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)
- Efficacy of ORACEA beyond 16 weeks and safety beyond 9 months have not been established (1.2).
- This formulation of doxycycline has not been evaluated in the treatment or prevention of infections (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)
- The dosage of ORACEA differs from that of doxycyline used to treat infections. Exceeding the recommended dosage may result in an increased incidence of side effects including the development of resistant microorganisms (2, 5.5)

----------DOSAGE FORMS AND STRENGTHS----------

40 mg capsule: beige opaque capsule imprinted with “GLD 40” (3)

----------CONTRAINDICATIONS----------

This drug 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)
- Anti-anabolic action of the tretracyclines may cause an increase in BUN (5.3)
- Photosensitivity (an exaggerated sunburn reaction) can occur with Oracea; Oracea should be discontinued(5.4)
- Tetracyclines have been associated with the development of autoimmune syndromes; discontinue Oracea immediately (5.5)
- Bacterial resistance to tetracycline may develop in patients using ORACEA (5.8).

----------ADVERSE REACTIONS----------

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 5/2010

FULL PRESCRIBING INFORMATION: CONTENTS*

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

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 capsule: 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 *[see Use in Specific Populations (8.1)]*.
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 *[see Use in Specific Populations (8.1)]*.

5.2 Pseudomembranous Colitis

Pseudomembranous colitis has been reported with nearly all antibacterial agents and may range from mild to life-threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhea subsequent to the administration of antibacterial agents.
Treatment with antibacterial agents alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by Clostridium difficile is a primary cause of “antibiotic-associated colitis”.
If a diagnosis of pseudomembranous colitis has been established, therapeutic measures should be initiated. Mild cases of pseudomembranous colitis usually respond to discontinuation of the drug alone. In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation, and treatment with an antibacterial drug clinically effective against Clostridium difficile colitis.

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.

5.5 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.

5.6 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 papiledema 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 candidiasis overgrowth

5.10 Laboratory Monitoring
Periodic laboratory evaluations of organ systems, including hematopoetic, 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 ≥ 1% for the active arm:

Table 3. Incidence (%) of Selected Adverse Reactions in Clinical Trails 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 decrese 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.

8.2 Labor and Delivery
The effect of tetracyclines on labor and delivery is unknown.

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.

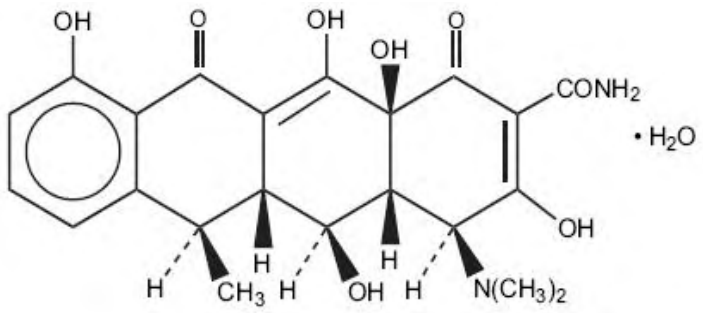
8.5 Geriatric Use
Clinical studies of ORACEA did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between elderly and younger patients. In general, dose selection for 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. 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 ($C_{22}H_{24}N_2O_8$).
The structural formula of doxycycline, USP is:



with an empirical formula of $C_{22}H_{24}N_2O_8 \bullet H_2O$ 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,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. 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 1.

Table 1. Pharmacokinetic Parameters [Mean (+ SD)] for ORACEA

	N	C_{max}* (ng/mL)	T_{max}+ (hr)	$AUC_{0-\infty}$* 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 (Cmax 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 Cmax 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 be used for treating bacterial infections, providing antibacterial prophylaxis, or reducing the numbers or eliminating microorganisms associated with any bacterial disease *[see Indications and Usage (1.2)]*. *In vivo* microbiological studies utilizing a similar drug exposure for up to 18 months demonstrated no detectable long term effects on bacterial flora of the oral cavity, skin, intestinal tract and vagina.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Doxycycline was assessed for potential to induce carcinogenesis in a study in which the compound was administered to Sprague-Dawley rats by gavage at dosages of 20, 75, and 200 mg/kg/day for two years. An increased incidence of uterine polyps was observed in female rats that received 200 mg/kg/day, a dosage that resulted in a systemic exposure to doxycycline approximately 12.2 times that observed in female humans who use ORACEA (exposure comparison based upon area under the curve (AUC) values). No impact upon tumor incidence was observed in male rats at 200 mg/kg/day, or in either gender at the other dosages studied. Evidence of oncogenic activity was obtained in studies with related compounds, i.e., oxytetracycline (adrenal and pituitary tumors) and minocycline (thyroid tumors).
Doxycycline demonstrated no potential to cause genetic toxicity in an in vitro point mutation study with mammalian cells (CHO/HGPRT forward mutation assay) or in an in vivo micronucleus assay conducted in CD-1 mice. However, data from an in vitro assay with CHO cells for potential to cause chromosomal aberrations suggest that doxycycline is a weak clastogen.
Oral administration of doxycycline to male and female Sprague-Dawley rats adversely affected fertility and reproductive performance, as evidenced by increased time for mating to occur, reduced sperm motility, velocity, and concentration, abnormal sperm morphology, and increased pre-and post-implantation losses. Doxycycline induced reproductive toxicity at all dosages that were examined in this study, as even the lowest dosage tested (50 mg/kg/day) induced a statistically significant reduction in sperm velocity. Note that 50 mg/kg/day is approximately 3.6 times the amount of doxycycline contained in the recommended daily dose of ORACEA for a 60-kg human when compared on the basis of AUC estimates. Although doxycycline impairs the fertility of rats when administered at sufficient dosage, the effect of ORACEA on human fertility is unknown.

14 CLINICAL STUDIES

The safety and efficacy of ORACEA in the treatment of only inflammatory lesions (papules and pustules) of rosacea was evaluated in two randomized, placebo-controlled, multi-centered, double-blind, 16-week Phase 3 studies involving 537 subjects (total of 269 subjects on ORACEA from the two studies) with rosacea (10 to 40 papules and pustules and two or fewer nodules). Pregnant and nursing women, subjects <18 years of age, and subjects with ocular rosacea and/or blepharitis/meibomianitis who require ophthalmologic treatment were excluded from study. Mean baseline lesion counts were 20 and 21 for ORACEA and placebo subject groups respectively.
At Week 16, subjects in the ORACEA group were evaluated using co-primary endpoints of mean reduction in lesion counts and a dichotomized static Investigator's Global Assessment of Clear or Almost Clear (defined as 1 to 2 small papules or pustules) when compared to the placebo group in both Phase 3 studies.

Table 2: Clinical Results of ORACEA versus Placebo

	Study 1		Study 2	
	ORACEA 40 mg	Placebo N=124	ORACEA 40 mg	Placebo N=144

	N=127		N=142	
Mean Change in Lesion Count from Baseline	-11.8	-5.9	-9.5	-4.3
No. (%) of Subjects Clear or Almost Clear in the IGA*	39 (30.7%)	24 (19.4%)	21 (14.8%)	9 (6.3%)

*Investigator's Global Assessment
Subjects treated with ORACEA did not demonstrate significant improvement in erythema when compared to those treated with placebo.

16 HOW SUPPLIED/STORAGE AND HANDLING

ORACEA (beige opaque capsule imprinted with "GLD 40") containing doxycycline, USP in an amount equivalent to 40 mg of anhydrous doxycycline. Bottle of 30 (NDC 0299-3822-30).

Storage:

All products are to be stored at controlled room temperatures of 15°C - 30°C (59°F - 86°F) and dispensed in tight, light-resistant containers (USP).
KEEP OUT OF REACH OF CHILDREN

17 PATIENT COUNSELING INFORMATION

17.1 Information for Patients

Patients taking ORACEA® (doxycycline, USP) Capsules 40 mg should receive the following information and instructions:

- It is recommended that ORACEA not be used by individuals of either gender who are attempting to conceive a child *[see Nonclinical Pharmacology (13.1), and Use in Specific Populations (8.1)]*.
- It is recommended that ORACEA not be used by pregnant or breast feeding women *[see Nonclinical Toxicology (13.1), Use in Specific Populations (8.1) and (8.3)]*.

Patients should be advised that pseudomembranous colitis can occur with doxycycline therapy. If patients develop watery or bloody stools, they should seek medical attention.

- Patients should be advised that pseudotumor cerebri can occur with doxycycline therapy. If patients experience headache or blurred vision they should seek medical attention.
- Photosensitivity manifested by an exaggerated sunburn reaction has been observed in some individuals taking tetracyclines, including doxycycline. Patients should minimize or avoid exposure to natural or artificial sunlight (tanning beds or UVA/B treatment) while using doxycycline. If patients need to be outdoors while using doxycycline, 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 sunburn.
- Concurrent use of doxycycline 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 doxycycline. 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 doxycycline therapy.
- Take ORACEA exactly as directed. Increasing doses beyond 40 mg every morning may increase the likelihood that bacteria will develop resistance and will not be treatable by other antibacterial drugs in the future.

17.2 FDA-Approved Patient Labeling

ORACEA® (Or-RAY-sha) (doxycycline, USP) Capsules 40 mg

Read the Patient Information that comes with ORACEA before you start taking it and each time you get a refill. There may be new information. This information does not take the place of talking with your doctor about your treatment or your medical condition. If you have any questions about ORACEA, ask your doctor or pharmacist.

What is ORACEA?
ORACEA is a prescription medicine to treat only the pimples or bumps on the face caused by a condition called rosacea. ORACEA did not lessen the facial redness caused by rosacea. ORACEA has not been studied for the treatment of rosacea of the eyes or of small blood vessels of the skin.
ORACEA should not be given to infants and children 8 years or younger. It may cause stained teeth in infants and children. The yellow, gray, brown colored staining will not go away.
ORACEA should not be used for the treatment of infections.
It is not known if ORACEA is effective for use for longer than 16 weeks. It is not known if ORACEA is safe for use longer than 9 months.

Who should not take ORACEA?
Do not take ORACEA if you are allergic to any medicine known as a tetracycline, including doxycycline and minocycline. If you are not sure, talk to your doctor or pharmacist.

What should I tell my doctor before taking ORACEA?
Tell your doctor about all your health conditions. Be sure to tell your doctor if you
- have had an allergic reaction to doxycycline or other medicines known as tetracyclines
- are pregnant or planning to become pregnant. ORACEA may harm your unborn baby.
- are breastfeeding. ORACEA passes into your breast milk and may harm your baby.
- have kidney problems
- have liver problems
- have had surgery on your stomach
- have or had a yeast or fungus infection in your mouth or vagina.
- spend time in sunlight or artificial sunlight, such as a tanning booth or sunlamp. ORACEA may cause you to get severe sunburns (photosensitivity).

Tell your doctor about all of the medicines you take, including prescription and non-prescription medicines, vitamins, and herbal supplements.
ORACEA and other medicines can affect each other causing serious side effects. Especially tell your doctor if you take
- blood thinners (anticoagulants), such as warfarin or Coumadin®. Your doctor may need to change your anticoagulant dose.
- any medicine to treat pimples (acne) or psoriasis, such as isotretinoin or acetretin

ORACEA may affect the way other medicines work, and other medicines may affect how ORACEA works. Especially tell your doctor if you take
- birth control pills. Talk to your doctor about other methods of birth control because birth control pills may not work as well when you are taking ORACEA.
- proton pump inhibitors or antacid medicines containing calcium, magnesium or aluminum

- products containing iron or bismuth subsalicylate
- any medicine to treat an infection, such as penicillin
- any medicine to treat seizures, such as barbiturates, Phenobarbital, carbamazepine, Tegretol®, phenytoin or Dilantin®

Know the medicines you take. Keep a list of your medicines and show it to your doctor and pharmacist when you get a new medicine.

How should I take ORACEA?

- Take ORACEA exactly as prescribed by your doctor. Do not change your dose unless told to do so by your doctor. Taking more than the prescribed dose may increase your chance of having side effects.
- The usual dose of ORACEA is one capsule in the morning on an empty stomach. You should take ORACEA at least one hour before or two hours after a meal.
- Take ORACEA with a full glass of water while sitting or standing. To prevent irritation to your throat, do not lay down right after taking ORACEA.
- Do not take ORACEA with or right after taking antacids or products that contain calcium, aluminum, magnesium, or iron. ORACEA may not work as well.
- If you take too much ORACEA, or overdose, stop taking ORACEA and talk to your doctor.
- If you miss a dose of ORACEA, skip that dose and take the next dose at your regular time.
- Do not take ORACEA to treat infections caused by bacteria germs or viruses.
- Your doctor may do blood tests from time to time to check for side effects of ORACEA.

What should I avoid while taking ORACEA?

- Do not spend time in sunlight or artificial sunlight, such as a tanning booth or sunlamp. You could get a severe sunburn. Use sunscreen and wear clothes that cover your skin if you have to be in sunlight.
- You should not take ORACEA if you are pregnant or breast feeding.
- You should not take ORACEA if you are a man or a woman trying to have a baby.

What are the possible side effects of ORACEA?

ORACEA may cause serious side effects. Stop taking ORACEA and talk to your doctor right away if you

- have any skin rash, redness, or unusual or severe sunburn
- have an allergic reaction, which may cause a skin rash, swelling, difficulty swallowing, or a feeling of tightness in your throat
- become pregnant
- have stomach cramps, high fever, and bloody diarrhea (pseudomembranous colitis)
- have fever, rash, joint pain, and feel tired. These may be symptoms of a problem where your body is attacking itself (autoimmune syndrome).

ORACEA may also cause

- darkening of your skin, scars, teeth, or gums
- severe headaches, dizziness, or double vision from high pressure in the fluid around the brain

Some common side effects of ORACEA are soreness in the nose and throat, diarrhea, sinus infection, high blood pressure, and increase in aspartate aminotransferase in the blood..

These are not all the possible side effects of ORACEA. For more information, ask your doctor or pharmacist.

Tell your doctor if you have a side effect that bothers you or that does not go away.

You may report side effects to FDA at 1-800-FDA-1088 or to GALDERMA LABORATORIES, L.P. at 1-866-735-4137

How should I store ORACEA?

- Store ORACEA at room temperature at 59°F to 86°F (15°C to 30°C).
- Keep ORACEA in a tightly closed container.
- Keep ORACEA inside container and out of light.
- **Keep ORACEA and all medicine out of the reach of children**.

General Information about ORACEA

Do not take ORACEA for a condition for which it was not prescribed. Do not give ORACEA to other people, even if they have the same symptoms you have. It may harm them.

This leaflet gives the most important information about ORACEA. For more information, talk with your doctor or health care provider. You can also ask your doctor or pharmacist for information that is written for health professionals.

What are the ingredients in ORACEA?

Active ingredient: doxycycline

Inactive ingredients: hypromellose, iron oxide red, iron oxide yellow, methacrylic acid copolymer, polyethylene glycol, Polysorbate 80, sugar spheres, talc, titanium dioxide, and triethyl citrate.

Rx Only

Patent Information: U.S. Patents 5,789,395; 5,919,775; 7,232,572; 7,211,267 and patents pending.

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