ORACEA™
(doxycycline, USP) Capsules 40 mg*

*30 mg Immediate Release & 10 mg Delayed Release beads

Rx Only
KEEP OUT OF REACH OF CHILDREN

The dosage of ORACEA differs from that of doxycycline used to treat infections. To reduce the development of resistant bacteria as well as to maintain the effectiveness of other antibacterial drugs, ORACEA should be used only as indicated.

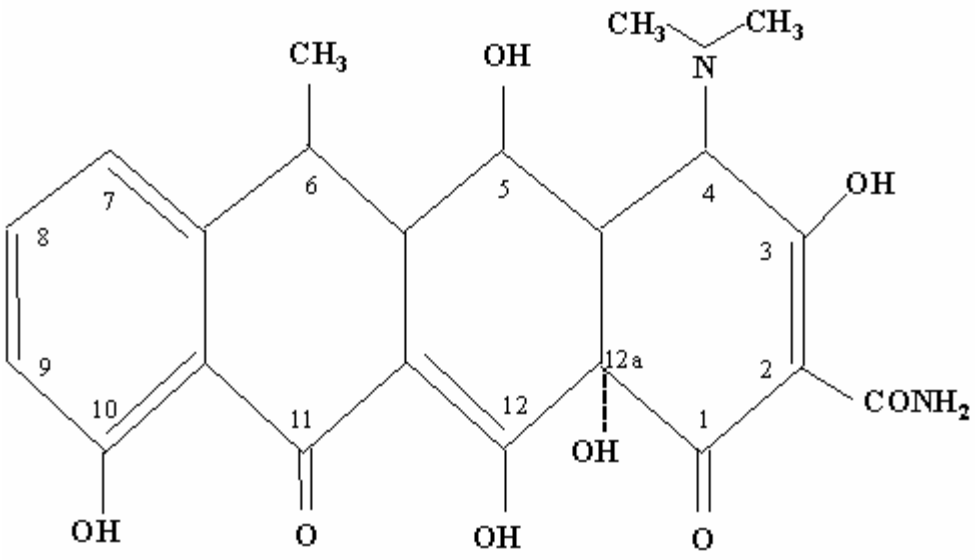
ORACEA is indicated for the treatment of only inflammatory lesions (papules and pustules) of rosacea in adult patients.

This formulation of doxycycline has not been evaluated as an antibacterial in the treatment of infections.

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:



.H_2O

with an empirical formula of $C_{22}H_{24}N_2O_8 \cdot H_2O$ and a molecular weight of 462.46. The chemical

1,4,4a,5,5a,6,11,12a-octahydro-3,5,10,12,12a-pentahydroxy-6-methyl-1,11-dioxo-, [4S-(4aα, 4aα, 5α, 5aα, 6a,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.

CLINICAL PHARMACOLOGY

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	Cmax * (ng/mL)	Tmax + (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 section).

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 PRECAUTIONS section)

MICROBIOLOGY

Doxycycline is a member of the tetracycline class of antibacterial drugs. The plasma concentrations of doxycycline achieved with ORACEA during administration (see CLINICAL PHARMACOLOGY AND DOSAGE AND ADMINISTRATION) are less than the concentration required to treat bacterial diseases. *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.

ORACEA should not be used for treating bacterial infections, providing antibacterial prophylaxis, or reducing the numbers or eliminating microorganisms associated with any bacterial disease.

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 patients (total of 269 patients on ORACEA from the two studies) with rosacea (10 to 40 papules and pustules and two or fewer nodules). Pregnant and nursing women, patients <18 years of age, and patients 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 patient groups respectively.

At Week 16, patients 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 N = 127	Placebo N = 124	ORACEA 40 mg N = 142	Placebo N = 144
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

Patients treated with ORACEA did not demonstrate significant improvement in erythema when compared to those treated with placebo.

INDICATIONS AND USAGE

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. ORACEA has not been evaluated for the treatment of the erythematous, telangiectatic, or ocular components of rosacea. Efficacy of ORACEA beyond 16 weeks and safety beyond 9 months have not been established.

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.

CONTRAINDICATIONS

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

WARNINGS

Teratogenic effects

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.

ORACEA should not be used during pregnancy (see PRECAUTIONS: Pregnancy).

2) 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.**

3) 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 PRECAUTIONS: Pregnancy section).

Gastrointestinal effects

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.

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.

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.

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