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. Do not use ORACEA for treating bacterial infections, providing antibacterial prophylaxis, or reducing the numbers or eliminating microorganisms associated with any bacterial disease. (1.2)
ORACEA has not been evaluated for the treatment of the erythematous, telangiectatic, or ocular components of rosacea. (1.2)

----------DOSAGE AND ADMINISTRATION----------
Take one ORACEA capsule (40 mg) once daily in the morning on an empty stomach, preferably at least one hour prior to or two hours after meals. (2.1)
Exceeding the recommended dosage may result in an increased incidence of side effects including the development of resistant microorganisms. (2.2, 5.9)

----------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 (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, 8.1, 8.4)
- Treatment with antibacterial agents alters the normal flora of the colon leading to overgrowth of *Clostridium difficile*. If *C. difficile* associated diarrhea occurs, discontinue ORACEA. (5.3)
- If renal impairment exists, ORACEA doses may need to be adjusted to avoid excessive systemic accumulations of the drug and possible liver injury. (5.4)
- Photosensitivity can occur with ORACEA; Patients should minimize or avoid exposure to natural or artificial sunlight. (5.5)
- Tetracyclines have been associated with the development of autoimmune syndromes; if symptoms develop, discontinue ORACEA immediately. (5.6)
- ORACEA may cause pseudotumor cerebri (benign intracranial hypertension). Discontinue ORACEA if symptoms occur. (5.8)
- Bacterial resistance to tetracyclines may develop in patients using ORACEA. It should only be used as indicated. (5.9)

----------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----------
Lactation: Breastfeeding is not recommended (8.2)

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

Revised: 12/2021

FULL PRESCRIBING INFORMATION: CONTENTS*

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

DOCKET ALARM
Find authenticated court documents without watermarks at docketalarm.com.

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. Do not use ORACEA 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.

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
Take one ORACEA capsule (40 mg) 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 other tetracyclines.

5 WARNINGS AND PRECAUTIONS

5. 1 Inhibition of Bone Growth During Fetal and Pediatric Development
Doxycycline, like other tetracycline-class drugs, may cause inhibition of bone growth when administered during the second and third trimesters of pregnancy, infancy, and childhood. 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. If doxycycline is used during the second or third trimester of pregnancy, advise the patient of the potential risk to the fetus *[see Use in Specific Populations (8.1)]*.

5.2 Tooth Discoloration During Fetal and Pediatric Development
The use of tetracycline class drugs orally 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. Use of tetracycline drugs is not recommended during tooth development *[see Use in Specific Populations (8.1)]*.

5.3 *Clostridium difficile* Associated Diarrhea (CDAD)
Clostridium difficile associated diarrhea (CDAD) has been reported with nearly all antibacterial agents, including doxycycline, 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 management should be instituted as clinically indicated.

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 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.

5.5 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.

5.6 Autoimmune Syndromes
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.

5.7 Tissue Hyperpigmentation
Tetracycline-class drugs are known to cause hyperpigmentation. Tetracycline therapy may induce hyperpigmentation in many organs, including nails, bone, skin, eyes

DOCKET ALARM
Find authenticated court documents without watermarks at docketalarm.com.

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.

5.8 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 papiledema while on treatment.

5.9 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.

5.10 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.

5.11 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.

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 ≥ 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)

DOCKET ALARM
Find authenticated court documents without watermarks at docketalarm.com.

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. 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)*].

Renal toxicity: Rise in BUN has been reported and is apparently dose-related [*see Warnings and Precautions (5.4)*].

Skin: maculopapular and erythematous rashes. Exfoliative dermatitis . Photosensitivity is discussed above [*see Warnings and Precautions (5.5)*].

Hypersensitivity reactions: urticaria, angioneurotic edema, anaphylaxis, anaphylactoid purpura, serum sickness, pericarditis, and exacerbation of systemic lupus erythematosus.
Blood: Hemolytic anemia, thrombocytopenia, neutropenia, and eosinophilia.

6.2 Postmarketing Experience
Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. The following adverse reactions have been identified during post approval use of ORACEA.*Nervous system:* Pseudotumor cerebri (benign intracranial hypertension), headache.

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 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.

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

7.7 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
Doxycycline may cause reversible inhibition of bone growth and permanent discoloration of deciduous teeth when administered during the second and third trimesters of pregnancy *[see Warnings and Precautions (5.1 and 5.2)]*. Available data from published studies have not shown a difference in major birth defect risk with doxycycline exposure in the first trimester of pregnancy compared to unexposed pregnancies. Avoid use of ORECEA during the second and third trimester of pregnancy.

The 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
Published studies, including epidemiological and observational studies, with use of doxycycline during the first trimester of pregnancy have not identified drug-related increases in major birth defects.

The use of tetracycline during tooth development (second and third trimester of pregnancy) may cause permanent discoloration of deciduous 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.

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

DOCKET ALARM
Find authenticated court documents without watermarks at docketalarm.com.

8.2 Lactation

Risk Summary

Based on available published data, doxycycline is likely to be present in human breast milk but the specific concentration in breastmilk is not clear. There is no information on the effects of doxycycline on the breastfed infant or the effects on milk production. Because there are other antibacterial drug options available to treat rosacea in lactating women and because of the potential for serious adverse reactions, including tooth discoloration and inhibition of bone growth, advise patients that breastfeeding is not recommended during treatment with ORACEA and for 5 days after the last dose.

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.

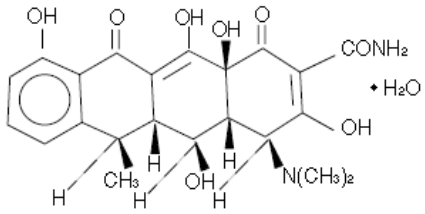
8.5 Geriatric Use

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 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.

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 ($C_{22}H_{24}N_2O_8$).

The structural formula of doxycycline, USP is:



with an empirical formula of $C_{22}H_{24}N_2O_8 \cdot H_2O$ and a molecular weight of 462.46. The chemical designation for doxycycline is 2-Naphthacenecar-boxamide,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,12aα)]-, 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.

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.

Table 2. Pharmacokinetic Parameters [Mean (±SD)] for ORACEA

	N	Cmax* (ng/mL)	Tmax+ (hr)	AUC_{0-oo}* (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)*]

DOCKET ALARM
Find authenticated court documents without watermarks at docketalarm.com.

DOCKET ALARM

Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts

Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research

With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips

Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS
Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS
Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS
Sync your system to PACER to automate legal marketing.