, unscored, film-coated tablets containing minocycline hydrochloride, USP equivalent to 105 mg minocycline and debossed with "TV" on one side and "H3" on the other side.
- 115 mg extended-release tablets: green, capsule-shaped, unscored, film-coated tablets containing minocycline hydrochloride, USP equivalent to 115 mg minocycline and debossed with "TV" on one side and "2133" on the other 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.

Minocycline hydrochloride extended-release tablets should not be used during pregnancy or by individuals of either gender who are attempting to conceive a child [*see Nonclinical Toxicology (13.1)* and *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

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, 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

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 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 (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 have 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 minocycline hydrochloride extended-release tablets, 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 hydrochloride extended-release tablets, it should be used only as indicated.

5.12 Superinfection

As with other antibiotic preparations, use of minocycline hydrochloride extended-release tablets may result in overgrowth of nonsusceptible organisms, including fungi. If superinfection occurs, minocycline hydrochloride extended-release tablets 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 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 Subjects

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 (5.9)*].

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 multi-center study to evaluate the effect of minocycline hydrochloride extended-release tablets on low dose oral contraceptives, hormone levels over one menstrual cycle with and without minocycline hydrochloride 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, 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 hydrochloride extended-release tablets 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

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PATIENT INFORMATION

Minocycline (min'' oh sye' kleen)
Hydrochloride (hye'' droe klor' ide)
Extended-release Tablets

Read this Patient Information leaflet that comes with minocycline hydrochloride extended-release tablets 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 are minocycline hydrochloride extended-release tablets?

Minocycline hydrochloride is a tetracycline-class drug. Minocycline hydrochloride extended-release tablets are 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 hydrochloride extended-release tablets are not effective for acne that is not red-looking (this means acne that is not inflammatory).

It is not known if minocycline hydrochloride extended-release tablets are:

- 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 hydrochloride extended-release tablets?

Do not take minocycline hydrochloride extended-release tablets 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 hydrochloride extended-release tablets?

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

Especially tell your doctor if you take:

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

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

If you take too much minocycline hydrochloride extended-release tablets, 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 hydrochloride extended-release tablets.

What should I avoid while taking minocycline hydrochloride extended-release tablets?

- Avoid sunlight, sunlamps, and tanning beds. Minocycline hydrochloride extended-release tablets 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 hydrochloride extended-release tablets affect you. Minocycline hydrochloride extended-release tablets may cause you to feel dizzy or lightheaded, or have a spinning feeling (vertigo).

What are possible side effects of minocycline hydrochloride extended-release tablets?

Minocycline hydrochloride extended-release tablets may cause serious side effects, including:

- **Harm to an unborn baby**. See "**What should I tell my doctor before taking minocycline hydrochloride extended-release tablets?**"
- **Permanent teeth discoloration**. Minocycline hydrochloride extended-release tablets may permanently turn a baby or child's teeth yellow-grey-brown during tooth development. Minocycline hydrochloride extended-release tablets 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 hydrochloride extended-release tablets?**"
- **Intestine infection** (pseudomembranous colitis). Pseudomembranous colitis can happen with most antibiotics, including minocycline hydrochloride extended-release tablets. 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 hydrochloride extended-release tablets 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 hydrochloride extended-release tablets?**" Central nervous system effects such as light headedness, dizziness, and a spinning feeling (vertigo) may go away during your treatment with minocycline hydrochloride extended-release tablets 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 hydrochloride extended-release tablets 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 hydrochloride extended-release tablets 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 hydrochloride extended-release tablets 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 hydrochloride extended-release tablets 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 hydrochloride extended-release tablets 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 hydrochloride extended-release tablets.

These are not all the side effects with minocycline hydrochloride extended-release tablets. 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 Teva Pharmaceuticals USA, Inc. at 1-888-838-2872.

How should I store minocycline hydrochloride extended-release tablets?

- Store minocycline hydrochloride extended-release tablets between 68º to 77ºF (20º to 25ºC).
- Keep minocycline hydrochloride extended-release tablets in the container that they come in and keep the container tightly closed.
- Keep minocycline hydrochloride extended-release tablets dry.

Keep minocycline hydrochloride and all medicines out of the reach of children.

General information about minocycline hydrochloride extended-release tablets

Medicines are sometimes prescribed for purposes other than those listed in the patient information leaflet. Do not use minocycline hydrochloride extended-release tablets for a condition for which they were not prescribed. Do not give minocycline hydrochloride extended-release tablets 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 hydrochloride extended-release tablets. If you would like more information, talk to your doctor. You can ask your doctor or pharmacist for information about minocycline hydrochloride extended-release tablets that is written for health professionals.

For more information, call 1-888-838-2872.

What are the ingredients in minocycline hydrochloride extended-release tablets?

Active Ingredient: minocycline hydrochloride.

Inactive Ingredients: carnauba wax, colloidal silicon dioxide, hypromellose, lactose monohydrate, magnesium stearate, polyethylene glycol, titanium dioxide and triacetin. The 55 mg tablets also contain iron oxide red; the 65 mg tablets also contain D&C red no. 27 aluminum lake, FD&C blue no. 2 aluminum lake and FD&C red no. 40 aluminum lake; the 105 mg tablets also contain iron oxide yellow, iron oxide red and iron oxide black; the 115 mg tablets also contain D&C yellow no. 10 aluminum lake and FD&C blue no. 2 aluminum lake.

This patient information has been approved by the U.S. Food and Drug Administration.

Teva Pharmaceuticals USA, Inc.
North Wales, PA 19454

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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 minocycline hydrochloride extended-release tablets). 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 hydrochloride extended-release tablets).

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 minocycline hydrochloride extended-release tablets). 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

Minocycline hydrochloride extended-release tablets are 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

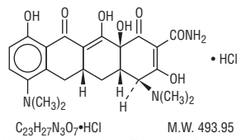
Clinical studies of minocycline hydrochloride extended-release tablets did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly 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, USP, a semi synthetic derivative of tetracycline, is [4*S*-(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

Minocycline Hydrochloride Extended-release Tablets USP for oral administration contain minocycline hydrochloride, USP equivalent to 55 mg, 65 mg, 80 mg, 105 mg or 115 mg of minocycline. In addition, 55 mg 65 mg, 80 mg, 105 mg and 115 mg tablets contain the following inactive ingredients: carnauba wax, colloidal silicon dioxide, hypromellose, lactose monohydrate, magnesium stearate, polyethylene glycol, titanium dioxide and triacetin. The 55 mg tablets also contain iron oxide red; the 65 mg tablets also contain D&C red no. 27 aluminum lake, FD&C blue no. 2 aluminum lake and FD&C red no. 40 aluminum lake; the 105 mg tablets also contain iron oxide yellow, iron oxide red and iron oxide black; the 115 mg tablets also contain D&C yellow no. 10 aluminum lake and FD&C blue no. 2 aluminum lake.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The mechanism of action of minocycline hydrochloride extended-release tablets for the treatment of acne is unknown.

12.2 Pharmacodynamics

The pharmacodynamics of minocycline hydrochloride extended-release tablets for the treatment of acne are unknown.

12.3 Pharmacokinetics

Minocycline hydrochloride extended-release tablets are not bioequivalent to non-modified release minocycline products. Based on pharmacokinetic studies in healthy adults, minocycline hydrochloride extended-release tablets produce a delayed T_{max} at 3.5 to 4 hours as compared to a non-modified release reference minocycline product (T_{max} at 2.25 to 3 hours). At steady-state (Day 6), the mean $AUC_{(0\ to\ 24)}$ and C_{max} were 33.32 mcg×hr/mL and 2.63 mcg/mL for minocycline hydrochloride extended-release tablets and 46.35 mcg×hr/mL and 2.92 mcg/mL for Minocin® 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 minocycline hydrochloride extended-release 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 hydrochloride extended-release tablets 55 mg, 80 mg, and 105 mg were shown to be dose-proportional to minocycline hydrochloride extended-release tablets 90 mg and 135 mg.

When minocycline hydrochloride extended-release 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.

12.4 Microbiology

Susceptibility Testing

For specific information regarding susceptibility test interpretive criteria and associated test methods and quality control standards recognized by FDA for this drug, please see: https://www.fda.gov/STIC.

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 hydrochloride extended-release tablets). 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 hydrochloride extended-release tablets) 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 hydrochloride extended-release tablets 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 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 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 mg/kg Dose
99 to 131	45 to 59	45	1 to 0.76
132 to 199	60 to 90	90	1.5 to 1
200 to 300	91 to 136	135	1.48 to 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 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%
No. (%) of Subjects Clear or Almost Clear on the EGSA[1]	52 (17.3%)	12 (7.9%)	50 (15.9%)	15 (9.5%)

1. Evaluator's Global Severity Assessment

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

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

Minocycline Hydrochloride Extended-release Tablets USP are available as follows:

The 55 mg extended-release tablets are pink, capsule-shaped, unscored, film-coated tablets containing minocycline hydrochloride, USP equivalent to 55 mg minocycline and debossed with "TV" on one side and "H1" on the other side, available in bottles of 30 tablets (NDC 0093-7741-56).

The 65 mg extended-release tablets are purple, capsule-shaped, unscored, film-coated tablets containing minocycline hydrochloride, USP equivalent to 65 mg minocycline and debossed with "TV" on one side and "2134" on the other side, available in bottles of 30 tablets (NDC 0093-2134-56).

The 80 mg extended-release tablets are white, capsule-shaped, unscored, film-coated tablets containing minocycline hydrochloride, USP equivalent to 80 mg minocycline and debossed with "TV" on one side and "H2" on the other side, available in bottles of 30 tablets (NDC 0093-7742-56).

The 105 mg extended-release tablets are brown, capsule-shaped, unscored, film-coated tablets containing minocycline hydrochloride, USP equivalent to 105 mg minocycline and debossed with "TV" on one side and "H3" on the other side, available in bottles of 30 tablets (NDC 0093-7743-56).

The 115 mg extended-release tablets are green, capsule-shaped, unscored, film-coated tablets containing minocycline hydrochloride, USP equivalent to 115 mg minocycline and debossed with "TV" on one side and "2133" on the other side, available in bottles of 30 tablets (NDC 0093-2133-56).

16.2 Storage

Store at 20º to 25°C (68° to 77ºF) [See USP Controlled Room Temperature].

16.3 Handling

KEEP THIS AND ALL MEDICATIONS OUT OF THE REACH OF CHILDREN.

Protect from light, moisture, and excessive heat.

Dispense in a tight, light-resistant container as defined in the USP, with a child-resistant closure (as required).

17 PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (Patient Labeling)

Patients taking minocycline hydrochloride extended-release tablets should receive the following information and instructions:

- Minocycline hydrochloride extended-release tablets 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 minocycline hydrochloride extended-release tablets 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.
- Minocycline hydrochloride extended-release tablets 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 hydrochloride extended-release tablets whole and not to chew, crush, or split the tablets.

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