

HIGHLIGHTS OF PRESCRIBING INFORMATION

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

ORACEA (doxycycline) capsules for oral use

Initial U.S. Approval: 1967

INDICATIONS AND USAGE

- ORACEA is a tetracycline-class drug indicated for the treatment of only inflammatory lesions (papules and pustules) of rosacea in adult patients (1.1)

Limitations of Use

- This formulation of doxycycline has not been evaluated in the treatment or prevention of infections (1.2)
- Efficacy of ORACEA beyond 16 weeks and safety beyond 9 months have not been established (1.2)

DOSAGE AND ADMINISTRATION

- One ORACEA Capsule (40 mg) should be taken once daily in the morning on an empty stomach, preferably at least one hour prior to or two hours after meals (2.1)
- The dosage of ORACEA differs from that of doxycycline used to treat infections. Exceeding the recommended dosage may result in an increased incidence of side effects including the development of resistant microorganisms (2.2, 5.5)

DOSAGE FORMS AND STRENGTHS

- 40 mg capsule (3)

CONTRAINDICATIONS

- ORACEA is contraindicated in persons who have shown hypersensitivity to doxycycline or other tetracyclines (4)

WARNINGS AND PRECAUTIONS

- The use of ORACEA 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 ORACEA (5.2)
- If renal impairment exists, ORACEA doses may need to be adjusted to avoid excessive systemic accumulations of the drug and possible liver injury. (5.3)

- Photosensitivity can occur with ORACEA; Patients should minimize or avoid exposure to natural or artificial sunlight (5.4)
- Tetracyclines have been associated with the development of autoimmune syndromes; if symptoms develop, discontinue ORACEA immediately (5.5)
- Bacterial resistance to tetracyclines may develop in patients using ORACEA. It should only be used as indicated (5.8)

ADVERSE REACTIONS

Some of the most common adverse reactions (incidence >2% and more common than with placebo) are nasopharyngitis, sinusitis, diarrhea, hypertension and aspartate aminotransferase increase (6)

To report SUSPECTED ADVERSE REACTIONS, contact Galderma Laboratories, L.P. at 1-866-735-4137 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- Patients on anticoagulant therapy may require downward adjustment of their anticoagulant dosage (7.1)
- Some bacteriostatic drugs may interfere with the bactericidal action of penicillin, it is advisable to avoid giving tetracycline-class drugs in conjunction with penicillin (7.2)
- The concurrent use of tetracycline and methoxyflurane has been reported to result in fatal renal toxicity (7.3)

USE IN SPECIFIC POPULATIONS

- Doxycycline 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 the teeth (5.1, 8.4)

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

Revised: 11/2012

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Indication

ORACEA is indicated for the treatment of only inflammatory lesions (papules and pustules) of rosacea in adult patients. No meaningful effect was demonstrated for generalized erythema (redness) of rosacea.

1.2 Limitations of Use

This formulation of doxycycline has not been evaluated in the treatment or prevention of infections. ORACEA should not be used for treating bacterial infections, providing antibacterial prophylaxis, or reducing the numbers or eliminating microorganisms associated with any bacterial disease. To reduce the development of drug-resistant bacteria as well as to maintain the effectiveness of other antibacterial drugs, ORACEA should be used only as indicated.

Efficacy of ORACEA beyond 16 weeks and safety beyond 9 months have not been established.

ORACEA has not been evaluated for the treatment of the erythematous, telangiectatic, or ocular components of rosacea.

2 DOSAGE AND ADMINISTRATION

2.1 General Dosing Information

One ORACEA Capsule (40 mg) should be taken once daily in the morning on an empty stomach, preferably at least one hour prior to or two hours after meals.

Administration of adequate amounts of fluid along with the capsules is recommended to wash down the capsule to reduce the risk of esophageal irritation and ulceration [see *Adverse Reactions (6)*].

2.2 Important Considerations for Dosing Regimen

The dosage of ORACEA differs from that of doxycycline used to treat infections. Exceeding the recommended dosage may result in an increased incidence of side effects including the development of resistant organisms.

3 DOSAGE FORMS AND STRENGTHS

40 mg beige opaque capsule imprinted with "GLD 40"

4 CONTRAINDICATIONS

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

5 WARNINGS AND PRECAUTIONS

5.1 Teratogenic Effects

ORACEA should not be used during pregnancy.

Doxycycline, like other tetracycline-class antibiotics, can cause fetal harm when administered to a pregnant woman. If any tetracycline is used during pregnancy or if the patient becomes pregnant while taking these drugs, the patient should be informed of the potential hazard to the fetus and treatment stopped immediately.

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 unless other drugs are not likely to be effective or are contraindicated.

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.

5.2 Pseudomembranous Colitis

Clostridium difficile associated diarrhea (CDAD) has been reported with nearly all antibacterial agents, including doxycycline, and may range in severity from mild 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 Metabolic Effects

The anti-anabolic action of the tetracyclines may cause an increase in BUN. While this is not a problem in those with normal renal function, in patients with significantly impaired function, higher serum levels of tetracycline-class antibiotics may lead to azotemia, hyperphosphatemia, and acidosis. If renal impairment exists, even usual oral or parenteral doses may lead to excessive systemic accumulations of the drug and possible liver toxicity. Under such conditions, lower than usual total doses are indicated, and if therapy is prolonged, serum level determinations of the drug may be advisable.

5.4 Photosensitivity

Photosensitivity manifested by an exaggerated sunburn reaction has been observed in some individuals taking tetracyclines. Although this was not observed during the duration of the clinical studies with ORACEA, patients should minimize or avoid exposure to natural or artificial sunlight (tanning beds or UVA/B treatment) while using ORACEA. If patients need to be outdoors while using ORACEA, they should wear loose-fitting clothes that protect skin from sun exposure and discuss other sun protection measures with their physician.

Tetracyclines have been associated with the development of autoimmune syndromes. 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.

5.6 Tissue Hyperpigmentation

Tetracycline-class drugs 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 pigmentation has been reported to occur upon prolonged administration. Skin pigmentation includes diffuse pigmentation as well as over sites of scars or injury.

5.7 Pseudotumor cerebri

Pseudotumor cerebri (benign intracranial hypertension) in adults has been associated with the use of tetracyclines. The usual clinical manifestations are headache and blurred vision. Bulging fontanels have been associated with the use of tetracyclines in infants. While both of these conditions and related symptoms usually resolve after discontinuation of the tetracycline, the possibility for permanent sequelae exists. Patients should be questioned for visual disturbances prior to initiation of treatment with tetracyclines and should be routinely checked for papilledema while on treatment.

5.8 Development of Drug Resistant Bacteria

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

5.9 Superinfection

As with other antibiotic preparations, use of ORACEA may result in overgrowth of non-susceptible microorganisms, including fungi. If superinfection occurs, ORACEA should be discontinued and appropriate therapy instituted. Although not observed in clinical trials with ORACEA, the use of tetracyclines may increase the incidence of vaginal candidiasis. ORACEA should be used with caution in patients with a history of or predisposition to Candida overgrowth.

5.10 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

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.

Adverse Reactions in Clinical Trials of ORACEA: In controlled clinical trials of adult subjects with mild to moderate rosacea, 537 subjects received ORACEA or placebo over a 16-week period. The following table summarizes selected adverse reactions that occurred in the clinical trials at a rate of $\geq 1\%$ for the active arm:

Table 1. Incidence (%) of Selected Adverse Reactions in Clinical Trials of ORACEA (n=269) vs. Placebo (n=268)		
	ORACEA	Placebo
Nasopharyngitis	13 (5)	9 (3)
Pharyngolaryngeal Pain	3 (1)	2 (1)
Sinusitis	7 (3)	2 (1)
Nasal Congestion	4 (2)	2 (1)
Fungal Infection	5 (2)	1 (0)
Influenza	5 (2)	3 (1)
Diarrhea	12 (5)	7 (3)
Abdominal Pain Upper	5 (2)	1 (0)
Abdominal Distention	3 (1)	1 (0)
Abdominal Pain	3 (1)	1 (0)
Stomach Discomfort	3 (1)	2 (1)
Dry Mouth	3 (1)	0 (0)
Hypertension	8 (3)	2 (1)
Blood Pressure Increase	4 (2)	1 (0)
Aspartate Aminotransferase Increase	6 (2)	2 (1)
Blood Lactate Dehydrogenase Increase	4 (2)	1 (0)

Blood Glucose Increase	3 (1)	0 (0)
Anxiety	4 (2)	0 (0)
Pain	4 (2)	1 (0)
Back Pain	3 (1)	0 (0)
Sinus Headache	3 (1)	0 (0)

Note: Percentages based on total number of study participants in each treatment group.

Adverse Reactions for Tetracyclines: The following adverse reactions have been observed in patients receiving tetracyclines at higher, antimicrobial doses:

Gastrointestinal: anorexia, nausea, vomiting, diarrhea, glossitis, dysphagia, enterocolitis, and inflammatory lesions (with vaginal candidiasis) in the anogenital region. Hepatotoxicity has been reported rarely. Rare instances of esophagitis and esophageal ulcerations have been reported in patients receiving the capsule forms of the drugs in the tetracycline-class. Most of the patients experiencing esophagitis and/or esophageal ulceration took their medication immediately before lying down [see *Dosage and Administration* (2)].

Skin: maculopapular and erythematous rashes. Exfoliative dermatitis has been reported but is uncommon. Photosensitivity is discussed above [see *Warnings and Precautions* (5.4)].

Renal toxicity: Rise in BUN has been reported and is apparently dose-related [see *Warnings and Precautions* (5.3)].

Hypersensitivity reactions: urticaria, angioneurotic edema, anaphylaxis, anaphylactoid purpura, serum sickness, pericarditis, and exacerbation of systemic lupus erythematosus.

Blood: Hemolytic anemia, thrombocytopenia, neutropenia, and eosinophilia have been reported.

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 bismuth subsalicylate, proton pump inhibitors, antacids containing aluminum, calcium or magnesium and iron-containing preparations.

7.5 Low Dose Oral Contraceptives

Doxycycline may interfere with the effectiveness of low dose oral contraceptives. To avoid contraceptive failure, females are advised to use a second form of contraceptive during treatment with doxycycline.

7.6 Oral Retinoids

There have been reports of pseudotumor cerebri (benign intracranial hypertension) associated with the concomitant use of isotretinoin and tetracyclines. Since both oral retinoids, including isotretinoin and acitretin, and the tetracyclines, primarily minocycline, can cause increased intracranial pressure, the concurrent use of an oral retinoid and a tetracycline should be avoided.

7.7 Barbiturates and Anti-epileptics

Barbiturates, carbamazepine, and phenytoin decrease the half-life of doxycycline.

7.8 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)].

Results from animal studies indicate that doxycycline crosses the placenta and is found in fetal tissues.

8.3 Nursing Mothers

Tetracyclines are excreted in human milk. Because of the potential for serious adverse reactions in infants from doxycycline, ORACEA should not be used in mothers who breastfeed.

8.4 Pediatric Use

ORACEA should not be used in infants and children less than 8 years of age [see *Warnings and Precautions* (5.1)]. ORACEA has not been studied in children of any age with regard to safety or efficacy, therefore use in children is not recommended.

8.5 Geriatric Use

Clinical studies of ORACEA 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 elderly and younger patients. In general, dose selection for

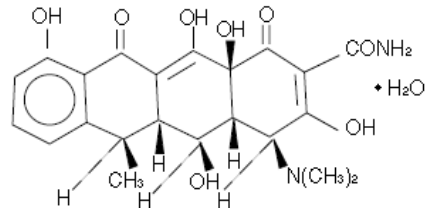
10 OVERDOSAGE

In case of overdosage, discontinue medication, treat symptomatically, and institute supportive measures. Dialysis does not alter serum half-life and thus would not be of benefit in treating cases of overdose.

11 DESCRIPTION

ORACEA (doxycycline, USP) Capsules 40 mg are hard gelatin capsule shells filled with two types of doxycycline beads (30 mg immediate release and 10 mg delayed release) that together provide a dose of 40 mg of anhydrous doxycycline (C₂₂H₂₄N₂O₈).

The structural formula of doxycycline, USP is:



with an empirical formula of C₂₂H₂₄N₂O₈•H₂O and a molecular weight of 462.46. The chemical designation for doxycycline is 2-Naphthacenecarboxamide,4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,5,10,12,12a-pentahydroxy-6-methyl-1,11-dioxo-, [4S-(4α, 4aα, 5α, 5aα, 6α,12α)]-, monohydrate. It is very slightly soluble in water.

Inert ingredients in the formulation are: hypromellose, iron oxide red, iron oxide yellow, methacrylic acid copolymer, polyethylene glycol, Polysorbate 80, sugar spheres, talc, titanium dioxide, and triethyl citrate. Active ingredients: Each capsule contains doxycycline, USP in an amount equivalent to 40 mg of anhydrous doxycycline.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The mechanism of action of ORACEA in the treatment of inflammatory lesions of rosacea is unknown.

12.3 Pharmacokinetics

ORACEA capsules are not bioequivalent to other doxycycline products. The pharmacokinetics of doxycycline following oral administration of ORACEA was investigated in 2 volunteer studies involving 61 adults. Pharmacokinetic parameters for ORACEA following single oral doses and at steady-state in healthy subjects are presented in Table 2.

	N	C _{max} * (ng/mL)	T _{max} [†] (hr)	AUC _{0-∞} * (ng•hr/mL)	t _{1/2} * (hr)
Single Dose 40 mg capsules	30	510 ± 220.7	3.00 (1.0-4.1)	9227± 3212.8	21.2 ± 7.6
Steady-State# 40 mg capsules	31	600 ± 194.2	2.00 (1.0-4.0)	7543 ± 2443.9	23.2 ± 6.2

*Mean †Median #Day 7

Absorption: In a single-dose food-effect study involving administration of ORACEA to healthy volunteers, concomitant administration with a 1000 calorie, high-fat, high-protein meal that included dairy products, resulted in a decrease in the rate and extent of absorption (C_{max} and AUC) by about 45% and 22%, respectively, compared to dosing under fasted conditions. This decrease in systemic exposure can be clinically significant, and therefore if ORACEA is taken close to meal times, it is recommended that it be taken at least one hour prior to or two hours after meals.

Distribution: Doxycycline is greater than 90% bound to plasma proteins.

Metabolism: Major metabolites of doxycycline have not been identified. However, enzyme inducers such as barbiturates, carbamazepine, and phenytoin decrease the half-life of doxycycline.

Excretion: Doxycycline is excreted in the urine and feces as unchanged drug. It is reported that between 29% and 55.4% of an administered dose can be accounted for in the urine by 72 hours. Terminal half-life averaged 21.2 hours in subjects receiving a single dose of ORACEA.

Special Populations

Geriatric: Doxycycline pharmacokinetics have not been evaluated in geriatric patients.

Pediatric: Doxycycline pharmacokinetics have not been evaluated in pediatric patients [see Warnings and Precautions (5.1)].

Gender: The pharmacokinetics of ORACEA were compared in 16 male and 14 female subjects under fed and fasted conditions. While female subjects had a higher C_{max} and AUC than male subjects, these differences were thought to be due to differences in body weight/lean body mass.

Race: Differences in doxycycline pharmacokinetics among racial groups have not been evaluated.

Renal Insufficiency: Studies have shown no significant difference in serum half-life of doxycycline in patients with normal and severely impaired renal function. Hemodialysis does not alter the serum half-life of doxycycline.

Hepatic Insufficiency: Doxycycline pharmacokinetics have not been evaluated in patients with hepatic insufficiency.

Gastric Insufficiency: In a study in healthy volunteers (N=24) the bioavailability of doxycycline is reported to be reduced at high pH. This reduced bioavailability may be clinically significant in patients with gastrectomy, gastric bypass surgery or who are otherwise deemed achlorhydric.

Drug Interactions: [see Drug Interactions (7)].

12.4 Microbiology

Doxycycline is a member of the tetracycline-class of drugs. The plasma concentrations of doxycycline achieved with ORACEA during administration [see Clinical Pharmacology (12.3) and Dosage and Administration (2.2)] are less than the concentration required to treat bacterial diseases. ORACEA should not

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