ONCE-DAILY

ORACEA®

(doxycycline) 40 mg modified-release, hard capsule

PRODUCT MONOGRAPH

GALDERMA

TABLE OF CONTENTS

OVERVIEW OF ROSACEA

Rosacea is a chronic skin disease with a relapsing-remitting course characterized by a variable spectrum of dermatologic symptoms with central facial predominance including flushing, persistent erythema, papules, pustules, and telangiectasia.[1] The signs of rosacea can be misdiagnosed as acne vulgaris, photoaging, or lupus erythematosus. Due to low disease awareness in the public, patients with rosacea often do not realize they have a medical condition that can be treated; this is 1 reason why rosacea is underdiagnosed. Without medical treatment, rosacea may progressively worsen and can have a substantial impact on patients' quality of life.

EPIDEMIOLOGY

Fair-skinned individuals of northern European descent are particularly prone to rosacea, even though it can occur in individuals of any race or ethnic background.[2] In dark-skinned patients, the prevalence of rosacea is not known, partly due to little suspicion of the disease. The majority of patients with rosacea are diagnosed between 30 and 50 years of age.[3] Women are affected more commonly than men.[1] However, men develop the phymatous subtype of rosacea more often than women (approximately 20:1).[4] Up to 30% of patients report a family history of rosacea.[5]

DIAGNOSIS AND CLASSIFICATION

Rosacea is a clinical diagnosis. There is no confirmatory laboratory test, and histology from skin biopsy is not characteristic. Rosacea is often difficult to diagnose because it develops gradually. Patients may be unaware of their condition and/or may not discuss their symptoms with their physician, thus contributing to underdiagnosis of the disease.[3] Rosacea can easily be misdiagnosed as acne or chronic sun damage.

In 2002, a provisional classification system was formulated by the American National Rosacea Society Expert Committee (NRSEC) to serve as a diagnostic tool and establish standardized terminology by grouping patients into subtypes.[6] Because knowledge concerning the pathophysiology of rosacea is lacking, the classification system is based on morphological characteristics of the disease.

OVERVIEW OF ROSACEA

The committee established primary and secondary diagnostic criteria in addition to subdividing clinical features of rosacea into 4 subtypes (erythematotelangiectatic, papulopustular, phymatous, and ocular) and 1 rare variant (granulomatous). The NRSEC classification system is described in detail below.[6]

PRIMARY AND SECONDARY DIAGNOSTIC CRITERIA

Diagnosis of rosacea is based on the presence of 1 or more primary features located on the central area of the face. Secondary features can coexist with 1 or more of the primary characteristics, yet they may occur independently in some patients (Table 1).

Table 1. Primary and secondary features of rosacea[6]

PRIMARY FEATURES (1 or more are usually present)	• Flushing (transient erythema is a common feature) • Nontransient erythema • Papules and pustules • Telangiectasia
SECONDARY FEATURES (May be present)	• Burning or stinging • Plaques • Dry appearance • Edema • Ocular manifestations • Peripheral location • Phymatous changes

OVERVIEW OF ROSACEA

CLINICAL PICTURE

Rosacea is characterized by a variety of facial skin and ocular features that differ by patient.[3] It is a disease that encompasses a combination of signs and symptoms including flushing, erythema, telangiectasia, edema, papules, pustules, ocular lesions, and phymatous changes/skin thickening.[6] They are expressed to a variable extent in different subtypes, which leads to clinical overlapping and might cause double counting of patients in epidemiological studies. Trigger factors are nonspecific events, environments, or conditions (eg, sun exposure, emotional stress, spicy foods, and hot drinks) under which the symptoms of rosacea may emerge. Patients must be advised to avoid trigger factors (Table 2).[7]

Table 2. Most common rosacea triggers (NRS survey of more than 1600 patients with rosacea)[8]

TRIGGER	PERCENT AFFECTED
SUN EXPOSURE	81%
EMOTIONAL STRESS	79%
HOT WEATHER	75%
WIND	57%
HEAVY EXERCISE	56%
ALCOHOL CONSUMPTION	52%
HOT BATHS	51%

NRS=National Rosacea Society.

OVERVIEW OF ROSACEA

SUBTYPES OF ROSACEA

The most common patterns or groups of signs or features are designated as specific subtypes of rosacea (Table 3). Patients may have characteristics of 1 or more rosacea subtypes simultaneously. Clinical signs and symptoms may evolve over time.[9] Subtypes 1 and 2 are the most common.

However, there are some limitations to the subtype classification system. It does not take into consideration progression from one subtype to another, although studies have shown that subjects with rosacea may progress from one subtype to another. Subtypes are also only based on physical findings and symptoms, and make no reference to pathophysiological factors.[10,11]

Table 3. Subtypes and variants of rosacea and their characteristics[9]

SUBTYPE	CHARACTERISTICS
SUBTYPE 1: Erythematotelangiectatic	Flushing and persistent central facial erythema with or without telangiectasia
SUBTYPE 2: Papulopustular	Persistent central facial erythema with transient, central facial papules or pustules or both
SUBTYPE 3: Phymatous	Thickening skin, irregular surface nodularities and enlargement. May occur on the nose, chin, forehead, cheeks, or ears
SUBTYPE 4: Ocular	Foreign body sensation in the eye, burning or stinging, dryness, itching, ocular photosensitivity, blurred vision, telangiectasia of the sclera or other parts of the eye, or periorbital edema
VARIANT: Granulomatous	Noninflammatory, hard brown, yellow, or red cutaneous papules; or nodules of uniform size

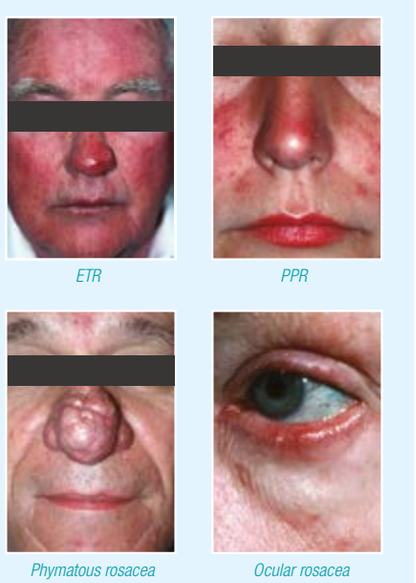


Figure 1. Examples of rosacea subtypes
ETR=erythematotelangiectatic rosacea; PPR=papulopustular rosacea.

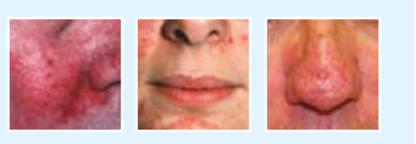


Figure 2. Examples of papulopustular rosacea

OVERVIEW OF ROSACEA

QUALITY OF LIFE

Without appropriate diagnosis and management, rosacea can progressively worsen and have a substantial impact, not only physically, but psychologically. Patients with rosacea experience a variety of emotional and social stigmas, most commonly feelings of low self-esteem in response to changes in facial features.[3] In surveys by the NRS, almost 70% of patients with rosacea reported their disease had lowered their self-esteem and self-confidence, and 41% reported it had caused them to avoid public contact or cancel social engagements. Among patients with severe rosacea symptoms, nearly 30% missed work due to their condition.[12] The anxiety that some patients with rosacea have about their disease may resemble panic disorders and can cause some patients to become reclusive. Additionally, patients also may feel that their facial imperfections lessen their sexual desirability or impede career advancement.[3] Adding to the embarrassing physical effects of rosacea are misconceptions the public has about the disease, such as those with the disease are alcoholics or rosacea is caused by poor hygiene.[12]

The results of a large, international study assessing the psychosocial impact of facial erythema of rosacea lended further evidence to the decrease in quality of life of these individuals. Over 60% of respondents reported feeling embarrassed by their rosacea. Two-thirds experienced a social impact, with 36% reporting feeling uncomfortable meeting new people. Over half felt it had affected their relationships and personal life, with nearly a third feeling uncomfortable when dating. However, diagnosis and appropriate medical treatment can help patients feel more in control of their rosacea. Those with physician-diagnosed rosacea were almost twice as likely to have their rosacea under control through lifestyle changes and medication as those who were undiagnosed (39% vs 20%).[13]

PATHOPHYSIOLOGY OF ROSACEA

The etiology of rosacea is not entirely understood; however, several factors have been implicated in its pathogenesis based on evidence of scientific studies.[14] Vascular, immunologic, and neural factors are key elements and others are also implicated.

VASCULATURE

Dilation of cutaneous vasculature and lymphatics have been reported in patients with rosacea. Some studies have shown increased cutaneous blood flow in affected skin and recent data have confirmed vascular and lymphatic dilation in ETR and PPR subtypes. Enlargement of vasculature, hyperpermeability, and fluid leakage are typical signs of tissue inflammation, with angiogenesis, lymphangiogenesis, vascular endothelial growth factor, and other markers for blood vessels and lymphatics shown to be increased in rosacea.[15]

Various trigger factors—such as spicy food, heat, cold, exercise, and alcohol—can lead to increased vasodilation. These triggers activate ion channels, such as members of the transient receptor potential (TRP) receptor family, which are involved in prolonged vasodilation and neurogenic inflammation. Patients with rosacea may experience a sustained activation of TRP channels on nociceptors, resulting in flushing and neurogenic inflammation with leukocyte infiltration. It has been noted that patients with rosacea have a high density of TRP vanilloid 1 (TRPV1)-positive nerve fibers and increased levels of TRPV1 mRNA expression.[16]

In lesional skin, blood flow is increased by approximately 3 to 4 times that of normal. However, it is unknown if this is a result of or cause of the condition.[17]

Upregulation of inducible endothelial nitric oxide synthetase (NOS) after UV radiation exposure also may contribute to vasodilation leading to erythema response.[18] Other proposed mediators of the vasodilatory response in rosacea include substance P, vasoactive intestinal peptide, gastrin, serotonin, histamine, and prostaglandins.[9] A recent study showed that mean arterial and diastolic blood pressure (DBP) fell following UV irradiation, but systolic BP did not change. DBP is a function of total peripheral resistance, and its marked drop in irradiated subjects suggests that UVA vasodilates the peripheral vasculature. In addition to changes in blood pressure, this study also showed that UVA increases blood flow in a NOS and temperature-independent manner and dose-dependent NO release within irradiated skin.[19]

PATHOPHYSIOLOGY OF ROSACEA

INNATE IMMUNE SYSTEM

Recent findings in research showed the innate immune system can have implications in the pathogenesis of rosacea. Some of the changes seen in rosacea include epidermal barrier dysfunction, inflammatory cell and molecular changes, and cathelicidin inflammatory upregulation.

Epidermal Barrier Dysfunction

Epidermal barrier dysfunction, involving increased transepidermal water loss, primarily in the central facial region, plays an important role in inflammatory rosacea, which partly explains the clinical observation of sensitive facial skin in rosacea.[20]

Inflammatory Cell and Molecular Changes

In rosacea, there is marked infiltration of T lymphocytes, macrophages, mast cells, and neutrophils (or B cells).[15,21] This pattern of inflammatory cell infiltration suggests involvement of the innate immune response in PPR. Although the adaptive immune response also is activated in other subtypes of rosacea, the greatest magnitude of activation appears to be in PPR.[15]

Cathelicidin Inflammatory Upregulation

In vitro and in vivo animal experiments have found elevated levels of cathelicidin peptides in skin affected by rosacea. Cathelicidin is a major antimicrobial peptide (AMP) found in keratinocytes that is physiologically responsible for antibacterial immune defense. Cathelicidin AMPs have been shown to be upregulated in the affected skin of patients with rosacea. Increased expression of cathelicidin AMP and concomitant increases in kallikrein-related peptidase 5 (KLK-5), an enzyme involved in cathelicidin processing, contributes to the chemoattraction of inflammatory cells, angiogenesis, vasoactivity, and alterations in the extracellular matrix. For example, a cathelicidin peptide product, LL-37, promotes neutrophil chemotaxis, potentially contributing to the formation of inflammatory lesions in PPR.[15,22]

PATHOPHYSIOLOGY OF ROSACEA

DEMODEX FOLLICULORUM

Demodex folliculorum is a mite that is often present in hair follicles of adults and has been implicated in the pathogenesis of rosacea.[9] *Demodex* mites often colonize in skin regions most often affected by rosacea: the forehead; malar, nasal, and paranasal regions of the face and neck; and upper chest areas. There is up to a 100% colonization rate of *Demodex* mites that steadily increases with age in adults. Increased density of *Demodex* has been found in rosacea-affected skin, which correlates with a generalized increase in inflammation markers; 35% to 50% of rosacea patients have increased *Demodex* load (>5 mites/cm^2). In a multicenter, prospective study assessing the relationship among *Demodex* load, rosacea subtype, and innate immune markers in the skin, a 6-fold increase in *Demodex* density in rosacea vs age-matched controls was demonstrated.[23,24]

INFLAMMATION: THE COMMON DENOMINATOR

Rosacea has long been viewed as a disorder that is caused by changes in the vasculature, climatic exposure leading to upregulation of inflammatory mediators, and/or microbial organisms. Recently, it also has been shown that aberrant innate immunity is central to this disease.

While a definitive pathophysiologic mechanism for rosacea has not been established, many theories point to chronic inflammation as the common pathogenic factor. The intimate relationship between the vasculature and immune system, as well as the success of anti-inflammatory agents, such as tetracyclines, in the treatment of rosacea, indicates that inflammatory cells, such as neutrophils, and other inflammatory mediators are key pathophysiologic factors in the development of rosacea.[7]

In rosacea, as in other similar disorders, inflammation may be triggered by otherwise benign stimuli. After inflammation is initiated it is inappropriately sustained, leading to disease progression. While the evolution of inflammatory response in rosacea has not been precisely elucidated, most experts cite a similar sequence of events (Figure 3)[25,26]:

- Initial erythema is caused by vasodilation of dermal capillaries, possibly mediated by histamine, prostacyclin, prostaglandin E_2 (PGE_2), NO, and other vasoactive compounds
- Prolonged dilation weakens the capillary wall, increasing its permeability and allowing neutrophils and proinflammatory cytokines, such as tumor necrosis factor-alpha (TNF-α) and certain interleukins (especially IL-1 and IL-6) to leak into the surrounding dermis

PATHOPHYSIOLOGY OF ROSACEA

- Inflammation and ongoing extravasation overwhelm the capacity of lymphatic vessels, leading to edema
- Additional neutrophils are recruited by chemotactic factors released from inflamed dermal tissues
- Activated neutrophils release destructive compounds, including matrix metalloproteinases (MMPs) such as collagenases and gelatinases, reactive oxygen species (ROS), and NO that exacerbate the inflammatory response and lead to tissue damage
- Continued vascular instability may lead to the development of telangiectasia, while chronic attacks by enzymes and oxygen free radicals lead to weakening and damage of skin structural elements

Figure 3. Intradermal pathophysiology in rosacea

UV-related photodamage is another possible cause of persistent erythema and telangiectasia formation in rosacea skin. UV-related photodamage is capable of triggering an innate immune response that can contribute to jump-starting and perpetuating underlying pathophysiological mechanisms, leading to inflammation, vasodilation, and angiogenesis. Factors that may contribute to UV-induced angiogenesis include ROS-induced increase in expression of MMP-9 and increased production of vascular endothelial growth factor (VEGF) by keratinocytes exposed to UVB.[15]

Growing evidence also points to the role of the AMP, cathelicidin, in rosacea. Cathelicidin expression correlates with effective antibacterial defense in skin tissue in dermatologic disorders. Given that the downstream effects of cathelicidin signaling mimic some features of rosacea, the proposed, abnormal expression of cathelicidin may be a chief aspect of this disease. Study results suggest that high expression and abnormal processing of cathelicidin might underlie the inflammation associated with rosacea. *Demodex* can be found in the skin of most healthy adults, but are highly prolific in rosacea-affected skin. It is possible that *Demodex* influences the expression levels and processing of cathelicidin, and thus, in some cases, interacts with the heightened innate immune response of rosacea-prone skin, particularly PPR.[23,27]

The pathophysiology of rosacea is still a subject of controversy; however, research suggests that various immune cells and inflammatory mediators play a role in the vascular, inflammatory, and hyperplasia stages of this disorder.[7]

MECHANISM OF ACTION OF TETRACYCLINES

Tetracycline agents, such as minocycline and doxycycline, exhibit intracellular and extracellular biological activities unrelated to their antimicrobial effects.[28] These activities result in less inflammation, reduced degradation of matrix components, and proinflammatory cytokine inhibition. The biological activities of tetracyclines that correlate with anti-inflammatory activities are summarized in Table 4. Several of the described biological activities may correlate with inhibition of pathophysiologic mechanisms possibly related to rosacea and appear to explain the therapeutic effects obtained with the use of tetracyclines, such as anti-inflammatory dose doxycycline.

Much early research evaluating the anti-inflammatory activities of tetracyclines was done in adult patients with periodontitis, an inflammatory gum disease.[28] Clinical evidence showed that tetracyclines independently inhibited MMP activity and stimulated new bone formation, thus preventing connective tissue breakdown and contributing to the prevention of net alveolar bone loss.[28] Further evidence showed that tetracyclines inhibit connective tissue breakdown through indirect and direct mechanisms, depending on the particular status of the tissues involved and stage of disease progression.[28] Tetracyclines directly inhibit active MMPs, such as MMP-1, MMP-8, MMP-13 (collagenases), MMP-2 and MMP-9 (gelatinases), as well as the oxidative activation of pro-MMPs.[28,29] Tetracyclines disrupt MMP activation by promoting excessive proteolysis of pro-MMPs into enzymatically inactive fragments. This inhibition of MMPs protects the alpha$_1$-proteinase inhibitor (α_1-PI), the major endogenous inhibitor of serine proteinases, and another class of tissue-destructive enzymes. Protection of α-$_1$ PI indirectly decreases the tissue activity of serine proteinases and protects endogenous levels of the naturally occurring MMP inhibitors known as the tissue inhibitors of MMPs.[28] Therefore, the ability of tetracyclines to inhibit MMPs results in the prevention of pathogenic tissue destruction directly and indirectly.

Tetracyclines also have been shown to inhibit the inflammatory processes associated with endogenous NO production and expression of inducible nitric oxide synthase (iNOS)[30] and those associated with phospholipase A_2 (PLA_2).[31] Akamatsu and colleagues suggested that the clinical effectiveness of doxycycline in the treatment of acne inflammation is due to its antioxidant effects on neutrophils.[32] Tetracyclines reduce abnormally high levels of NO by downregulating iNOS.[30] In addition to their antioxidant effects, tetracyclines have been shown to block arachidonic acid metabolism by PLA_2 and downregulate the expression of proinflammatory mediators, including cytokines such as IL-1 and TNF-α, thus inhibiting extracellular matrix breakdown.[33]

MECHANISM OF ACTION OF TETRACYCLINES

Table 4. Summary of the biological, anti-inflammatory effects of tetracycline derivatives,* including anti-inflammatory dose doxycycline†[32-34]

BIOLOGIC EFFECTS	IMPACT OF EFFECT
Inhibition of activity of several MMP and MMP precursors	• Inhibition of MMP activity and breakdown of extracellular matrix in vitro and in vivo • Inhibition of collagenase-3 (MMP-13), collagenase-2 (MMP-8), collagenase-1 (MMP-1) • Inhibition of gelatinase A (MMP-2), gelatinase B (MMP-9), and macrophage metalloelastase (MMP-12)
Inhibition of NOS	• Reduced NO production leading to decreased inhibition of extracellular matrix synthesis (eg, collagen, proteoglycan) • Decreased expression of MMPs • Reduced vasodilation related to decreased NO production by endothelial cell
Reduced activity of ROS	• Decreased extracellular matrix (eg, collagen) degradation • Decreased inactivation of MMP inhibitors • Reduced activation of pro-MMPs
Decreased cytokine expression	• Downregulation of proinflammatory cytokine production (eg, TNF-α, IL-1β) • Reduced inflammatory recruitment
Inhibition of protein kinase C activity	• Decreased transcriptional activity of several MMPs
Inhibition of Ca^{++}/calmodulin pathway	• Decreased MMP-mediated breakdown of extracellular matrix • Reduced activity of endothelial constitutive NO synthetase • Decreased production of NO resulting in reduced vasodilation (vascular smooth muscle relaxation)
Reduced proinflammatory activity of PLA_2	• Inhibition of arachidonic acid production from glycerophospholipid precursors in cell membranes with decreases in metabolites that served as proinflammatory cell regulators such as PGE_2 • Reduced inflammatory activity

*Biologic effects based on multiple in vitro and in vivo experimental methods.
†Separation of antibiotic effects and biological activities confirmed with doxycycline based on pharmacokinetic profile and microbiological assays evaluating dose response; confirmed with anti-inflammatory dose doxycycline.

EMERGENCE OF ANTIBIOTIC-RESISTANT BACTERIA STRAINS

Increased rates of bacterial resistance to antibiotics have an impact on all disciplines of medicine, including dermatology. Based on data from 2003, dermatologists were responsible for 8.8 million oral antibiotic prescriptions, representing 19.6% of all prescriptions written by dermatologists.[35] Several antibiotic-resistant bacterial strains have emerged among pathogens that are common in dermatologic infections and inflammatory disorders, including macrolide-resistant *Streptococcus pyogenes* and *Propionibacterium acnes*, that are resistant to tetracyclines, macrolides, and lincosamides.[36,37] To tackle this problem, a recommendation on the prudent use of antimicrobial agents in human medicine was adopted by the European Council in 2001. In addition, European Antibiotic Awareness Day is held annually to raise awareness of this issue among both healthcare professionals and the public.

Mechanisms of Bacterial Resistance

Bacteria develop resistance to antibiotics through the acquisition of genes, either via inheritance, random mutation, or in an exchange with other bacterial cells (Figure 4a). Most resistance genes are carried on extrachromosomal plasmids, rather than on the bacterial chromosome itself, thereby facilitating transfer between pathogens. Some resistance genes encode for efflux pumps that eject antibiotics from cells. Other genes give rise to enzymes that degrade or chemically alter antibiotics, thus inactivating them. Cross-resistance to different antibiotics occurs in bacteria that use the same mechanism to resist the effects of more than 1 drug in an antibiotic class.[38]

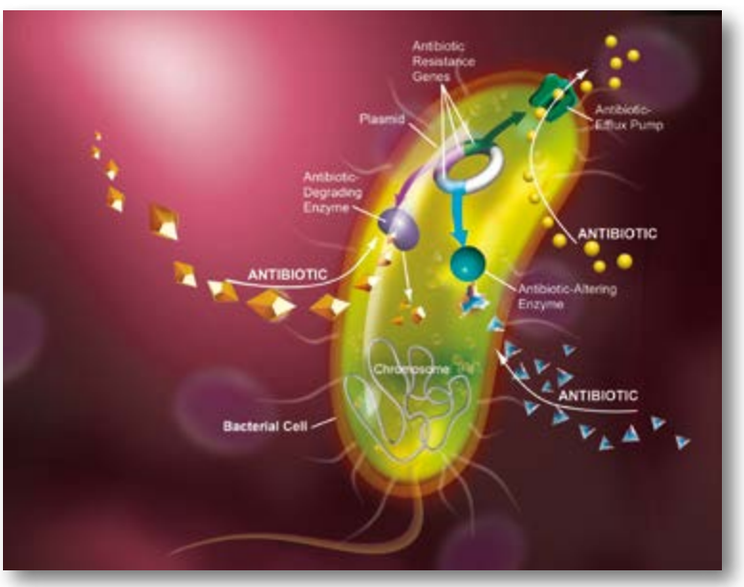


Figure 4a. Bacteria develop resistance to antibiotics through acquisition of resistance genes, either via inheritance, random mutation, or in an exchange with other bacterial cells[38]

EMERGENCE OF ANTIBIOTIC-RESISTANT BACTERIA STRAINS

Bacteria acquire resistance traits from other bacteria of the same or different species by exchanging or transferring DNA. Bacteria often obtain resistance genes from other bacteria in 1 of 3 ways (Figure 4b)[38]:

- Transfer from a donor cell of whole plasmids that contain the resistance gene
- Carriage of resistance genes via viruses that transfer genes between bacteria
- Scavenging of gene-bearing fragments of DNA from dead cells in the vicinity. Genes obtained from dead cells persist in the bacterium if they become incorporated into the recipient's chromosome or into an extrachromosomal plasmid

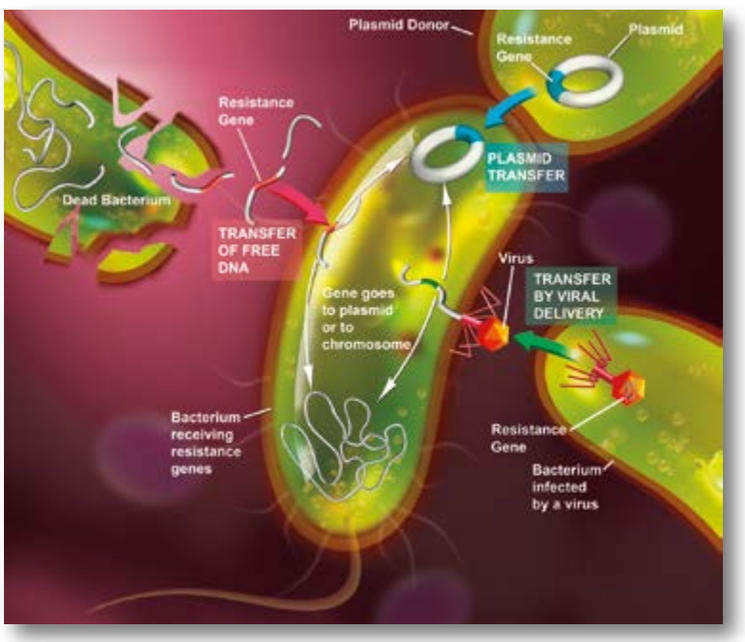


Figure 4b. Three routes of acquired bacterial resistance to antibiotic drugs[38]

Regardless of how bacteria acquire resistance genes, exposure to antibiotics can promote the survival and propagation of antibiotic-resistant strains through selective pressure. When an antibiotic attacks a group of bacteria, cells that are highly susceptible to the antibiotic will die. However, cells that have some resistance, through mutation or gene exchange, survive and face reduced competition from susceptible bacteria, and will continue to proliferate.[38]

Antibiotics also promote resistance by killing common and nonpathogenic bacteria that would normally limit the expansion of infecting pathogens. Eliminating these nonpathogenic bacteria facilitates the growth of resistant bacteria. Additionally, nonpathogenic bacteria can acquire antibiotic resistance. Consequently, the reservoir of resistant traits is increased. These nonpathogenic bacteria also have been known to become agents of disease.[38]

CHEMISTRY AND PRODUCT FORMULATION

The chemical structure of doxycycline monohydrate 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. The molecular formula is $C_{22}H_{24}N_2O_8 \cdot H_2O$ and the molecular weight is 462.46. The structural formula is shown in Figure 5.

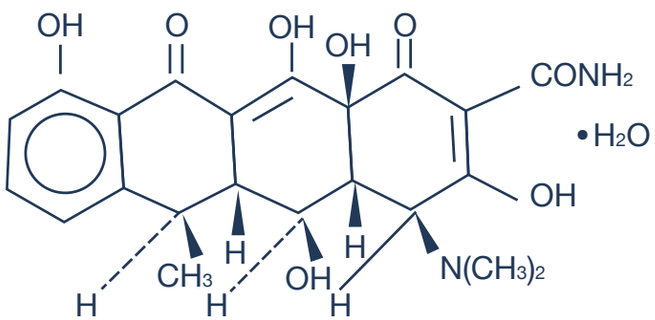


Figure 5. Structural formula of doxycycline

Oracea capsules 40 mg are hard gelatin capsules filled with 2 types of beads (immediate-release bead provides 30 mg of doxycycline and delayed-release bead provides 10 mg of doxycycline) that together provide a dose of 40 mg of anhydrous doxycycline over a 24-hour period (Figure 6).

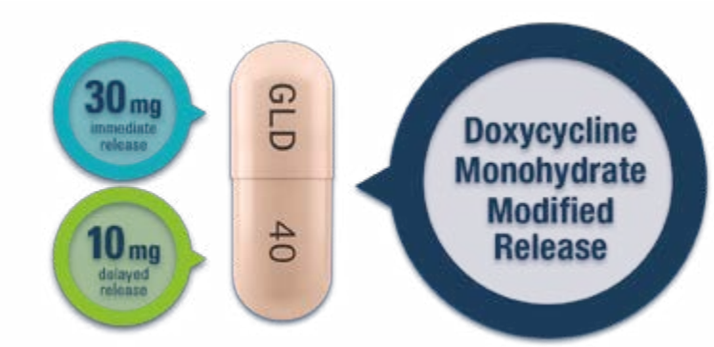


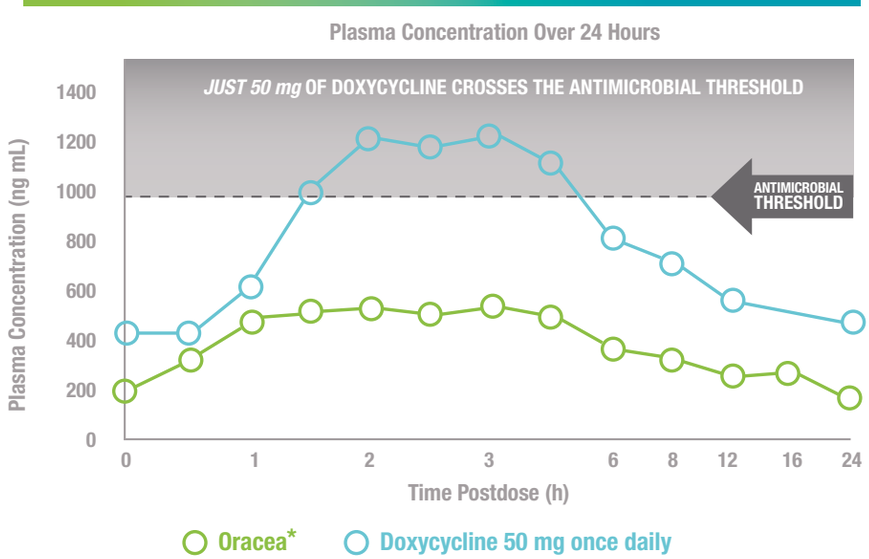
Figure 6. Formulation of Oracea

CLINICAL PHARMACOLOGY

MICROBIOLOGY

Doxycycline is a member of the tetracycline class of antibacterial drugs. The plasma concentration of doxycycline achieved with Oracea during administration is less than the level required to inhibit microorganisms commonly associated with bacterial diseases. Figure 7 shows that the steady-state plasma concentration of Oracea in healthy adults remains well below the antimicrobial threshold (ie, levels required for an antimicrobial effect). Further, a 9-month study showed no evidence of an increase in bacterial resistance to doxycycline or other antibiotics.[39] In vivo microbiological studies utilizing a similar drug exposure of anti-inflammatory dose doxycycline for up to 18 months' duration demonstrated no detectable long-term effects on bacterial flora of the oral cavity, skin, intestinal tract, and vagina. However, it cannot be excluded that long-term use of Oracea can lead to emergence of resistant intestinal bacteria such as Enterobacteriaceae and enterococci, as well as to enrichment of resistance genes.

! ORACEA SHOULD NOT BE USED FOR THE TREATMENT OF BACTERIAL INFECTIONS, FOR PROVIDING ANTIBACTERIAL PROPHYLAXIS, OR FOR REDUCING THE NUMBER OF OR ERADICATING MICROORGANISMS ASSOCIATED WITH ANY BACTERIAL DISEASE.



*Sixteen healthy subjects in the Oracea arm measured at 7 days; mean weight 75 kg (steady-state plasma concentration) (n=31).

Figure 7. Steady-state doxycycline plasma concentrations[40]

ONCE-DAILY Oracea® (doxycycline) 40 mg modified-release, hard capsule

CLINICAL PHARMACOKINETICS

Oracea is not bioequivalent to other doxycycline products. The pharmacokinetics of doxycycline following oral administration was investigated in 2 studies involving 61 healthy adults. The pharmacokinetic parameters for Oracea at steady state and following single oral doses in healthy subjects are presented in Table 5.

Absorption: Doxycycline is almost completely absorbed after oral administration. Following oral administration of Oracea, mean peak plasma concentrations were 510 ng/mL after a single dose and 600 ng/mL at steady state (day 7). Peak plasma levels were generally achieved 2 to 3 hours after administration. Coadministration with a high-fat, high-protein meal that included dairy products reduced the bioavailability (AUC) of doxycycline from Oracea by about 20% and reduced the peak plasma level by 43%.

Table 5. Pharmacokinetic parameters for Oracea at steady state and following single oral doses in healthy subjects (mean [±SD])

	N	C_{max}* (ng/mL)	T_{max}† (h)	$AUC_{0-\infty}$* (ng•h/mL)	$t_{½}$* (h)
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 [after a pretreatment of 7 days]	31	600 ± 194.2	2.00 (1.0-4.0)	7543 ± 2443.9	23.2 ± 6.2

*Mean.
†Median.
‡Day 7.

Distribution: Doxycycline is more than 90% bound to plasma proteins and has an apparent volume of distribution of 50 L.

Metabolism: Major metabolic pathways of doxycycline have not been identified but enzyme inducers decrease the half-life of doxycycline.

Elimination: Doxycycline is excreted in the urine and feces as unchanged active substance. Between 40% and 60% of an administered dose can be accounted for in the urine by 92 hours and approximately 30% in the feces. The terminal elimination half-life of doxycycline after administration of Oracea was approximately 21 hours after a single dose and approximately 23 hours at steady state.

CLINICAL PHARMACOKINETICS

PHARMACOKINETICS IN SPECIAL POPULATIONS

Geriatric: The pharmacokinetics of doxycycline have not been evaluated in geriatric subjects.

Pediatric: The pharmacokinetics of doxycycline have not been evaluated in pediatric subjects. Oracea is contraindicated in infants and children up to 12 years of age.

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.

Renal Insufficiency: The half-life of doxycycline is not significantly altered in patients with severely impaired renal function. Doxycycline is not eliminated to any great extent during hemodialysis. No dosage adjustment is necessary in patients with renal impairment.

Hepatic Insufficiency: There is no information about the pharmacokinetics of doxycycline in patients with hepatic impairment. Oracea should be administered with caution to patients with hepatic impairment or to those receiving potentially hepatotoxic medicinal products.

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. Patients known to have, or suspected to have, achlorhydria or who have had surgery that bypasses or excludes the duodenum must not be prescribed doxycycline.

CLINICAL EFFICACY AND SAFETY: PHASE III STUDIES

PHASE III STUDIES[34]

Two phase III, parallel-group, multicenter (537 patients, 14 sites for each study), randomized, double-blind, placebo-controlled trials (studies A and B) were conducted to evaluate the efficacy and safety of Oracea (doxycycline 40-mg modified-release capsules) once daily versus placebo for the treatment of adults with rosacea. The studies were collectively inclusive of 269 patients who received Oracea and 268 patients who received placebo. Both studies included patients with a marked number of total inflammatory lesions (10-40 papules and pustules and <2 nodules), moderate to severe erythema, and presence of telangiectasia.

Study Design[34]

Studies A and B were conducted in parallel between June 2004 and April 2005 in the United States and Puerto Rico. The study protocols for both studies were virtually identical with the exception of a post-therapy assessment in study B that evaluated the persistence of efficacy and the safety profile 4 weeks after the end of the treatment period.

Study Populations[34]

Patients aged at least 18 years were eligible for enrollment if, at study entry, they had moderate to severe rosacea, defined as the presence of 10 to 40 papules and pustules and ≤2 nodules and a score of ≥2 on the Investigator Global Assessment (IGA) scale, a subjective 5-point measure of overall disease severity. IGA scores range from 0 to 4: 0=no signs or symptoms present (clear); 1=1-2 small, noninflammatory papules (near clear); 2=3-10 papules/pustules (mild); 3=11-19 papules/pustules (moderate); and 4=20 or more papules/pustules and nodules (severe). Patients also were required to have telangiectasia and moderate to severe erythema as per the Clinician Erythema Assessment (CEA) scale. Potential scores on the CEA scale range from 0 to 4: 0=none (no redness present); 1=mild (slight pinkness); 2=moderate (definite redness); 3=significant (marked erythema); and 4=severe (fiery redness). Total CEA scores are derived by summing scores over 5 facial areas (forehead, chin, nose, and right and left cheek) and range from 0 to 20. In the 2 studies reported here, moderate to severe erythema was defined as at least 1 area-specific CEA score ≥2 and a total CEA score of ≥5. Female patients of childbearing potential were eligible for enrollment only if they were using birth control, were not nursing, and had a negative pregnancy test at entry. Patients were not eligible for enrollment in the studies if they met any of the following criteria: initiation of or change in hormonal method of contraception within 4 months of baseline or during the study; use of topical acne treatments, or topical or systemic antibiotics within 4 weeks of baseline; use of an investigational drug within 90 days of baseline; known hypersensitivity to tetracyclines; use of clinically significant concomitant drug therapy (eg, chronic use of nonsteroidal anti-inflammatory drugs); use of systemic anti-inflammatories or corticosteroids in the 4 weeks before baseline or during the study use of vasodilators or alpha-adrenergic receptor-blocking agents 6 weeks prior to baseline or during the study; or ocular rosacea and/or blepharitis/meibomianitis requiring treatment by an ophthalmologist.

CLINICAL EFFICACY AND SAFETY: PHASE III STUDIES

Study Medication and Treatment Regimens[34]

Patients were randomized to receive Oracea or placebo once daily in the morning for 16 weeks. In both studies, study medication was distributed at baseline and again at week 12. Patients in both studies returned for evaluations at weeks 3, 6, 12, and 16. At the end of the treatment period in study B, patients in both treatment arms were instructed not to take any systemic or topical medications for the treatment of rosacea or acne or any of the medications prohibited at entry into the study, and they were re-evaluated at week 20.

At each visit, patients were evaluated for number and types of lesions, IGA scores, CEA scores, concomitant medication usage, adverse events (AEs), vital signs, height, and weight. At the week 16 visit, female patients of childbearing potential were again administered a urine pregnancy test.

Efficacy and Safety Evaluations[34]

In both studies, the primary efficacy end point was the mean change from baseline in total inflammatory lesion count (papules, pustules, and nodules) at week 16. Secondary end points included the mean change from baseline in CEA and IGA scores at week 16. Additionally, the static dichotomized IGA score (yes/no), defined as patients who achieved a score of 0 (clear) or 1 (near clear), at week 16 was analyzed.

The efficacy variables for the 4-week post-therapy assessment conducted in study B included the mean change in total inflammatory lesion count (papules, pustules, and nodules) and the mean changes in CEA and IGA scores from week 16 to week 20.

Safety was evaluated at each study visit by recording AEs, concomitant medication use, and vital signs at each study visit and by routine laboratory tests conducted at week 16. AEs were evaluated as mild, moderate, or severe, and any relationship to study medication were determined by the study investigator.

Results[34]

A total of 537 patients were enrolled in the 2 studies with 251 patients in study A (127 from the active-treatment arm and 124 from the placebo arm) and 286 patients from study B (142 from the active-treatment arm and 144 from the placebo arm). A total of 160 patients were enrolled in the 4-week post-therapy assessment conducted in study B (84 from the active-treatment arm and 76 from the placebo arm).

CLINICAL EFFICACY AND SAFETY: PHASE III STUDIES

Results (cont'd)[34]

Patient demographics, disposition and baseline data for efficacy variables were similar between treatment groups in the 2 studies and also were similar between the 2 studies (Table 6). More than 40% (239/537) of the patients in each study were 36 to 50 years of age (47% [118/251] in study A and 42% [121/286] in study B). Seventeen percent [42/251] and 20% (57/286) of the patients in studies A and B, respectively, were 18 to 35 years of age, and 32% (79/251) and 33% (95/286) of the patients were 51 to 70 years of age. Seventy percent [375/537] of the patients in the 2 studies were women and 91% (491/537) were Caucasian. The mean total inflammatory lesion count was 19.9 and 20.8 for the patients participating in studies A and B, respectively. The mean CEA scores were 9.6 and 9.3 for the patients participating in studies A and B, respectively. Approximately half of the patients in each study had an IGA score of 3 (moderate rosacea) and about 90% of the patients had an IGA score of 3 to 4 (moderate to severe rosacea). There were no statistically significant differences between treatment arms in either study in terms of mean lesion counts (papules, pustules, nodules, total lesions) or mean CEA and IGA scores.

The mean exposure to Oracea was 103.1 days in study A and 101.2 days in study B for a combined exposure to active treatment of 26,377 person–days. Compliance with the per-protocol treatment regimen was generally very good; 474 of the 537 (88%) patients in the 2 studies took at least 80% of the assigned study medication.

The majority of patients (81% [437/537]) completed the 2 studies. The rates of discontinuation due to AEs were higher among patients in the active-treatment groups in both studies (7.9% [10/127] in study A and 6.3% [9/142] in study B) than among patients in the placebo arms of the studies (3.2% [4/124] in study A and 4.9% [7/144] in study B). However, discontinuations due to insufficient efficacy were low in both studies among patients in either treatment arm.

CLINICAL EFFICACY AND SAFETY: PHASE III STUDIES

Table 6. Patient demographics and disposition, baseline values for efficacy assessments, and study medication usage[34]

PARAMETER	STUDY A		STUDY B	
	ORACEA (n=127)	PLACEBO (n=124)	ORACEA (n=142)	PLACEBO (n=144)
AGE, YEARS (SD)	46.8 (13.2)	47.6 (11.5)	46.3 (12.7)	47.6
FEMALE, n (%)	91 (71.7)	95 (76.6)	94 (66.2)	95 (66.0)
LESION COUNT, MEAN (SD)				
PAPULES	15.2 (7.9)	16.4 (9.2)	17.4 (10.8)	17.8 (10.9)
PUSTULES	4.1 (5.2)	3.7 (4.7)	3.0 (4.5)	3.3 (6.0)
NODULES	0.2 (0.6)	0.2 (0.5)	0.1 (0.5)	0.1 (0.5)
TOTAL	19.5 (8.8)	20.3 (10.4)	20.5 (11.7)	21.2 (12.5)
CEA, MEAN (SD)	9.7 (3.0)	9.5 (2.7)	9.5 (2.9)	9.1 (2.5)
IGA, n (%)				
0=CLEAR	0	0	0	0
1=NEAR CLEAR	0	0	0	0
2=MILD	8 (6.3)	10 (8.1)	17 (12.0)	7 (4.9)
3=MODERATE	67 (52.8)	65 (52.4)	77 (54.2)	80 (55.6)
4=SEVERE	52 (40.9)	49 (39.5)	48 (33.8)	57 (39.6)
EXPOSURE TO STUDY MEDICATION (DAYS), MEAN (SD)	103.1 (30.1)	106.9 (24.2)	101.2 (29.8)	106.9 (28.7)
COMPLETERS, n (%)*	101 (79.5)	103 (83.1)	115 (81.0)	118 (81.9)
DISCONTINUATIONS, n (%)				
AEs	10 (7.9)	4 (3.2)	9 (6.3)	7 (4.9)
INSUFFICIENT EFFICACY	2 (1.6)	2 (1.6)	1 (0.7)	4 (2.8)
LOST TO FOLLOW-UP	4 (3.1)	2 (1.6)	5 (3.5)	5 (3.5)
PROTOCOL VIOLATION	2 (1.6)	2 (1.6)	4 (2.8)	5 (3.5)
OTHER†	8 (6.3)	11 (8.8)	8 (5.6)	5 (3.5)
TOTAL	26 (20.5)	21 (16.8)	27 (18.9)	26 (18.2)

*Percent of patients taking ≥80% of the assigned study medication.
†Other reasons for withdrawal include illness not related to study drug, lost to follow-up, patient withdrawal for personal reasons, and administrative reasons.

CLINICAL EFFICACY AND SAFETY: PHASE III STUDIES

EFFICACY ASSESSMENTS

Total Inflammatory Lesion Counts[34]

In both studies, patients in the intent-to-treat (ITT) population who received active treatment demonstrated significantly greater reductions from baseline in total inflammatory lesions at week 16 compared with patients who received placebo. The mean number of total inflammatory lesions in the active-treatment group decreased by 61% in study A and 46% in study B, compared with 29% and 20%, respectively, in the placebo arms (both $P<.001$; Figures 8 and 9). There was a significantly greater decrease in lesion count in the active-treatment group when compared with the placebo group starting at the initial 3-week follow-up visit ($P=.005$) that continued at week 6 ($P<.001$), week 12 ($P<.001$), and week 16 ($P<.001$). To illustrate the clinical changes in inflammatory lesions throughout the 16-week study period, Figures 10 and 11 show the inflammatory lesions of 3 patients at baseline and then again at week 16.

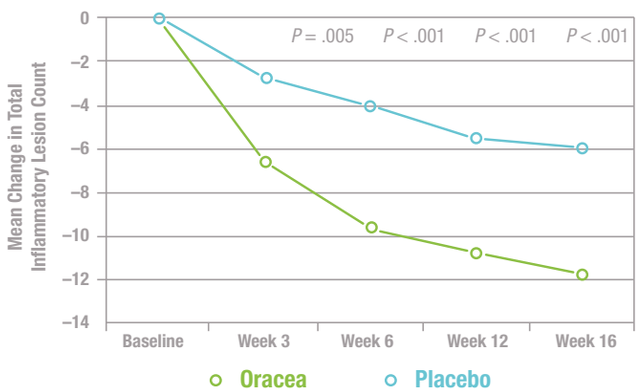


Figure 8. Mean percent change from baseline in total inflammatory lesion counts (papules, pustules, and nodules) through week 16 in study A[34]

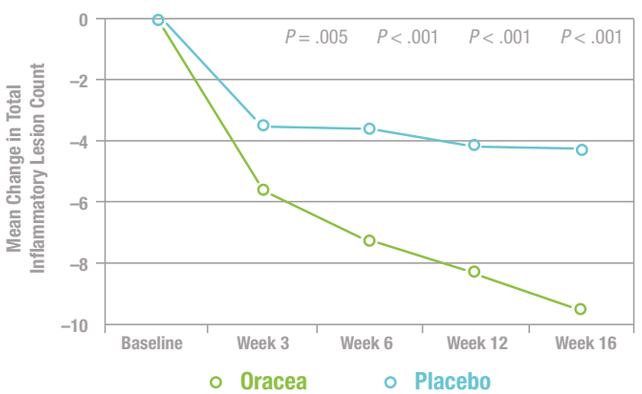


Figure 9. Mean percent change from baseline in total inflammatory lesion counts (papules, pustules, and nodules) through week 16 in study B[34]

CLINICAL EFFICACY AND SAFETY: PHASE III STUDIES

Total Erythema Scores[34]

In study A, the reduction from baseline in the mean total erythema score (defined as the CEA score) was significantly (*P*=.017) greater at week 16 in the active-treatment arm compared with the placebo arm. At week 16, the mean change from baseline in the total erythema score was –2.7 and –1.8 for the active-treatment and placebo groups, respectively (Figure 12). The decrease in total erythema score that was observed in the active-treatment group became statistically significant by week 6 when compared with the placebo group (*P*=.013). There was a continual progressive reduction in the total erythema score through week 16 when the active-treatment arm was compared to the placebo arm with the latter exhibiting a plateau effect from week 12 through week 16. In study B, the change from baseline in total erythema scores indicated that facial redness decreased in patients in the active-treatment group (Figure 13); however, the between-group difference did not reach statistical significance.

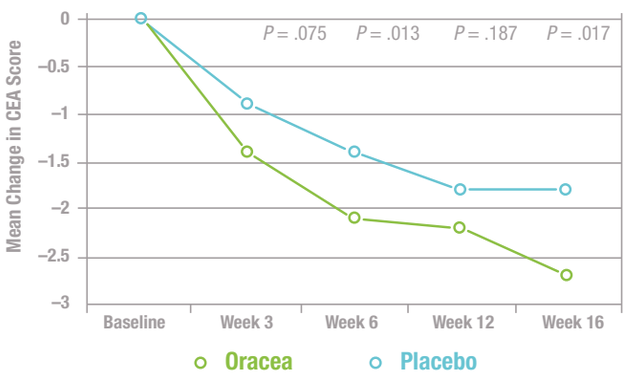


Figure 12. Mean change from baseline in the CEA score through week 16 in study A[34]

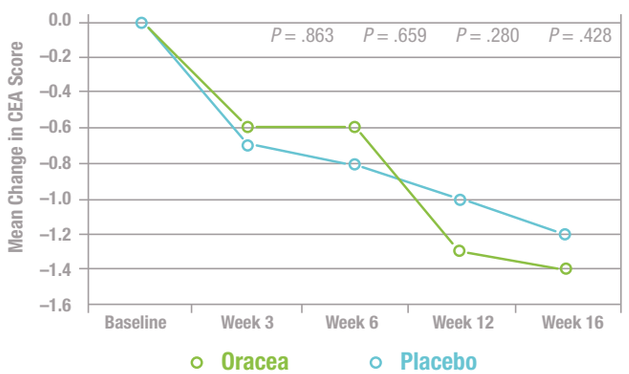


Figure 13. Mean change from baseline in the CEA score through week 16 in study B[34]

CLINICAL EFFICACY AND SAFETY: PHASE III STUDIES

Investigator Global Assessment[34]

The active-treatment group demonstrated significantly greater improvement in IGA score at the study end point compared with the placebo group in both studies. In study A, 45.7% (58/127) of the patients in the active treatment group achieved at least a 2-point improvement in IGA score at week 16 compared with just 25.8% (32/124) of the patients in the placebo group ($P<.001$). In the same study, a significantly larger percentage of actively treated patients achieved an IGA score of 0 (clear) or 1 (near clear) when compared with placebo-treated patients (30.7% [39/127] vs 19.4% [24/124]; $P=.036$). In study B, 22.5% (32/142) of the patients in the active-treatment arm achieved at least a 2-point improvement in IGA score at week 16 compared with 16.0% (23/144) in the placebo arm ($P=.004$). A significantly larger proportion of patients in the active-treatment arm in study B achieved an IGA score of 0 (clear) or 1 (near clear) when compared with patients in the placebo arm (14.8% [21/142] vs. 6.3% [9/144]; $P=.012$).

Four-Week Post-therapy Assessment[34]

Patients receiving active treatment through week 16 maintained a greater overall treatment benefit through week 20 than those receiving placebo. Four weeks after discontinuation of therapy (week 20), mean total lesion counts were 10.3 in the active-treatment group and 15.3 in the placebo group (mean treatment difference of 5 lesions). There were no significant differences in CEA and IGA scores between weeks 16 and 20 in either treatment group.

SAFETY ANALYSIS[34]

Both Oracea and placebo were well-tolerated throughout both studies A and B. No major safety issues or concerns were identified during the course of either study, including assessments of reported AEs, vital signs, weight, and laboratory values. Table 7 lists pooled data for AEs reported during the 16-week treatment period in 2 or more patients in either treatment group (ITT analysis). No cases of photosensitivity were reported in either treatment group and no cases were suspected by investigators.* Among female patients in both studies, vaginal mycotic infections, including candidiasis, were reported in 4 patients in the placebo group and in none of the patients in the active-treatment group.

*All patients receiving doxycycline, including Oracea, should be advised to avoid excessive sunlight or artificial UV light while receiving doxycycline and to discontinue therapy if phototoxicity (eg, skin eruption, etc) occurs. Use of sunscreen or sunblock should be considered. Treatment should cease at the first sign of photosensitivity.

CLINICAL EFFICACY AND SAFETY: PHASE III STUDIES

Adverse Events[34]

In study A, 44.1% (56/127) and 38.7% (48/124) of patients in the active-treatment and placebo groups, respectively, reported AEs over the 16-week study period. Most of these AEs were rated as mild or moderate in severity in both the active-treatment arm (82.1% [46/56]) and placebo arm (87.5% [42/48]). AEs considered by the investigator to be possibly or probably related to study drug were experienced by 19.7% (25/127) of patients in the active-treatment group and 13.7% (17/124) in the placebo group.

In study B, 65.5% (93/142) of the patients in the active-treatment arm and 51.4% (74/144) in the placebo arm noted AEs over the 16-week study period. The majority of these AEs were rated as mild or moderate in severity in both the active-treatment group (93.5% [87/93]) and placebo group (95.9% [71/74]). AEs judged by the investigator to be possibly or probably related to study drug were experienced by 21.8% (31/142) of patients in the active-treatment group and 14.6% (21/144) in the placebo group. In the 4-week follow-up period from week 16 through week 20, AEs were experienced by 4.8% (4/84) of the patients initially randomized to the active-treatment arm and 9.2% (7/76) of patients initially randomized to the placebo arm.

Vital Signs/Weight[34]

Vital signs and weight assessments demonstrated only minimal mean changes from baseline, and there were no apparent differences between groups in either study. No changes in blood pressure levels were considered to be AEs, except for 1 patient in the active-treatment group in study B. This patient experienced a marked increase in blood pressure that was reported as an AE but was not considered to be related to the study drug.

Laboratory Evaluations[34]

In both trials, all randomized patients underwent hematology and serum chemistry panels at baseline and week 16. Overall, in both studies, there were no notable changes or emergent trends in abnormal laboratory values in either treatment group from baseline to end point in any hematologic or serum chemistry indices.

CLINICAL EFFICACY AND SAFETY: PHASE III STUDIES

Table 7. Pooled data of treatment-emergent AEs reported from studies A and B[34]

ADVERSE EVENT,* n (%)	ORACEA (n=269)	PLACEBO (n=268)
NASOPHARYNGITIS	13 (4.8)	9 (3.3)
DIARRHEA	12 (4.4)	7 (2.6)
HEADACHE	12 (4.4)	16 (5.9)
UPPER RESPIRATORY TRACT INFECTION	9 (3.3)	20 (7.4)
HYPERTENSION	8 (2.9)	2 (0.7)
SINUSITIS	7 (2.6)	2 (0.7)
ASPARTATE AMINOTRANSFERASE	6 (2.2)	2 (0.7)
ABDOMINAL PAIN, UPPER	5 (1.8)	1 (0.3)
FUNGAL INFECTION†	5 (1.8)†	1 (0.3)
INFLUENZA	5 (1.8)	3 (1.1)
NAUSEA	5 (1.8)	8 (2.9)

*Reported AEs not necessarily determined to be probably or possibly related to study drug.
†There were no cases of vaginal candidiasis or photosensitivity in the active-treatment arm.

CLINICAL EFFICACY AND SAFETY: PHASE III STUDIES

CONCLUSIONS[34]

The results from the 2 pivotal, 16-week, phase III clinical trials demonstrate the efficacy and safety of Oracea administered once daily for the treatment of moderate to severe PPR. Oracea produced a significant reduction in inflammatory lesions within the first 3 weeks of therapy, followed by a progressive, continued reduction over the treatment period. Furthermore, marked improvement was noted over a wide range of clinical severity. Reduction in erythema also was observed in both studies. Oracea had a good safety profile in both studies, with the frequency of AEs similar to those of patients who received placebo.

Large scale, randomized, vehicle-controlled, phase III trials have been reported with topical metronidazole 1% gel and topical azelaic acid 15% gel. In the present studies (A and B), the mean total inflammatory lesion count decreased by 61% and 46%, respectively, in patients receiving active treatment for 16 weeks compared with 29% and 20% in patients receiving placebo. In the 10-week metronidazole 1% gel trial, the mean reductions were 51% with once-daily active treatment and 33% with vehicle ($P<.0001$). In two 12-week trials of azelaic acid 15% gel, the mean reductions were 58% and 51% with twice-daily active treatment and 40% and 39% with vehicle ($P=.0001$ and $P=.02$). It is important to note that it is not entirely valid to directly compare results between clinical trials because of differences in study design, protocol requirements, and patient populations.

In summary, Oracea is an effective, well-tolerated therapy for the treatment of rosacea, as demonstrated in 2 pivotal phase III studies where 269 patients received the active treatment. Oracea is an important and innovative approach to rosacea therapy due to its anti-inflammatory effectiveness at plasma levels below the antimicrobial threshold, and thus may decrease emergence of resistant-bacterial strains. The availability of a once-daily oral formulation for the treatment of rosacea offers advantages to both physicians and patients, including ease of use and optimal compliance.

CLINICAL EFFICACY AND SAFETY: ORACEA vs DOXYCYCLINE 100 mg

ORACEA VERSUS DOXYCYCLINE 100 MG IN THE TREATMENT OF ROSACEA[41]

The study evaluated the safety and efficacy of Oracea (doxycyline 40-mg modified-release capsules) administered once daily versus doxycycline 100 mg once daily in the treatment of moderate to severe rosacea for 16 weeks. In addition, both groups also applied topical metronidazole 1% gel once daily. This was a multicenter, outpatient, prospectively randomized, double-blind, active-control study of 91 patients. The study was inclusive of 47 patients who received doxycycline 100 mg and 44 patients who received Oracea. The study included patients with a marked number of total inflammatory lesions (8-40 papules and pustules, ≤2 nodules), moderate to severe erythema, and presence of telangiectasia.

STUDY DESIGN[41]

Subjects were randomized to receive daily administration of drugs in the following groups: 100 mg doxycycline and topical metronidazole 1% gel (Group 1), and Oracea (40 mg) and topical metronidazole 1% gel (Group 2) for 16 weeks.

STUDY POPULATION[41]

Patients aged at least 18 years were eligible for enrollment if, at study entry, they had moderate to severe inflammatory (papulopustular) rosacea, 8 to 40 papules and pustules, ≤2 nodules, a score of 2 to 5 on the IGA, a subjective 6-point measure of overall disease severity. IGA scores range from 0 to 5: 0=skin is completely clear of inflammatory lesions (clear); 1=1-4 papules and pustules, no nodules (near clear); 2=5-10 papules and pustules, no nodules (mild); 3=11-17 papules and pustules, 0 or 1 nodule may present (moderate); 4=18-25 papules and pustules, 1 or 2 nodules must be present, perilesional erythema is present (severe); and 5 to more than 25 papules and pustules, nodules must be present, perilesional erythema plus edema are a hallmark of this patient (very severe). Patients were also required a total erythema score of 5 to 20 with at least 1 pentad (1 of 5 facial areas) specific score of ≥2 on the CEA scale and the presence of telangiectasia. Potential scores on the CEA scale range from 0 to 4: 0=none (no redness present); 1=mild (slight pinkness); 2=moderate (definite redness); 3=significant (marked erythema); and 4=severe (fiery redness). Total CEA scores are derived by summing scores over 5 facial areas (forehead, chin, nose, and right and left cheek) and range from 0 to 20. Female patients of childbearing potential were eligible for enrollment only if they were using birth control, were not nursing, and had a negative pregnancy test at entry.

Exclusion criteria included changes in hormonal contraception methods within 4 months of baseline, the use of any rosacea treatments within 2 weeks of baseline, subjects with a known sensitivity to study drugs, and use of clinically significant concomitant drug therapy including corticosteroids and vasodilatory agents.

EFFICACY AND SAFETY EVALUATION[41]

The primary efficacy end point was the change in total lesion count (papules, pustules, and nodules) from baseline to week 16. The secondary efficacy end points were changes in IGA from baseline, changes in CEA from baseline, and changes in total lesion counts at each time point including weeks 4, 8, 12, and 16. AEs were monitored throughout the study.

CLINICAL EFFICACY AND SAFETY: ORACEA vs DOXYCYCLINE 100 mg

RESULTS[41]

A total of 91 patients were enrolled in this study (47 for the doxycyline 100-mg arm and 44 for the Oracea arm). Subject demographics are summarized in Table 8. The majority of patients completed the treatment (73.6% [67/91]). The rates of discontinuation due to AEs or serious AEs were slightly higher for the Oracea group (11.4% [5/44]) than the doxycycline 100-mg group (8.5% [4/47]). Number of reported AEs were lower for the Oracea group (13.6% [6/44]) than for doxycycline 100 mg (55.3% [26/47]) (Table 9).

Table 8. Patient demographic profile[41]

	ORACEA (n=44)	DOXYCYCLINE 100 mg (n=47)	TOTAL (n=91)
SEX			
MALE	15	12	27
FEMALE	29	35	64
RACE			
CAUCASIAN	43	44	87
MEAN AGE (YEARS)	44.3	45.2	—
COMPLETED	30	37	67
DISCONTINUED FROM STUDY	14	10	24
AE OR SERIOUS AE	5	4	9
PROTOCOL VIOLATION	3	1	4
LOST TO FOLLOW-UP	4	0	4
PATIENT WITHDREW CONSENT	0	4	4
OTHER	2	1	3

CLINICAL EFFICACY AND SAFETY: ORACEA vs DOXYCYCLINE 100 mg

EFFICACY ASSESSMENT

Primary Efficacy Variables[41]

In both arms, the mean change from baseline to week 16 in inflammatory lesion count was similar in both study groups and at all study visits (Figure 14). Small differences that were observed are neither statistically nor clinically significant ($P \geq .8$) for the primary efficacy analysis. End point represents the primary efficacy end point using a last observation carried forward (LOCF) approach to account for missing data of subjects who discontinued early.

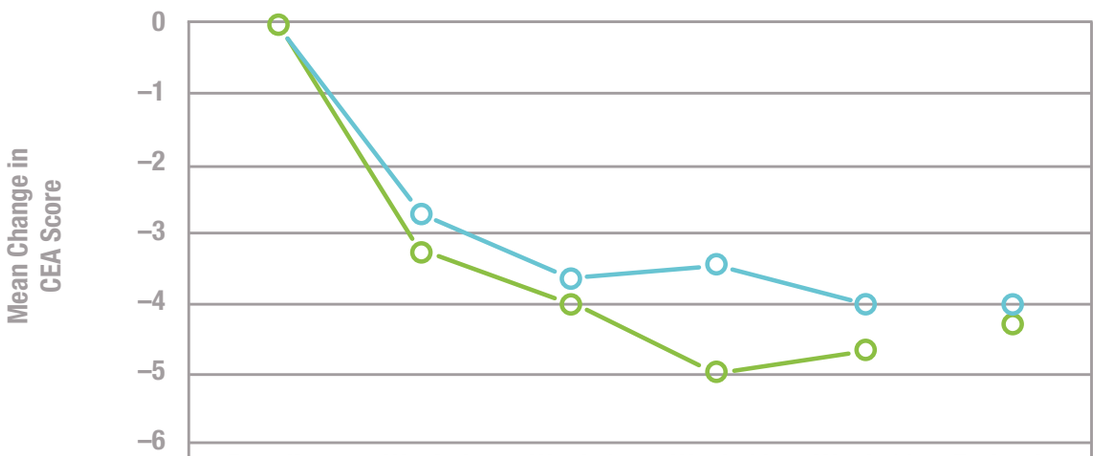
	Baseline	Week 4	Week 8	Week 12	Week 16	End point
Oracea	0.0	–9.3	–12.4	–12.5	–14.3	–12.5
Doxycycline 100 mg	0.0	–10.9	–12.3	–12.6	–13	–12.2
P value		.61	.84	.84	.51	.83

Figure 14. Total inflammatory lesion count: mean change from baseline[41]

CLINICAL EFFICACY AND SAFETY: ORACEA vs DOXYCYCLINE 100 mg

Secondary Efficacy Variables[41]

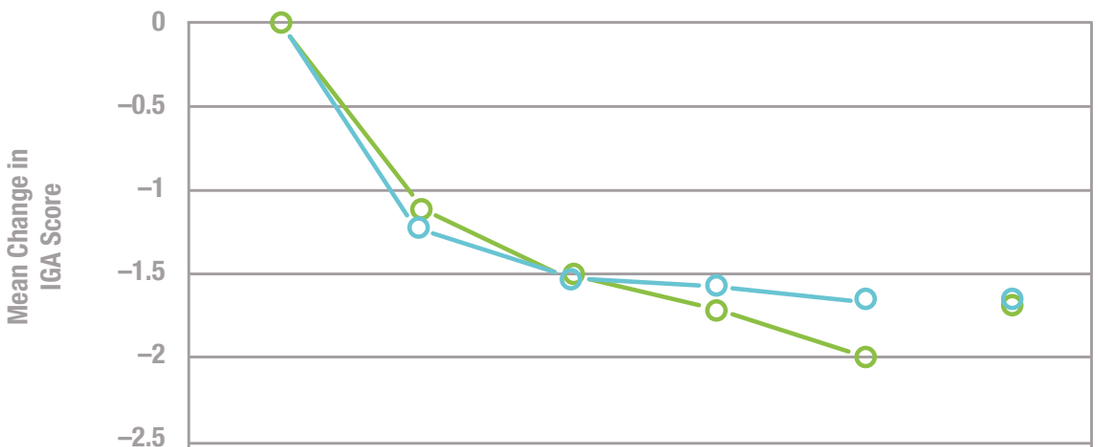
The mean change from baseline in erythema score (CEA score) was slightly greater at all time points in the Oracea group (Figure 15). The difference was statistically significant at week 12 where the mean decrease in erythema score was –4.97 in the Oracea group and –3.47 in the 100-mg doxycycline group ($P<.04$), but not at week 16 (Figure 15). There were no significant intergroup differences in IGA scores (Figure 16).



	Baseline	Week 4	Week 8	Week 12	Week 16	End point
Oracea	0.0	–3.3	–3.9	–5.0	–4.6	–4.2
Doxycycline 100 mg	0.0	–2.8	–3.7	–3.5	–4.0	–4.0
P value	.0	.27	.56	.04	.17	.50

Figure 15. Mean change from baseline in the CEA score (not statistically significant)[41]

CLINICAL EFFICACY AND SAFETY: ORACEA vs DOXYCYCLINE 100 mg



	Baseline	Week 4	Week 8	Week 12	Week 16	End point
Oracea	0.0	–1.1	–1.5	–1.7	–2.0	–1.6
Doxycycline 100 mg	0.0	–1.2	–1.5	–1.6	–1.7	–1.6
P value	.0	.91	.79	.55	.24	.86

Figure 16. Mean change from baseline in IGA score (not statistically significant)[41]

CLINICAL EFFICACY AND SAFETY: ORACEA vs DOXYCYCLINE 100 mg

Table 9. Treatment-emergent AE data[41]

AE, n	ORACEA	DOXYCYCLINE 100 mg
NAUSEA	—	8
HEADACHE	2	3
INFLUENZA	—	3
NASOPHARYNGITIS	3	2
URTICARIA	1	2
DIARRHEA	—	2
ESOPHAGEAL PAIN	—	2
VOMITING	—	2
ABDOMINAL PAIN	—	1
ABDOMINAL PAIN, UPPER	—	1

Conclusions[41]

Both Oracea and doxycycline 100 mg are equally effective once-daily treatments for moderate to severe rosacea for up to 16 weeks. Doxycycline at a dosage of 100 mg does not have a more rapid onset of action than Oracea, and is associated with a higher incidence of AEs than Oracea.

CLINICAL EFFICACY AND SAFETY: ORACEA + METRONIDAZOLE GEL 1%

ORACEA + METRONIDAZOLE TOPICAL GEL 1% FOR THE TREATMENT OF ROSACEA[42]

This study investigated the efficacy and safety of Oracea + metronidazole for the treatment of rosacea. The study also evaluated the efficacy and safety of Oracea for maintenance therapy after the discontinuation of metronidazole. This was a randomized, multicenter, outpatient, double-blind, placebo-controlled trial of 72 subjects lasting 16 weeks.

Study Design[42]

Subjects were randomized into 2 groups. Group 1 received Oracea + metronidazole and group 2 received placebo + metronidazole. Metronidazole was discontinued at week 12 in both groups, while treatment with Oracea or placebo was continued through week 16. Subjects were evaluated at baseline and weeks 4, 8, 12, and 16.

Study Population[42]

The study included a total of 72 healthy subjects (56 female, 16 male) aged ≥18 years with rosacea. Their mean age was 47.8 years. Subjects were determined to have rosacea by the following criteria: 8 to 40 total lesions (papules and pustules), ≤2 nodules, IGA score of ≥2 (mild to very severe), presence of moderate to severe erythema, and the presence of telangiectasia. Exclusion criteria included use of topical rosacea/acne treatments, use of systemic corticosteroids, and use of vasodilators.

The mean IGA score was 3 in group 1 and 2.88 in group 2. Baseline total inflammatory lesion counts were 21.3 in group 1 and 18.7 in group 2. Baseline erythema scores were 8.6 in group 1 and 9.2 in group 2.

Efficacy and Safety Evaluation[42]

The primary end point was the mean change in total inflammatory lesion count (papules, pustules, and nodules) from baseline to end points at weeks 4, 8, 12, and 16.

Secondary end points included:

- Change in IGA scores from baseline to end points at weeks 4, 8, 12, and 16
- Mean percent change in total inflammatory lesion count from baseline
- Change in CEA score from baseline to weeks 4, 8, 12, and 16

Results[42]

Sixty-four subjects completed the study out of the 72 who were enrolled. Of these, 30 were in group 1 and 34 were in group 2. Discontinuations were due to AEs (4 subjects), consent withdrawal (1 subject), lost to follow-up (2 subjects), and protocol violation (1 subject).

CLINICAL EFFICACY AND SAFETY: ORACEA + METRONIDAZOLE GEL 1%

Primary Efficacy End Point[42]

The mean change in inflammatory lesion counts was significantly better in the group receiving Oracea + metronidazole by as early as week 4 (–9.69 in group 1 vs –2.86 in group 2; *P*=.008). These significant results continued through to week 12 (–13.86 in group 1 vs –8.47 in group 2; *P*=.002). In addition, results were maintained up to week 16 in subjects receiving Oracea as maintenance therapy. In the group receiving only the placebo, improvement declined from weeks 12 to 16 (Figure 18).

Secondary Efficacy End Points[42]

The mean percent change from baseline in inflammatory lesions was significantly greater at all time points, except week 8, in subjects receiving Oracea + metronidazole. Significant results were achieved as early as week 4, with a 47.1% reduction in group 1 vs 17.9% in group 2 (*P*=.004). At week 12, the mean percent reduction in inflammatory lesions was 66.4% in group 1 vs 48.2% in group 2 (*P*=.008). After metronidazole was discontinued between weeks 12 and 16, the mean percent reduction in inflammatory lesions was slightly less in both groups, but still significantly greater in the subjects receiving Oracea (*P*=.005) (Figure 19).

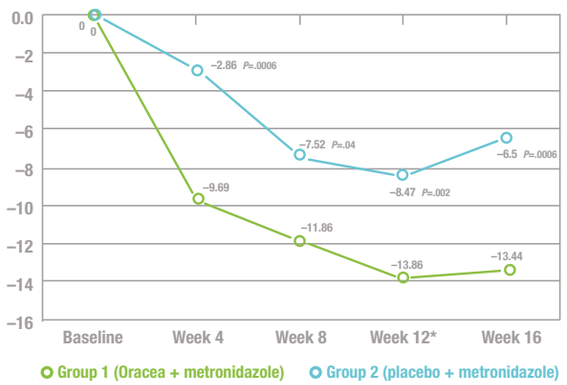


Figure 18. Mean change in inflammatory lesion counts from baseline[42]

*Metronidazole discontinued at week 12.

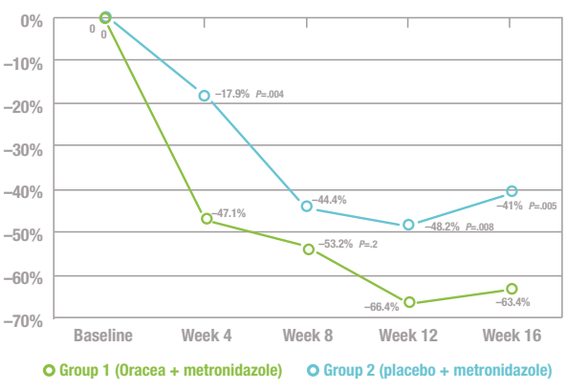


Figure 19. Mean percent change from baseline in inflammatory lesion counts[42]

CLINICAL EFFICACY AND SAFETY: ORACEA + METRONIDAZOLE GEL 1%

There was a greater improvement in IGA scores at all time points in group 1, but they only achieved statistical significance at weeks 12 and 16 (*P*=.01). A mean IGA score of –1.3 was maintained between weeks 12 and 16 in subjects receiving Oracea after metronidazole was discontinued. In subjects receiving placebo, mean IGA scores began to increase (–0.7) (Figure 20).

The mean changes in erythema scores from baseline were reduced in both groups, although the differences did not achieve statistical significance.

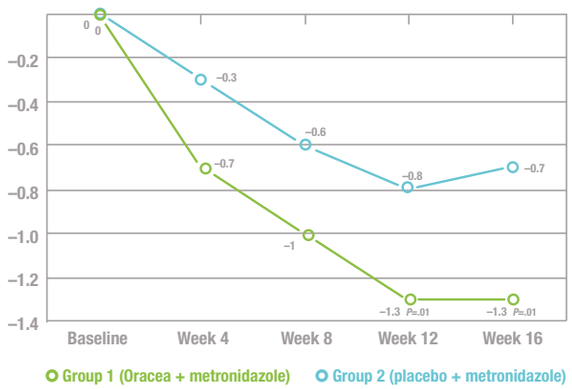


Figure 20. Mean change from baseline in IGA score[42]

Safety Assessments[42]

Oracea was well tolerated when used in combination with metronidazole. The safety profiles of both treatments were similar and AEs were generally mild in severity. Treatment-emergent AEs are shown in Table 10.

Table 10. Treatment-emergent AEs[42]

AE	Group 1 (Oracea + metronidazole), n	Group 2 (placebo + metronidazole), n
NASOPHARYNGITIS	5	5
INFLUENZA	5	0
SINUSITIS	5	1
UPPER RESPIRATORY TRACT INFECTION	4	4
MUSCLE STRAIN	4	0
NAUSEA	3	3
DIARRHEA	1	3
SUNBURN	3	0
DERMATITIS	3	0
STOMACH DISCOMFORT	1	2
EAR INFECTION	2	1
NASAL CONGESTION	2	1
COUGH	0	2
RASH	1	1

CLINICAL EFFICACY AND SAFETY: ORACEA + METRONIDAZOLE GEL 1%

Conclusion[42]

The results of this trial demonstrate that concomitant use of Oracea and metronidazole produces a faster and greater reduction in the inflammatory lesions of rosacea than metronidazole alone. Significant results were seen as early as week 4 and continued throughout the first 12 weeks of the trial. From weeks 12 to 16, monotherapy with Oracea maintained the results of combination therapy. This is an important finding in that use of Oracea as maintance therapy is an option that avoids long-term use of topical or systemic antibiotics. The combination of Oracea + metronidazole should be considered as a safe and effective option for the first-line treatment of rosacea.

CLINICAL EFFICACY AND SAFETY: ORCA TRIAL

ORCA (**O**RACEA FOR **R**OSACEA: A **C**OMMUNITY-BASED **A**SSESSMENT): A LARGE-SCALE, COMMUNITY-BASED, PHASE IV TRIAL[43]

The objective of the ORCA trial was to provide evidence of the efficacy and safety of Oracea in a real-world setting. This community-based, 12-week clinical study included 1421 subjects with mild, moderate, and severe PPR. The trial had 3 goals: (1) to evaluate the efficacy and safety of Oracea as monotherapy, (2) to evaluate the efficacy and safety of Oracea as add-on treatment to existing topical therapies for PPR, and (3) to explore the effects of PPR and its treatments on quality of life. The results from this trial serve to provide healthcare providers with a reasonable expectation of the outcomes they can achieve in their daily practice when treating patients with PPR.

An Open-label, Community-Based, 12-Week Assessment of the Effectiveness and Safety of Monotherapy With Doxycycline 40 mg (30-mg Immediate-Release and 10-mg Delayed-Release Beads)[43]

This study assessed the efficacy and safety of Oracea as monotherapy in 1197 subjects for 12 weeks. The primary end point was change in IGA score at week 12. Secondary end points included change in CEA score, IGA success rate, and AEs.

IGA score was significantly improved from baseline to week 12, with 75% of patients achieving clear or near clear results (Figure 21). CEA score also was significantly improved from baseline to week 12 and 75% of subjects had no or mild erythema at week 12 (*P*<.0001). Treatment-related AEs occurred in 6.7% of subjects and most were mild to moderate in severity. The AEs that occurred in >1% of subjects included diarrhea (1.2%), nausea (1.3%), and headache (1%).

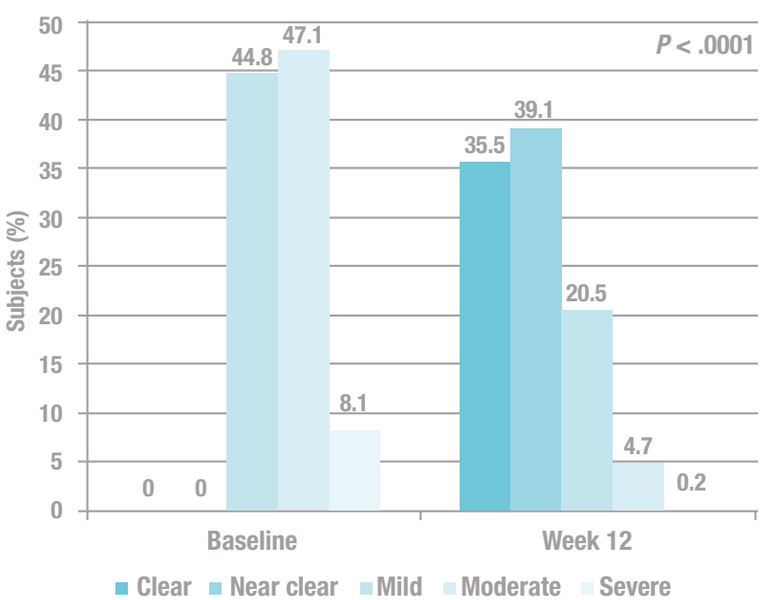


Figure 21. IGA scores at baseline and week 12 in the monotherapy population[43]

CLINICAL EFFICACY AND SAFETY: ORCA TRIAL

Effectiveness and Safety of Doxycycline 40 mg (30-mg Immediate-Release and 10-mg Delayed-Release Beads) Once Daily as Add-on Therapy to Existing Topical Regimens for the Treatment of Papulopustular Rosacea: Results From a Community-Based Trial[43]

The efficacy and safety of Oracea as add-on therapy was evaluated in 224 subjects receiving topical therapy (metronidazole, azelaic acid, or sodium sulfacetamide-sulfur) for PPR, but were still experiencing symptoms. IGA score, CEA score, and safety were evaluated over the course of 12 weeks.

Seventy-six percent of subjects demonstrated a clear or near clear IGA score at week 12, which was a statistically significant change from baseline (P=.0012) (Figure 22). CEA scores also significantly improved (P≤.0252). At baseline, almost all patients had moderate to significant erythema and by week 12, 64% of subjects had only mild erythema. Treatment-related AEs occurred in 7% of subjects and most were mild to moderate in severity. The most common AEs were diarrhea (2.7%), nausea (1.8%), and rash (1.3%).

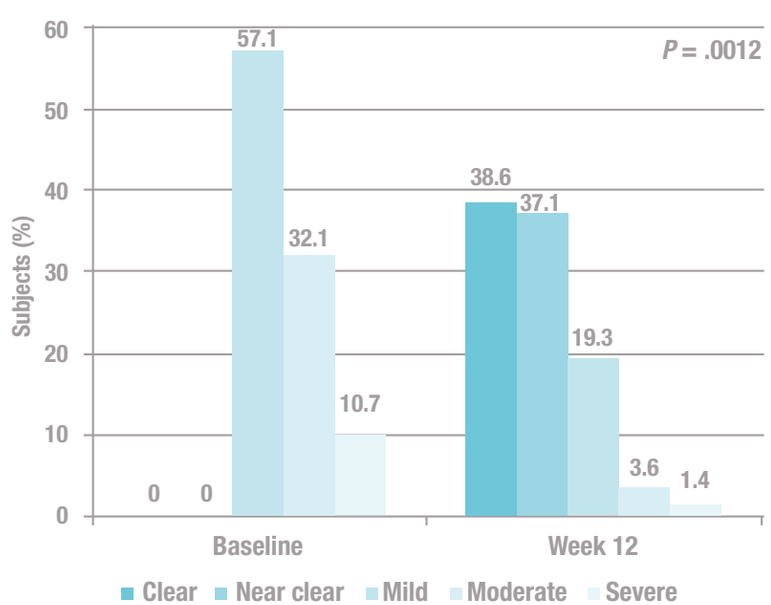


Figure 22. IGA scores in the add-on therapy population (n=140)[43]

ONCE-DAILY Oracea® (doxycycline) 40 mg modified-release, hard capsule

SUMMARY OF PRODUCT CHARACTERISTICS

SWEDEN

Oracea 40 mg kapsel
Varje kapsel innehåller 40 mg doxycyklin (som monohydrat). Rx. J01AA02. Oracea är indicerat för att reducera papulopustulara lesioner hos vuxna patienter med rosacea i ansiktet. Oracea får inte användas till att behandla infektioner som orsakats av organismer som är känsliga för (eller misstänks vara känsliga) för doxycyklin. Produktresumé: 2016-04-05. EF. För mer information: www.fass.se. www.galdermanordic.com

FINLAND

ORACEA 40 mg kovat depotkapselit. Vaikuttava aine: doksisykliini (monohydraattina).
Käyttöaiheet: Kasvojen papulopustulaaristen ruusufinnileesioiden vähentämiseen aikuisilla. **Annostus ja antotapa:** 40 mg vuorokaudessa. Kapseli otetaan aamulla riittävän vesimäärän kera pystyasennossa istuen tai seisten ruokatorviärsytyksen ja haavaumien riskin pienentämiseksi. Potilaan tila arvioidaan hoidon kestettyä 6 viikkoa, ja jos parannusta ei ole tapahtunut, tulee hoidon lopettamista harkita. Kun kliinisissä tutkimuksissa 16 viikkoa kestänyt hoito lopetettiin, potilaiden iho-oireet pyrkivät uusiutumaan 4 viikon seurannan jälkeen. Siksi on suositeltavaa arvioida potilaan tila 4 viikon kuluttua hoidon lopettamisesta.
Vasta-aiheet: Yliherkkyys vaikuttavalle aineelle, muille tetrasykliineille tai apuaineille. Imeväiset ja alle 12-vuotiaat lapset. 2. ja 3. raskauskolmannes. Samanaikainen hoito oraalisilla retinoideilla. Aklorhydria tai epäilty aklorhydria. Pohjukaissuolen ohitus tai erottaminen ruoansulatuksesta.
Varoitukset ja käyttöön liittyvät varotoimet: Oraceaa ei saa käyttää doksisykliinille herkkien mikro-organismien aiheuttamien infektioiden hoitoon. Oraceaa tulee antaa varoen potilaille, joilla on anamneesissa toistuvia hiivatulehduksia. Resistenttien suolistobakteerien ilmaantumisen mahdollisuutta Oraceaa saavilla potilailla ei voida sulkea pois. Oraceaa tulee antaa varoen maksan vajaatoimintaa sairastaville tai mahdollisesti maksatoksisia lääkevalmisteita saaville potilaille sekä myasthenia gravis -potilaille. Potilaiden tulee välttää liiallista auringossa oleskelua ja keinotekoista UV-valoa. Muiden mikrobilääkkeiden tavoin doksisykliinihoitoon liittyy pseudomembranoottisen koliitin riski. Oraceaa ei tule antaa potilaille, joille ruusufinni on aiheuttanut silmäoireita. Tetrasykliinien käyttö hampaiden kehitysvaiheessa voi aiheuttaa pysyvää hampaiden värjäytymistä. Keskosilla tetrasykliini voi aiheuttaa pohjeluun kasvuhäiriöitä. Vaikean äkillisen yliherkkyysreaktion kehittyessä on hoito lopetettava välittömästi ja ryhdyttävä asianmukaisiin toimenpiteisiin. Potilaiden, joilla on harvinainen perinnöllinen fruktoosi-intoleranssi, glukoosi-galaktoosi-imeytymishäiriö tai sakkaroosi-isomaltaasin vajaatoiminta, ei tule käyttää Oraceaa.
Yhteisvaikutukset: Seuraavat yhteisvaikutukset perustuvat antimikrobiaalisissa doksisykliinimuodoissa yleensä käytettäviin annoksiin, mutta saatavana olevat tiedot eivät riitä vahvistamaan, ettei näitä yhteisvaikutuksia voisi esiintyä myös Oracea-hoidon yhteydessä. *Doksisykliinin tehoon vaikuttavat yhteisvaikutukset:* Tietyt bi- ja trivalentit ionit, kuten alumiini, sinkki ja kalsium, magnesium, rauta, lääkehiili, kolestyramiini, vismuttikelaatit, sukralfaatti, mahan pH-arvoa suurentavat lääkevalmisteet, kinapriili, rifampisiini, barbituraatit, karbamatsepiini, difenyylihydantoiini, primidoni, fenytoiini, krooninen alkoholin väärinkäyttö, siklosporiini. *Muiden lääkevalmisteiden tehoon vaikuttavat yhteisvaikutukset:* isotretioniini, penisilliinit, beetalaktaamiantibiootit. *Muut yhteisvaikutukset:* metoksifluraani, sulfonyyliureat, dikumarolityyppiset antikoagulantit, ehkäisytabletit.
w**Fertiliteetti, raskaus ja imetys:** Ks. vasta-aiheet. Imettävät äidit saavat käyttää doksisykliiniä vain lyhyitä aikoja.
Haittavaikutukset: Yleisiä Oracealla todettuja haittavaikutuksia: nasofaryngiitti, sinuiitti, sieni-infektio, ahdistus, sinuspäänsärky, hypertensio, ripuli, ylävatsakipu, suun kuivuminen, selkäkipu, kipu, ASAT-arvon, verenpaineen, veren LDH-arvon ja verensokerin nousu. Myös tetrasykliiniantibioottien käytön yhteydessä esiintyvät haittavaikutukset ovat mahdollisia.
Pakkaukset ja hinnat (Vmh + alv 2/2016): 56 kapselia, 52,16 e. **Huom.** Lue valmisteyhteenveto ennen lääkkeen määräämistä.
Korvattavuus: Ei SV-korvattava resptilääke.
Lisätietoja: Pharmaca Fennica ja Galderma Nordic AB, www.galdermanordic.com 2/2016

SUMMARY OF PRODUCT CHARACTERISTICS

NORWAY

C Oracea «Galderma» *Lavdosert tetrasyklin.* ATC-nr.: J01A A02 **KAPSLER MED MODIFISERT FRISETTING**, harde 40 mg: Hver kapsel inneh.: Doksysyklin (som monohydrat) 40 mg, sukrose 102-150 mg, gelatin, hjelpestoffer. Fargestoff: Allurarød AC (E 129), brilliantblå FCF (E 133), indigokarmin (E 132), gult, rødt og sort jernoksid (E 172), kinolingult (E 104), skjellakk, titandioksid (E 171).
Indikasjoner: Reduksjon av papulopustuløse lesjoner hos voksne med rosacea i ansiktet.
Dosering: Voksne og eldre: Daglig dose er 40 mg (1 kapsel). Pasienten bør vurderes etter 6 uker. Dersom ingen effekt sees, bør det vurderes å avbryte behandlingen. I kliniske studier ble pasientene behandlet i 16 uker. Etter avsluttet behandling kom lesjonene tilbake etter 4 uker, og pasienten bør derfor undersøkes etter 4 uker uten behandling. Barn og ungdom <12 år: Kontraindisert. Spesielle pasientgrupper: Nedsatt leverfunksjon: Administreres med forsiktighet ved nedsatt leverfunksjon eller ved bruk av potensielt hepatotoksiske legemidler. Nedsatt nyrefunksjon: Dosejustering er ikke nødvendig. Administrering: Tas peroralt om morgenen sammen med tilstrekkelig mengde vann for å redusere risikoen for irritasjon og ulcerasjon i øsofagus. Bør svelges i oppreist eller stående stilling. Bør ikke tas sammen med matvarer som inneholder kalsium, se Interaksjoner.
Kontraindikasjoner: Overfølsomhet for doksysyklin, andre tetrasykliner eller noen av hjelpestoffene. Spedbarn og barn <12 år. 2. og 3. trimester av graviditeten. Samtidig behandling med perorale retinoider. Pasienter som har eller mistenkes å ha aklorhydri, eller som har hatt operative inngrep som medfører bypass eller som ekskluderer duodenum.
Forsiktighetsregler: Preparatet inneholder doksysyklin i en konsentrasjon beregnet for å gi antiinflammatoriske plasmanivåer under antimikrobiell konsentrasjon. Skal ikke brukes til behandling av infeksjoner forårsaket av doksysyklinfølsomme organismer (eller organismer som mistenkes å være følsomme). Det er ikke observert oppvekst av opportunistiske mikroorganismer slik som gjærsopp i studier med Oracea, men tetrasyklinbehandling i høyere doser kan gi oppvekst av ikke-følsomme mikroorganismer, inkl. gjærsopp. Det er ikke observert økt hyppighet av vaginal candidiasis i studier med Oracea, men tetrasyklinbehandling i høyere doser kan gi økt hyppighet. Bør brukes med forsiktighet til pasienter predisponert for oppvekst av candidiasis. Ved mistanke om superinfeksjon må nødvendige tiltak igangsettes, inkl. vurdering om seponering. Behandling med høyere tetrasyklindoser er forbundet med fremvekst av resistente intestinale bakterier slik som enterokokker og enterobacter, men er ikke observert med lavdose doksysyklin (40 mg/dag). Utvikling av resistens i den normale mikroflora kan likevel ikke utelukkes. Serumkonsentrasjonen av doksysyklin er lavere ved behandling med Oracea enn ved behandling med konvensjonelle antimikrobielle doksysyklinpreparater. Likevel bør Oracea gis med forsiktighet ved nedsatt leverfunksjon eller ved bruk av potensielt hepatotoksiske legemidler. Den antianabole virkningen av tetrasykliner kan gi økning i BUN (blood-urea-nitrogen). Studier indikerer at dette ikke skjer ved bruk av doksysyklin ved nedsatt nyrefunksjon. Forsiktighet må utvises ved myasthenia gravis, da det kan være risiko for forverring av tilstanden. Pasienter skal anmodes om å unngå for mye sollys eller kunstig ultrafiolett lys under behandlingen, og om å avslutte behandlingen ved første tegn på fototoksisitet (f.eks. hudblemmer etc.). Beskyttelse (solkrem med faktor) bør vurderes. Risiko for utvikling av pseudomembranøs kolitt ved behandling med antimikrobielle midler. Pseudomembranøs kolitt bør vurderes ved utvikling av diaré under behandlingen, og passende behandling må være tilgjengelig (seponering av doksysyklin, bruk av spesifikk antibotikabehandling). Peristaltikkhemmende midler bør ikke brukes i denne situasjonen. Bør ikke brukes ved okulær manifest rosacea (slik som okulær rosacea og/eller blefaritt/meibomianitt) pga. begrensede sikkerhets- og effektdata. Dersom dette oppstår under behandlingen så bør behandlingen avsluttes og pasienten henvises til oftalmolog. Tetrasykliner kan gi permanent misfarging av tenner (gul-grå-brun) ved bruk under tannutvikling. Permanent misfargning er mer vanlig ved langtids bruk, men er også observert etter gjentatte korttidsbehandlinger. Emaljehypoplasi er også rapportert. Tetrasykliner danner et stabilt kalsiumkompleks i bendannende vev. Reduksjon i fibulavekst er observert hos premature barn som har fått tetrasykliner peroralt i doser på 25 mg/kg hver 6. time, men var reversibel etter avsluttet behandling. Behandlingen må stoppes umiddelbart ved alvorlige akutte overfølsomhetsreaksjoner (f.eks. anafylaksi), og vanlig førstehjelpsbehandling gis (f.eks. administrering av antihistaminer, kortikosteroider, sympatomimetika og dersom nødvendig, kunstig åndedrett). Bør ikke brukes ved sjeldne arvelige problemer som fruktoseintoleranse, glukose-galaktosemalabsorpsjon eller sukrase-isomaltasemangel. Fargestoffet allurarød AC (E 129) kan gi allergiske reaksjoner.
Interaksjoner: Anbefalingene nedenfor er basert på generelt større doksysyklindoser. Det finnes ikke tilstrekkelige data til å kunne utelukke at interaksjonene ikke viloppstå ved bruk av lavdose doksysyklin. Interaksjoner som påvirker doksysyklin: Absorpsjon av doksysyklin fra mage-tarmkanalen kan hemmes av bi- og trivalente ioner slik som aluminium, sink, kalsium (f.eks. melk, meieriprodukter og fruktjuice med kalsium), magnesium (f.eks. antacida) eller jernpreparater, aktivt kull, kolestyramin, vismut-chelater og sukralfat. Slike legemidler og matvarer bør derfor

ONCE-DAILY Oracea® (doxycycline) 40 mg modified-release, hard capsule

SUMMARY OF PRODUCT CHARACTERISTICS

tas 2-3 timer etter inntak av doksysyklin. Legemidler som øker pH i magen kan gi redusert absorpsjon av doksysyklin og bør inntas minst 2 timer etter inntak av doksysyklin. Quinapril kan redusere absorpsjon av doksysyklin pga. høyt magnesiuminnhold. Rifampicin, barbiturater, karbamazepin, difenylhydantoin, primidon, fenytoin og kronisk alkoholmisbruk kan akselerere nedbrytningen av doksysyklin pga. enzyminduksjon i leveren. Samtidig bruk kan gi subterapeutiske doksysyklinkonsentrasjoner. Samtidig bruk av ciklosporin nedsetter halveringstiden for doksysyklin. Interaksjoner som påvirker andre legemidler: Når doksysyklin gis kort tid før, under eller etter isotretinoin, kan potensering mellom legemidlene være mulig, med reversibel intrakraniell trykkøkning (intrakraniell hypertensjon). Samtidig administrering bør derfor unngås. Bakteriostatiske legemidler, inkl. doksysyklin, kan interferere med den baktericide virkningen av penicillin og betalaktamantibiotika. Doksysyklin og betalaktamantibiotika bør derfor ikke kombineres. Andre interaksjoner: Samtidig bruk av tetrasykliner og metoksyfluran kan gi fatal nyreforgiftning. Doksysyklin potenserer den hypoglykemiske effekten av perorale sulfonylurea antidiabetika. Ved kombinasjon bør blodglukosenivåene måles, og dersom nødvendig bør sulfonylureadosen reduseres. Doksysyklin nedsetter protrombinaktiviteten i plasma, og potenserer dermed effekten av antikoagulantia av dikumaroltypen. Ved samtidig bruk bør koagulasjonsparametre, inkl. INR, måles og dersom nødvendig bør dosen av antikoagulantia reduseres. Muligheten for økt blødningsrisiko bør iaktas. Samtidig bruk av tetrasykliner og orale antikonseptiva har i noen få tilfeller gitt blødning eller graviditet.

Graviditet, amming og fertilitet: Graviditet: Dyrestudier har ikke vist teratogen effekt. Hos mennesker har bruk av tetrasykliner under et begrenset antall graviditeter ikke påvist noen spesifikke misdannelser inntil nå. Administrering under 2. og 3. trimester kan gi permanent misfarging av melketenner hos barnet. Følgelig er doksysyklin kontraindisert i 2. og 3. trimester. Amming: Lave nivåer av tetrasykliner utskilles i morsmelk. Doksysyklin kan brukes av ammende i en kort periode. Langtids bruk kan gi betydelig absorpsjon hos det diende barnet, og er derfor ikke anbefalt pga. teoretisk risiko for misfarging av tenner og redusert benvekst hos barnet. Fertilitet: Oral administrering av doksysyklin til rotter påvirket fertilitet og reproduksjonsevnen betydelig. Effekten på human fertilitet er ukjent.

Bivirkninger: Mest vanlig er nasofaryngitt, diaré og hypertensjon. Vanlige (≥1/100 til <1/10): Gastrointestinale: Diaré, øvre abdominalsmerter, munntørrhet. Hjerte/kar: Hypertensjon. Infeksiøse: Nasofaryngitt, sinusitt, soppinfeksjon. Muskel-skjelettsystemet: Ryggsmerter. Nevrologiske: Sinushodepine. Psykiske: Angst. Undersøkelser: ASAT-økning, økt blodtrykk, blod-LDH og blodglukose. Øvrige: Smerter. Ukjent: Benign intrakraniell hypertensjon og hodepine (rapportert etter overvåkning og markedsføring. Sett ved bruk av tetrasykliner: Det er mindre sannsynlig at typiske tetrasyklinbivirkninger skal oppstå med Oracea, pga. redusert dose og relativt lave plasmakonsentrasjoner. Legen bør imidlertid alltid være oppmerksom på muligheten og bør følge opp pasienten iht. dette. Sjeldne (≥1/10 000 til <1/1000): Blod/lymfe: Trombocytopeni, nøytropeni, eosinofili. Gastrointestinale: Kvalme, oppkast, diaré, anoreksi. Hjerte/kar: Perikarditt. Hud: Makulopapuløst og erytematøst utslett, hudfotosensitivitet, urticaria. Immunsystemet: Overfølsomhetsreaksjoner inkl. anafylaksi. Anafylaktisk purpura er også rapportert. Lever/galle: Hepatotoksisitet. Nevrologiske: Benign intrakraniell hypertensjon[1]. Nyre/urinveier: Økt blodurea. Svært sjeldne (<1/10 000): Blod/lymfe: Hemolytisk anemi. Endokrine: Brun-svart mikroskopisk misfarging av thyreoideavev ved langtidsbruk. Thyreoideafunksjonen er normal. Gastrointestinale: Glossitt, dysfagi, enterokolitt. Øsofagitt og ulcerasjon i øsofagus er hyppigst rapportert hos pasienter som har fått hyklatsalt i kapselform, og ved inntak rett før sengetid. Hud: Eksfoliativ dermatitt, angionevrotisk ødem. Infeksiøse: Anogenital candidiasis. Muskel-skjelettsystemet: Eksaserbasjon av systemisk lupus erythematosus. Nevrologiske: Utvidet fontanell hos spedbarn1. 1 Behandlingen bør avbrytes ved utvikling av økt intrakranielt trykk. Tilstanden forsvant raskt etter seponering. Klassifisering: Bredspektret antibiotikum, tetrasyklin.

Pakninger og priser: 01.12.2013: 56 stk. kr 345,50. Har ikke refusjon.

Sist endret: 25-01-2016.

Innehaver av markedsføringstillatelsen: Galderma Nordic AB.

SUMMARY OF PRODUCT CHARACTERISTICS

DENMARK

Oracea® 40 mg doxycyclin, hård kapsel med modificeret udløsning
Indikationer: Oracea er indiceret til reducering af papulopustulære læsioner hos voksne patienter med rosacea i ansigtet.
Dosering: Oral anvendelse. Den daglige dosis er 40 mg (1 kapsel). Kapslen bør tages om morgenen med rigelige mængder vand med henblik på at reducere risikoen for irritation og ulceration i spiserøret. Patienterne bør evalueres efter seks uger, og hvis der ikke ses nogen virkning, bør det overvejes at standse behandlingen.
Kontraindikationer: Overfølsomhed over for det aktive stof, over for andre tetracykliner eller over for et eller flere af hjælpestofferne. Spædbørn og børn op til 12 år. Andet og tredje trimester i graviditeten. Samtidig behandling med orale retinoider. Patienter, der vides at have, eller som mistænkes at have, aklorhydri, eller patienter som har gennemgået kirurgi, der leder mavesækkens indhold uden om duodenum (gastrisk bypass eller eksklusion af duodenum), må ikke ordineres doxycyclin.
Særlige advarsler og forsigtighedsregler vedrørende brugen: Oracea indeholder doxycyclin i en formulering, der er beregnet til at producere anti-inflammatoriske plasmaniveauer under den antimikrobielle grænse. Oracea må ikke anvendes til behandling af infektioner, der er forårsaget af organismer, der kan påvirkes af (eller som mistænkes at kunne påvirkes af) doxycyclin. For at undgå irritation og ulceration i spiserøret bør patienten drikke tilstrækkelig væske (vand) sammen med dette lægemiddel. Oracea bør synkes, mens patienten sidder i oprejst stilling eller står op. Oracea bør anvendes med forsigtighed hos patienter med en anamnese med prædisponering for candidiasisovervækst. Hvis der er mistanke om en superinfektion, bør der tages passende forholdsregler, og det bør overvejes at afbryde behandlingen med Oracea. Selv om det ikke er observeret i kliniske forsøg med lave doser doxycyclin (40 mg/dag), kan risikoen for at udvikle modstandsdygtighed i den normale mikroflora ikke udelukkes hos patienter, der behandles med Oracea. Oracea bør administreres med forsigtighed til patienter med nedsat leverfunktion samt til patienter, der modtager potentielt levertoksiske lægemidler. Der skal udvises forsigtighed i behandlingen af patienter med myasthenia gravis, hvor der kan være risiko for, at deres tilstand forværres. Alle patienter, der modtager doxycyclin, herunder Oracea, bør rådgives til at undgå for meget sollys eller kunstigt ultraviolet lys, mens de modtager doxycyclin, og de skal rådes til at afbryde behandlingen, hvis der optræder fototoksicitet (f.eks. hududslæt). Ligesom med anvendelse af antimikrobielle lægemidler generelt er der risiko for at udvikle pseudomembran colitis i forbindelse med doxycyclin-behandling. Oracea bør ikke anvendes hos patienter med okulære manifestationer af rosacea (såsom okulær rosacea og/eller blefaritis/meibomitis), da der er begrænsede data vedrørende virkning og sikkerhed i denne population. Hvis disse manifestationer optræder under behandlingsforløbet, bør Oracea behandlingen afbrydes, og patienten henvises til en oftalmolog. Hos mennesker kan brugen af tetracykliner under tandudviklingen forårsage permanent misfarvning af tænderne (gul-grå-brun). Denne reaktion optræder hyppigst ved langtidsbehandling med stoffet men er set efter gentagne korttidsbehandlinger. Emaljehypoplasi er ligeledes indberettet. Som andre tetracykliner danner doxycyclin et stabilt calciumkompleks i knogledannende væv. Hos for tidligt fødte spædbørn, der er behandlet med orale tetracykliner i doser på 25 mg/kg hver 6. time, er der set en nedgang i væksthastigheden af fibula. Dette fænomen viste sig at være reversibelt ved ophør af behandlingen. I tilfælde af en svær akut overfølsomhedsreaktion (f.eks. anafylakse) skal behandlingen med Oracea afbrydes omgående, og de sædvanlige forholdsregler tages. Patienter med sjældne arvelige problemer med fruktoseintolerans, glukose-galaktose-malabsorption eller sukrase-isomaltase-mangel bør ikke tage dette lægemiddel. Kapslens trykblæk indeholder allura rød AC aluminiumlak (E129) som kan medføre allergiske reaktioner.
Graviditet og Amning: Graviditet: Administration af tetracykliner under andet og tredje trimester resulterede i permanent misfarvning af barnets mælketænder Som konsekvens heraf er doxycyclin kontraindiceret i andet og tredje trimester af graviditet. Amning: Lave niveauer af tetracykliner udskilles i mælken hos ammende mødre. Doxycyclin må kun anvendes i kort tid af ammende mødre. Oral administration af doxycyclin til mandlige og kvindelige Sprague-Dawley rotter påvirker negativt fertilitet og reproduktionsevne. Effekten af Oracea på human fertilitet er ukendt.
Bivirkninger: Bivirkninger (defineret som bivirkninger, hvis hyppighed med Oracea var højere end med placebo (med mindst 1 %), hos Oracea-gruppen i pivotale, placebokontrollerede studier hos patienter med rosacea: Almindelig: Hyppighed ≥ 1/100, < 1/10. Inf*ektioner og parasitære sygdomme*: nasofaryngitis, sinusitis, svampeinfektion. *Psykiske forstyrrelser:* angst. *Nervesystemet:* sinus-hovedpine. *Vaskulære sygdomme:* hypertension. *Mave-tarmkanalen:* diare, mavesmerte, øvre del af maven, mundtørhed. *Knogler, led, muskler og bindevæv:* rygsmerte. *Almene symptomer og reaktioner på administrationsstedet:* smerte. *Undersøgelser:* ASAT forhøjet, blodtryk

ONCE-DAILY Oracea® (doxycycline) 40 mg modified-release, hard capsule

SUMMARY OF PRODUCT CHARACTERISTICS

forhøjet, LDH i blodet forhøjet, blodsukker forhøjet. Benign intrakraniel hypertension og hovedpine (ukendt frekvens: kan ikke estimeres ud fra forhåndenværende data) er blevet rapporteret under Oracea postmarketing overvågning. De hyppigheder, der er typiske for lægemidler i gruppen af tetracykliner, vil optræde med mindre sandsynlighed under medicinering med Oracea på grund af den reducerede dosering og de relativt lave plasmaniveauer. Lægen bør dog altid være opmærksom på, at der kan opstå bivirkninger og overvåge patienterne i overensstemmelse hermed. Følgende bivirkninger er observeret hos patienter, der får tetracykliner: *Blod og lymfesystem:* sjælden: trombocytopeni, neutropeni, eosinofili. *Immunsystemet:* sjælden: overfølsomhedsreaktioner, herunder anafylakse, anafylaktoid purpura. *Nervesystemet:* sjælden: benign intrakraniel hypertension. *Hjerte:* sjælden: pericarditis. *Mave-tarmkanalen:* sjælden: kvalme, opkastning, diare, anoreksi. *Lever og galdeveje:* sjælden: levertoksicitet. *Hud og subkutane væv:* sjælden: makulopapulært og erytematøst udslæt, lysoverfølsomhed af huden, urticaria. *Nyrer og urinveje:* sjælden: forhøjet blodurea.

Udlevering B, Ej tilskud, 56 kapslar, pris 363,60 kr. Priser fra 23 sept 2016. Søg dagsaktuel pris på www.medicinpriser.dk.

Teksten er afskrevet og forkortet i forhold til det af Lægemiddelstyrelsen godkendte produktresumé. Produktresumeet kan vederlagsfrit rekvireres fra Galderma Nordic AB. Dato for udarbejde af material: 8. sept 2016.

THE ROLE OF ORACEA IN CLINICAL PRACTICE

Rosacea is an increasingly common diagnosis affecting an estimated 2% to 10% of the European population.[44] The disease is characterized by inflammatory lesions and the appearance of erythema that usually affects the nose, cheeks, and forehead. Stinging, burning, and/or telangiectasia are usually present. The etiology and pathogenesis of rosacea are poorly understood; however, inflammation is believed to be one of the key factors in the underlying development of the disease. Treatment options include topical agents, oral agents, laser treatments, and surgical procedures. Topical and systemic antimicrobial agents are routinely prescribed for extended periods of time in patients with rosacea. However, the emergence of antibiotic-resistant organisms has led to new treatment approaches. The development of Oracea, an anti-inflammatory dose of doxycycline, is an alternative to the long-term use of antibiotics, and represents a novel approach to the use of oral agents in rosacea.

Oracea is a formulation of doxycycline that is suitable for long-term use in patients with rosacea. It has a formulation that permits once-daily dosing and results in a pharmacokinetic profile that is unlike that of conventional doxycycline. Microbiological studies of Oracea showed that this regimen provided maximum concentrations consistently below those required for an antimicrobial effect. In vivo microbiological studies with 40 mg/day anti-inflammatory dose doxycycline demonstrated no detectable long-term effects on bacterial flora of the oral cavity, skin, intestinal tract, and vagina for up to 18 months.

Oracea exhibits all of the anti-inflammatory activities associated with conventional doses of doxycycline and other tetracyclines. Many of these anti-inflammatory effects are associated with the inhibition of mediators identified or suspected of contributing to the pathophysiology of rosacea. For example, tetracyclines inhibit connective tissue breakdown through indirect and direct mechanisms, depending on the particular status of the tissues involved and stage of disease progression. Tetracyclines directly inhibit active MMPs, such as type IV collagenase (MMP-1, MMP-2, MMP-8, MMP-9, and MMP-13) as well as inhibiting the oxidative activation of pro-MMPs. Additionally, tetracyclines have been shown to inhibit several neutrophil-associated proinflammatory processes including those associated with PLA_2, endogenous NO production, activity of ROS, and expression of iNOS and IL-6.

Oracea is an effective and well-studied treatment for patients with rosacea, as shown by the results of 2 pivotal trials. Both studies achieved their primary end point by demonstrating a greater reduction in inflammatory lesion count from baseline in patients who received Oracea than in patients who received placebo. Patients receiving Oracea had a 61% and 46% reduction in inflammatory lesions in studies A and B, respectively, compared with 29% and 20%, respectively, in patients receiving placebo ($P<.001$ for each study). Furthermore, the efficacy of Oracea was:

- Equivalent to doxycycline 100 mg when both were combined with metronidazole 1%
- Greater when used in combination with metronidazole 1% compared with metronidazole alone
- Superior to vehicle when used as montherapy or as add-on therapy to topical treatments as confirmed in a real-world setting

In addition, Oracea was well tolerated throughout both phase III studies, with a placebo-like safety profile and when compared to doxycycline 100 mg combined with metronidazole 1% (5% of gastrointestinal symptoms vs 26% for the doxycycline-metronidazole 1% group). In all studies, the majority of AEs observed were rated as mild or moderate in severity in both study arms, and Oracea was not associated with any cases of vaginal candidiasis and photosensitivity, as shown in the phase III studies.

Rosacea is a chronic disorder that has an impact on the psychosocial lives of patients. It requires long-term therapy; therefore, a major advantage of any first-choice treatment is an absence of antibiotic activity. Oracea is the first and only oral therapy approved both by European health authorities and US Food and Drug Administration to reduce papulopustular lesions in patients with rosacea. It provides therapeutic efficacy in the treatment of rosacea through anti-inflammatory mechanisms. Patients with rosacea will benefit from this once-daily formulation of doxycycline. The availability of Oracea, an effective systemic treatment, is a major advance for both physicians and patients in the treatment of rosacea.

REFERENCES

1. Buechner SA. Rosacea: an update. *Dermatology.* 2005;210(2):100-108. **2.** Powell FC. Clinical practice: rosacea. *N Engl J Med.* 2005;352(8):793-803. **3.** Blount BW, Pelletier AL. Rosacea: a common, yet commonly overlooked, condition. *Am Fam Physician.* 2002;66(3):435-440. **4.** Roberts JO, Ward CM. Rhinophyma. *J R Soc Med.* 1985;78(8):678-681. **5.** Rebora A. The red face: rosacea. *Clin Dermatol.* 1993;11(2):225-234. **6.** Wilkin J, Dahl M, Detmar M, et al. Standard grading system for rosacea: report of the National Rosacea Society Expert Committee on the Classification and Staging of Rosacea. *J Am Acad Dermatol.* 2004;50;907-912. **7.** Millikan L. The proposed inflammatory pathophysiology of rosacea: implications for treatment. *Skinmed.* 2003;2(1):43-47. **8.** Rosacea triggers survey. National Rosacea Society website. http://www.rosacea.org/patients/materials/triggersgraph.php. Accessed December 14, 2015. **9.** Diamantis S, Waldorf HA. Rosacea: clinical presentation and pathophysiology. *J Drugs Dermatol.* 2006;5(1):8-12. **10.** Jansen T. Clinical presentations and classification of rosacea. *Ann Dermatol Venereol.* 2011;138:S192-S200. **11.** Tan J, Blume-Peytavi U, Ortonne JP, et al. An observational cross-sectional survey of rosacea: clinical associations and progression between subtypes. *Br J Dermatol.* 2013;169:555-562. **12.** 14 million Americans urged to face up to rosacea before it gets worse. National Rosacea Society website. http://www.rosacea.org/press/archive/20050401.php. Accessed December 11, 2015. **13.** Dirschka T, Micali G, Papadopoulos L, Tan J, Layton A, Moore S. Perceptions on the psychological impact of facial erythema associated with rosacea: results of international survey. *Dermatol Ther.* 2015;5(2):117-127. **14.** Crawford GH, Pelle MT, James WD. Rosacea: I. Etiology, pathogenesis, and subtype classification. *J Am Acad Dermatol.* 2004;51(3):327-341. **15.** Del Rosso JQ. Advances in understanding and managing rosacea: part 1. Connecting the dots between pathophysiological mechanisms and common clinical features of rosacea with emphasis on vascular changes and facial erythema. *J Clin Aesthet Dermatol.* 2012;5(3):16-25. **16.** Steinhoff M, Schmelz M, Schauber J. Facial erythema of rosacea – aetiology, different pathophysiologies and treatment options [published online December 30, 2015]. *Acta Derm Venereol.* doi:10.2340/00015555-2335. **17.** Gomaa AH, Yaar M, Eyada M, Bhawan J. Lymphangiogenesis and angiogenesis in non-phymatous rosacea. *J Cutan Pathol.* 2007;34:748-753. **18.** Warren JB. Nitric oxide and human skin blood flow responses to acetylcholine and ultraviolet light. *FASEB J.* 1994;8(2):247-251. **19.** Liu D, Fernandez BO, Hamilton A, et al. UVA irradiation of human skin vasodilates arterial vasculature and lowers blood pressure independently of nitric oxide synthase. *J Invest Dermatol.* 2014;134:1839-1846. **20.** Del Rosso JQ, Baum EW. Comprehensive medical management of rosacea: an interim study report and literature review. *J Clin Aesthetic Derm.* 2008;1(1):20-25. **21.** Steinhoff M, Buddenkotte J, Aubert J, et al. Clinical, cellular, and molecular aspects in the pathophysiology of rosacea. *J Investig Dermatol Symp Proc.* 2011;15:2-11. **22.** Yamasaki K, Gallo RL. The molecular pathology of rosacea. *J Dermatol Sci.* 2009;55:77-81. **23.** Casas C, Paul C, Lahfa M, et al. Quantification of Demodex folliculorum by PCR in rosacea and its relationship to skin innate immune activation. *Exp Dermatol.* 2012;21:906-910. **24.** Holmes AD. Potential role of microorganisms in the pathogenesis of rosacea. *J Am Acad Dermatol.* 2013;69:1025-1032. **25.** Bhatia N. Oracea 40 mg Capsules for papulopustular rosacea. *The Dermatologist.* 2013;(suppl):1-4. **26.** Wise RD. Submicrobial doxycycline and rosacea. *Comp Ther.* 2007:33(2):78-81. **27.** Jarmuda S, McMahon F, Z˙aba R, et al. Correlation between serum reactivity to *Demodex*-associated *Bacillus oleronius* proteins, and altered sebum levels and *Demodex* populations in erythematotelangiectatic rosacea patients. *J Med Microbiol.* 2014;63:258-262. **28.** Weinberg JM. The anti-inflammatory effects of tetracyclines. *Cutis.* 2005;75(4 suppl):6-11. **29.** Sapadin AN, Fleischmajer R. Tetracyclines: nonantibiotic properties and their clinical implications. *J Am Acad Dermatol.* 2006;54(2):258-265. **30.** Amin AR, Attur MG, Thakker GD, et al. A novel mechanism of action of tetracyclines: effects on nitric oxide synthases. *Proc Natl Acad Sci USA.* 1996;93:14014-14019. **31.** Pruzanski W, Greenwald RA, Street IP, Laliberte F, Stefanski E, Vadas P. Inhibition of enzymatic activity of phospholipases A_2 by minocycline and doxycycline. *Biochem Pharmacol.* 1992;44(6):1165-1170. **32.** Akamatsu H, Asada M, Komura J, Asada Y, Niwa Y. Effect of doxycycline on the generation of reactive oxygen species: a possible mechanism of action of acne therapy with doxycycline. *Acta Derm Venereol (Stockh).* 1992;72(3):178-179. **33.** Golub LM, Lee H-M, Ryan ME, Giannobile WV, Payne J, Sorsa T. Tetracyclines inhibit connective tissue breakdown by multiple non-antimicrobial mechanisms. *Adv Dent Res.* 1998;12(2):12-26. **34.** Del Rosso JQ, Webster GF, Jackson M, et al. Two randomized phase III clinical trials evaluating anti-inflammatory dose doxycycline (40-mg doxycycline, USP capsules) administered once daily for treatment of rosacea. *J Am Acad Dermatol.* 2007;56(5):791-802. **35.** Del Rosso JQ. Antibiotic resistance: overview and significance in dermatology. *Cutis.* 2005;75(suppl 4):12-18. **36.** Guay DRP. Treatment of bacterial skin and skin structure infections. *Expert Opin Pharmacother.* 2003;4(8):1259-1275. **37.** Eady AE, Cove JH, and Layton AM. Is antibiotic resistance in cutaneous propionibacteria clinically relevant? Implications of resistance for acne patients and prescribers. *Am J Clin Dermatol.* 2003;4(12):813-831. **38.** Levy SB. The challenge of antibiotic resistance. *Sci Am.* 1998;278(3):46-53. **39.** Preshaw PM, Novak MJ, Mellonig J, et al. Modified-release subantimicrobial dose doxycycline enhances scaling and root planing in subjects with periodontal disease. *J Periodontol.* 2008;79:440-452. **40.** Data on file. Galderma Laboratories, L.P. **41.** Del Rosso JQ, Schlessinger J, Werschler P. Comparison of anti-inflammatory dose doxycycline versus doxycycline 100 mg in the treatment of rosacea. *J Drugs Dermatol.* 2008;7(6):573-576. **42.** Fowler JF Jr. Combined effect of anti-inflammatory dose doxycycline (40-mg doxycycline, USP monohydrate controlled-release capsules) and metronidazole topical gel 1% in the treatment of rosacea. *J Drugs Dermatol.* 2007;6(6):641-645. **43.** Webster GF. An open-label, community-based, 12-week assessment of the effectiveness and safety of monotherapy with doxycycline 40 mg (30-mg immediate-release and 10-mg delayed release beads). *Cutis.* 2010;86(suppl 5S[i]):7-15. **44.** Lehman PM. Rosacea: epidemiology, pathogenesis, clinical presentation, and treatment. *Dtsch Arztebl.* 2007;104(24):1741-1746.

ONCE-DAILY Oracea® (doxycycline) 40 mg modified-release, hard capsule

GALDERMA

Galderma Nordic AB, Seminariegatan 21, SE-752 28 Uppsala
Tel +46 18 444 03 30, fax +46 18-444 03 35, www.galdermanordic.com