tions. 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)

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See 17 for PAT labeling.

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or su 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 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

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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	C_{max}* (ng/mL)	T_{max}+ (hr)	AUC_{0-00}* (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 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

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