DermatologyTimes®

Managing Papulopustular Rosacea With Once-daily ORACEA® (doxycycline, USP) 40 mg* Capsules

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Rosacea is a visible, inflammatory skin disease that affects an estimated 415 million people globally and most commonly presents in those aged between 30 and 50 years.[1,2] The relapsing-remitting course of rosacea is characterized by a variety of facial skin and ocular features that differ by patient.[3] It is marked by a variable spectrum of dermatologic signs and symptoms with central facial predominance including flushing; persistent erythema, papules, pustules, and telangiectasia; ocular lesions; phymatous changes; and skin thickening.[4] Symptoms can be triggered and worsen for periods of time from factors such as sun exposure, emotional stress, and exercise.[3,5] Overall, the etiology and pathogenesis of rosacea are poorly understood; however, inflammation is believed to be a key factor in the underlying development of the disease.[3,4]

The burden of rosacea, treatment goals, and treatment options were reviewed in a discussion between **Hilary E. Baldwin, MD**, medical director of the Acne Treatment and Research Center in New York and a clinical associate professor at Rutgers Robert Wood Johnson Medical School; and **Jeffrey S. Fromowitz, MD**, managing partner and medical director of Dermatology of Boca and an adjunct assistant professor of medicine at Florida Atlantic University College of Medicine. During the conversation, they emphasized the importance of a patient-focused management approach and reviewed *ORACEA*® (doxycycline, USP) 40 mg* Capsules, indicated for the treatment of inflammatory lesions of rosacea, as an effective treatment option for rosacea papules and pustules that did not contribute to antibiotic resistance in a 9-month study.[6-10]

Rosacea Diagnosis and Classification

Rosacea is clinically diagnosed; however, there are no laboratory tests to confirm diagnosis.[11] In general, rosacea can be underdiagnosed, due in part to patients being unaware of their condition or not discussing their symptoms with their physician. Also, physicians may not always distinguish the symptoms for differential diagnosis. Diagnostic challenges can lead to misdiagnoses for conditions such as acne vulgaris, chronic sun damage (ie, photoaging), or lupus erythematosus.[3]

A rosacea diagnosis is based on the presence of 1 or more primary features located on the central area of the face (**Table 1**).[5,12] Secondary features can coexist with 1 or more of the primary characteristics of rosacea, but they may present independently in some patients. Patients often have characteristics of 1 or more rosacea features simultaneously.[5] Rosacea is classified based on phenotype, which allows for rosacea diagnosis and management according to a patient's presenting disease features rather than grouping into prespecified subtypes, thus individualizing care and optimizing treatment outcomes.[5,12,13] The 4 major phenotypes involve flushing, telangiectasia, ocular manifestations, and inflammatory lesions. The inflammatory type is marked by dome-shaped red papules that are sometimes accompanied by pustules and/or nodules. These lesions often come in groups in the centrofacial region. Some patients with the inflammatory type also report experiencing secondary phenotypes such as stinging or burning, which may also involve itching. Facial edema can sometimes occur after extended erythema or flushing. A dry appearance may also develop, with rough and scaly facial skin that may be accompanied by burning or stinging.[5]

Without treatment, rosacea may progress in severity and may develop additional phenotypes due to the underlying shared inflammatory mechanisms.[3,5,14]

Understanding the Burden of Rosacea

The clinically assessed disease severity of rosacea may not accurately indicate overall well-being of the patient. Patients' mental and emotional experiences with rosacea can have a negative effect on their quality of life.[12] "Be aware that quality of life matters," advised Fromowitz. "We need to make sure we are covering these topics in our [patient] visits."

Table 1. Major Diagnostic Phenotypes and Clinical Manifestations of Inflammatory Rosacea[5,12]

PHENOTYPES	**Inflammatory Papulopustular Phenotype** Persistent central facial erythema with transient, central facial papules or pustules or both	▪ Dome-shaped red papules ▪ Sometimes with pustules and/or nodules ▪ Lesions appear in groups in centrofacial region
CLINICAL MANIFESTATIONS	1 or more PRIMARY FEATURES are usually present	▪ Flushing[a] ▪ Nontransient erythema ▪ Papules and pustules ▪ Telangiectasia
	SECONDARY FEATURES may also be present	▪ Burning or stinging ▪ Plaques ▪ Dry appearance ▪ Edema ▪ Ocular manifestations ▪ Peripheral location ▪ Phymatous changes

[a]Transient erythema is a common feature.

Patient quality of life can be measured by the Dermatology Life Quality Index (DLQI), a well-recognized measure in the dermatology community. A DLQI score of 0 to 1 indicates no impact of rosacea on life at all, whereas a score between 21 and 30 indicates a very large impact on quality of life.[14] The most relevant elements measured by the DLQI are itching, soreness, pain, or stinging on the face; embarrassment or self-consciousness; and an effect on social or leisure activities.[12]

The DLQI was used in a self-administered online survey to understand the burden of rosacea. The survey was given to 544 physicians and 710 patients from France, Germany, Italy, the United Kingdom, Canada, and the United States. Participants were recruited using the Kantar online panel. To maximize the sample size, no quota was set, so the sample is not necessarily representative of the entire rosacea population of each country.[14] Of the adults with rosacea who were included in the analysis[14]:

- **50% experience a reduced quality of life**
- **33% have a high burden of disease**
- **55% experience decreased work productivity**
- **86% modify daily activities to avoid triggers**
- **87% experience flare-ups despite trigger avoidance**
- **82% do not feel their disease is properly controlled**

Overall, the results of this study demonstrated that rosacea poses a substantial burden on the lives of many patients. Patients with rosacea experience a variety of emotional and social stigmas, most commonly feelings of losing confidence. Those with a high DLQI can be particularly affected, and they report spending up to 3.5 hours more on their skincare regimen per week than patients with a low-to-moderate DLQI; they also visit their doctors more than twice as often.[14]

The mental and emotional burdens of rosacea are important to discuss when establishing a treatment plan with patients. Fromowitz admitted that it can be more challenging when he, rather than the patient, initiates this conversation, but he cuts right to the chase. "I ask them about their skin health, about their appearance, and how they feel about their skin," he said. "Then we talk about what I'm seeing." Baldwin said she likes to have patients look into a mirror while she's describing all the aspects of rosacea on their face—including telangiectasia and red eyes. "I point out each of the different aspects," she said. "It is important to get patients to buy into the process at the beginning so we can start to discuss which of these [aspects] bother them the most. Then we can start talking about therapy." Treatment decision-making should involve the patient—especially when setting treatment goals.[12] Appropriate diagnosis and selection of treatment can help patients feel more in control of their rosacea.

Management Approach and Goals of Therapy

When treating rosacea, achieving clear skin vs almost clear skin should be the primary objective.[12] On the 5-point Investigator Global Assessment (IGA), a "clear" status equates to IGA 0, indicating there are no inflammatory lesions or erythema. Higher IGA scores indicate greater severity. The highest score is IGA 5, which describes numerous small and/or large papules and pustules and severe erythema.[8,15] Treatment success for rosacea is usually defined as reaching a score of IGA 0 (clear) or IGA 1 (almost clear).[16] The Global ROSCO (ROSacea COnsensus) international expert panel, composed of 19 dermatologists and 2 ophthalmologists who reach consensus on critical aspects of rosacea diagnosis and treatment, recommends aiming for clear to maximize time to disease relapse, maximize patient satisfaction from treatment, and minimize disease impact on patients' quality of life (**Table 2**).[12,13] "We used to be very satisfied with the almost clear," said Fromowitz. "But [now] when we drive the patient to clear, we provide them with a greater disease-free interval and even the opportunity for a treatment holiday." Baldwin noted that achieving a clear status increases patient satisfaction.

> "We used to be very satisfied with the almost clear, but [now] when we drive the patient to clear, we provide them with a greater disease-free interval and even the opportunity for a treatment holiday."
>
> **Jeffrey S. Fromowitz, MD**

With this goal in mind, clinicians and patients together can devise an optimal treatment regimen. Achieving a clear status can be challenging, as rosacea is complex to treat and requires ongoing management and monitoring.[12] Providers should educate patients on general skincare guidelines that include managing secondary features of rosacea, such as stinging sensations and dry appearance, and ways to maximize treatment outcomes, such as avoiding trigger factors.[13] Fromowitz noted the importance of educating patients on the actions they can take in their own lives to help manage rosacea. "As we [increase the degree of] patient awareness, [managing rosacea] becomes a shared responsibility," he said. Baldwin stressed the importance of being gentle when discussing trigger factors and lifestyle modifications. "We have to help them recognize what their triggers are," she said. "But we also need to be relatively gentle in our suggestions to avoid the triggers that are particularly important to them in their lives."

Providers should review treatment options with their patients to identify the right approach that can optimize the outcome for each individual patient. Treatments for rosacea include topical agents, an oral agent, laser treatments, and surgical procedures. Topical and systemic antimicrobial agents are recommended as pharmacologic treatment options for managing inflammatory papules and pustules and are routinely prescribed for extended periods of time in patients with rosacea. Oral doxycycline is often considered for inflammatory papules and pustules of rosacea due to its anti-inflammatory effects.[13] Fromowitz stated that he nearly always gives an oral medication for the treatment of inflammatory papules and pustules. "I tend to treat a little bit more aggressively from onset, with the idea of getting as clear as quickly as I can," he said. "And then titrate off medications…clear the skin and maintain with a topical."

Setting treatment goals and expectations can be a "difficult job," said Baldwin. "Our job is to make every aspect of their rosacea better…the problem is that not everything bothers the patient." For example, a patient may hate the redness but not care about the papules. Baldwin asks patients which aspects of rosacea they'd like to deal with, and which they would like to tackle first, while ensuring that they understand that addressing more symptoms may require more medications and therapies, such as laser and light treatment, which incur additional cost. With each therapy, patients should understand treatment duration, time to onset of efficacy, potential for adverse events (AEs), and chances of achieving clear skin. When devising a treatment plan, Baldwin noted the importance of recognizing the patient's sense of urgency.

Table 2. ROSCO 2019 Recommended Management Strategy for Inflammatory Papules/Pustules[12,13]

General skincare management	Pharmacological	
	Mild to moderate	Severe
▪ Sunscreen (sun protection factor 30+) ▪ Frequent use of moisturizers ▪ Gentle over-the-counter cleansers ▪ Trigger avoidance	**Topical** Azelaic acid Ivermectin Metronidazole	**Topical** Ivermectin
	Oral Doxycycline	**Oral** Doxycycline
	Only on-label treatment options are shown.	

Achieving clear skin vs almost-clear skin should be the primary objective when treating rosacea.

ROSCO 2019 Treatment Goal for Clear Skin (IGA 0):

IGA, Investigator Global Assessment; ROSCO, Global ROSacea COnsensus international expert panel.

> "Our job is to make every aspect of their rosacea better…the problem is that not everything bothers the patient."
>
> **Hilary E. Baldwin, MD**

ORACEA® (doxycycline, USP) 40 mg* Capsules

ORACEA® (doxycycline, USP) 40 mg* Capsules are indicated for only the treatment of inflammatory lesions of rosacea, which are also known as papules and pustules, in adult patients. They do not lessen the facial redness caused by rosacea.[6] *ORACEA* Capsules are the only FDA-approved oral formulation for inflammatory lesions of rosacea precisely formulated to remain below the antimicrobial threshold.[7]

ORACEA Capsules contain a unique formulation of 30-mg beads that immediately release doxycycline in the stomach at a pH of 1.1, and 10-mg beads with an enteric coating that dissolve and release doxycycline at a pH of 6.0 for delayed absorption in the small intestine.[6,10] One capsule should be taken once daily either

Table 3. Clinical Efficacy and Safety of *ORACEA*® (doxycycline, USP) 40-mg* Capsules vs Placebo[6,8]

Clinical results of *ORACEA* vs placebo				
	STUDY 1		STUDY 2	
	ORACEA Capsules n = 127	Placebo n = 124	*ORACEA* Capsules n = 142	Placebo n = 144
Mean change in lesion count from baseline	–11.8	–5.9	–9.5	–4.3
Number of patients with clear or almost-clear in the IGA (%)	39 (30.7%)	24 (19.4%)	21 (14.8%)	9 (6.3%)

Most common adverse events in both studies, combined (%)		
	ORACEA Capsules n = 269	Placebo n = 268
Nasopharyngitis	4.8%	3.3%
Diarrhea	4.4%	2.6%
Hypertension	2.9%	0.7%
Sinusitis	2.6%	0.7%
Elevated AST	2.2%	0.7%

AST, aspartate aminotransferase; IGA, Investigator Global Assessment.

*30-mg immediate-release and 10-mg delayed-release beads.

The safety and efficacy of *ORACEA* Capsules in the treatment of inflammatory lesions (papules and pustules) of rosacea was evaluated in 2 randomized, placebo-controlled, multicenter, double-blind, 16-week phase 3 trials involving 537 patients (total of 269 patients on *ORACEA* from the 2 trials) with rosacea (10 to 40 papules and pustules and 2 or fewer nodules).

in the morning on an empty stomach (preferably at least 1 hour prior to a meal) or 2 hours after a meal.[6]

Clinical Efficacy and Tolerability vs Placebo

The safety and efficacy of *ORACEA* Capsules in the treatment of inflammatory lesions of rosacea were evaluated in 2 randomized, placebo-controlled, multicenter, double-blind, parallel-group, 16-week phase 3 trials. Across both trials, patients were aged at least 18 years with moderate-to-severe rosacea defined by the presence of 10 to 40 papules and pustules and 2 or fewer nodules (N = 537). Patients had an IGA score of 2 to 4. In both studies, the primary efficacy end point was the mean change from baseline in total inflammatory lesion count, including the combination of papules, pustules, and nodules at week 16. A secondary outcome evaluated the percentage of patients who achieved an IGA score of 0 (clear) or 1 (almost clear) at week 16.[8]

The efficacy and tolerability results from both studies are presented in **Table 3**.[6,8] Overall, *ORACEA* Capsules demonstrated a rapid onset of action and produced a significant reduction in inflammatory lesions within the first 3 weeks of therapy, followed by a continued reduction over the entire study period. Patients treated with *ORACEA* Capsules also demonstrated significantly greater improvements in IGA scores by week 16 than that of the placebo group in both studies. A greater portion of patients treated with *ORACEA* Capsules achieved an IGA score of clear or almost clear than placebo-treated patients.[8]

In these 2 pivotal clinical studies, *ORACEA* Capsules demonstrated a similar AE profile to placebo across the 16 weeks of treatment. The most common treatment-related AEs with an incidence of more than 2% for *ORACEA* Capsules were nasopharyngitis, sinusitis, diarrhea, hypertension, and elevated aspartate aminotransferase. Importantly, there were no cases of photosensitivity or vaginal candidiasis reported. *ORACEA* Capsules proved to be safe in both studies, with the frequency of AEs similar to those of patients who received placebo.[8]

A post hoc analysis evaluated the efficacy of *ORACEA* Capsules in reducing inflammatory lesions of rosacea, as well as the association of body weight and baseline severity of rosacea. The analysis used pooled data from the 16-week pivotal clinical trial and data from another phase 3 trial. In this subgroup analysis, patients were categorized by different baseline lesion counts (from 10 to 40) and body weight (normal weight, overweight, and obese) based on body mass index ranges. Treatment with *ORACEA* Capsules provided consistent results independent of patient body weight and number of lesions. In the obese patient

subgroup, all patients achieved a statistically significant difference in the mean percentage change of inflammatory lesion count (**Figure 1**).[17]

Clinical Efficacy and Tolerability vs Doxycycline 100 mg

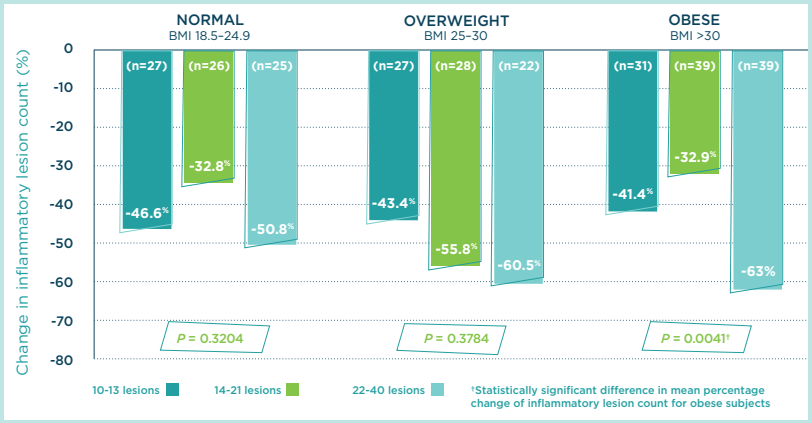
The safety, efficacy, and onset of action of *ORACEA* Capsules were compared with those of doxycycline 100 mg/day in a randomized, multicenter, outpatient, double-blind, active-controlled, noninferiority trial. A total of 91 adult patients with rosacea were randomized to receive once-daily doses of either *ORACEA* Capsules (n = 44) or doxycycline 100 mg (n = 47), each in combination with metronidazole cream, 1%, for 16 weeks. IGA scores ranging from 0 to 5 were used in this study. Patients enrolled were aged at least 18 years with inflammatory (or papulopustular) rosacea, with 8 to 40 papules and pustules, up to 2 nodules, and a score of 2 to 5 on the IGA. The primary end point was the change in total lesion count from baseline to week 16. Patients were evaluated at weeks 4, 8, 12, and 16.[9]

ORACEA Capsules demonstrated a fast onset of action with a substantial reduction in inflammatory lesions at Week 16 (**Figure 2**).[9] 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. By week 4, patients in the *ORACEA* Capsules treatment group achieved a 50% reduction in mean inflammatory lesion count from baseline. By 16 weeks, there was a 73% reduction in mean inflammatory lesion count from baseline.[9]

In the safety analysis, *ORACEA* Capsules demonstrated favorable gastrointestinal tolerability. As shown in **Table 4,** no cases of nausea, diarrhea, abdominal pain, or vomiting were reported for *ORACEA* Capsules compared with doxycycline 100 mg (17%, 4.3%, 2%, and 4.3% respectively).[9]

"The choice between full-strength [dosing] and sub-antimicrobial dosing used to be more difficult until we had some of these more recent data," said Fromowitz.

Figure 1. Consistent Results With *ORACEA*® (doxycycline, USP) 40 mg* Capsules Independent of Body Weight and Number of Lesions[17]



BMI, body mass index.

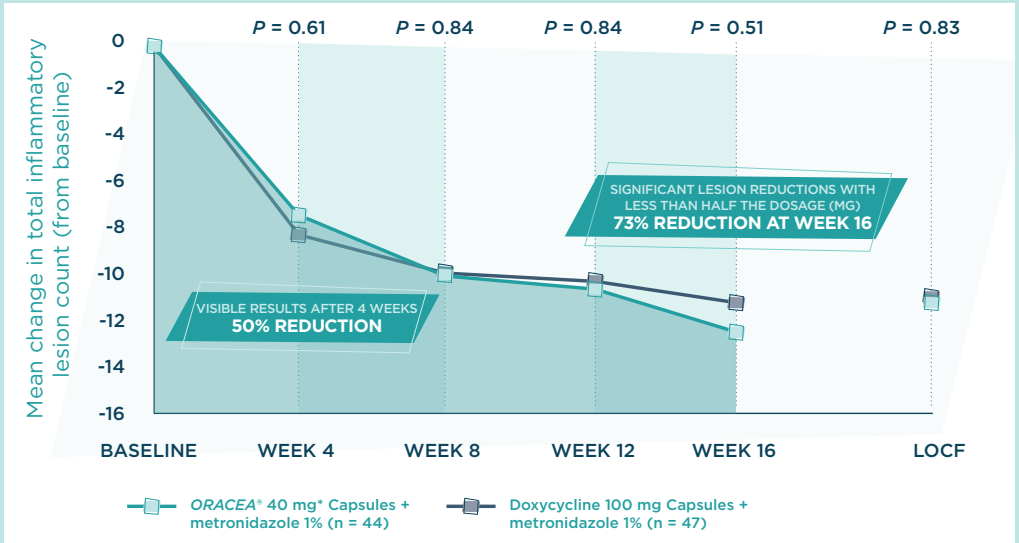
*30-mg immediate-release and 10-mg delayed-release beads.

Table 4. Most Common Treatment-related Adverse Events (>2%) for *ORACEA*® (doxycycline, USP) 40 mg* Capsules vs Doxycycline 100 mg[9]

	ORACEA Capsules n = 44	Doxycycline 100 mg n = 47
Nausea	0%	17.0%
Headache	4.5%	6.4%
Influenza	0%	6.4%
Nasopharyngitis	6.8%	4.3%
Urticaria	2.3%	4.3%
Diarrhea	0%	4.3%
Esophageal pain	0%	4.3%
Vomiting	0%	4.3%
Abdominal pain	0%	2.0%
Abdominal pain, upper	0%	2.0%

*30-mg immediate-release and 10-mg delayed-release beads.

Figure 2. Fast Onset of Action With Significant Reduction in Inflammatory Lesions With *ORACEA*® (doxycycline, USP) 40 mg* Capsules vs Doxycycline 100 mg[9]



LOCF, last observation carried forward.

*30-mg immediate-release and 10-mg delayed-release beads.

"When we have a noninferiority trial, that shows us that sub-antimicrobial–dose doxycycline delivers similar efficacy to full-strength doxycycline, [and it] has a significantly better AE profile. To me, it's an easy decision...[*ORACEA* Capsules offer] a really nice choice for our patients with inflammatory lesions."

Considerations of Antibiotic Stewardship

Traditional doses of doxycycline (50 mg or more) can contribute to the risk of antibiotic resistance.[18] This is a growing concern. Each year, more than 2 million people in the United States are infected with antibiotic-resistant bacteria.[19] Doxycycline accounts for nearly 1 of every 3 prescriptions for tetracyclines, which are the most commonly prescribed antibiotics by dermatologists.[20] Dermatologists prescribe more antibiotics each year than any other specialists, writing more than 7.1 million prescriptions for them annually.[21] This trend places dermatologists in an important position regarding antibiotic stewardship. "We have to take a great deal of responsibility for this," said Baldwin. "[Dermatologists] are a big part of the problem, at least with the tetracycline class of antibiotics in the United States."

Antimicrobial Doses of Doxycycline Contributing to the Emergence of Resistant Bacteria

With doxycycline 100 mg, antibiotic resistance was induced as early as 7 days in a prospective, placebo-controlled, randomized, double-blind trial in 29 healthy volunteers. Daily administration of oral doxycycline of 100 mg was associated with a significant increase in doxycycline-resistant nasopharyngeal flora measured at days 7 and 14; the increase was noted for at least 2 weeks after cessation of therapy. In other words, when doxycycline 100-mg administration was stopped at day 14, microbial resistance continued through day 28—that is 2 weeks of additional activity.[22] In addition to contributing to antibiotic resistance, doxycycline of 50 mg or more can alter commensal microflora by exerting selection pressure.[18]

Because no clinical studies demonstrate additional anti-inflammatory effects of doxycycline when it is taken at a dose above 40 mg in patients with rosacea,[23] it is preferable to use a non-antibiotic dose option that maintains anti-inflammatory activity and has not been shown to contribute to antibiotic resistance.[13]

ORACEA Capsules are the only FDA-approved oral formulation for the inflammatory lesions of rosacea offered at a nonantibiotic dose.[7] The dose has shown a sustained anti-inflammatory effect with low plasma variability. In healthy patients treated with *ORACEA* Capsules, the steady-state plasma concentration of *ORACEA* Capsules measured at 7 days remained well below the antimicrobial threshold, whereas doxycycline 50-mg crossed the threshold.[24,25] In a separate 9-month study, treatment with *ORACEA* Capsules showed no evidence of an increase in bacterial resistance to doxycycline or other antibiotics (**Table 5**).[26] Bacterial samples were collected from 70 patients, including 34 patients treated with *ORACEA* Capsules and 36 treated with placebo. At baseline and after 9 months of treatment, the bacterial samples were cultured and tested for resistance to doxycycline. The change in the mean percentage of flora resistant to doxycycline across 9 months was 5.09% in the *ORACEA* Capsules group and 5.38% in the placebo group.[26]

Fromowitz noted, "When we look at the data from clinical trials, we know that sub-antimicrobial dosing with *ORACEA* Capsules provides a similar efficacy to full-strength [dosing]. There is no reason why I would choose full-strength over sub-antimicrobial dosing, especially in light of this growing and emerging problem [with antibiotic resistance]."

Table 5. Evidence of Antibacterial Resistance Associated With *ORACEA*® (doxycycline, USP) 40 mg* Capsules in a 9-Month Study[26]

MEAN PERCENTAGE OF RECOVERED FLORA RESISTANT TO DOXYCYCLINE (4 µg/ml) FOR EACH TREATMENT				
	ORACEA Capsules		Placebo	
	MEAN (%)	SD (+/-)	MEAN (%)	SD (+/-)
Baseline	12.69	23.16	3.95	7.39
9 months	17.79	20.85	9.33	20.64
Change from baseline	5.09	31.17	5.38	22.02

*30-mg immediate-release and 10-mg delayed-release beads.

Conclusions

ORACEA Capsules provide an immediate and consistent anti-inflammatory response that is comparable with that of doxycycline 100 mg while staying below the antimicrobial threshold.[6-10] It is important to remember that rosacea is a chronic disorder that has an impact on the psychosocial well-being of patients. "The most important take-home point for me," said Fromowitz, "is to not underestimate the emotional impact that rosacea has on our patients. [We need to be] aggressive in our therapies...and thoughtful in our selection of agents." Because rosacea requires long-term therapy, a major advantage of any first-choice treatment is the absence of antibiotic activity. Choosing a rosacea therapy that achieves results equivalent to doxycycline 100 mg while staying below the antimicrobial threshold can help reduce the global concern of antibiotic resistance.[9] *ORACEA* Capsules are an effective and well-studied treatment for patients with rosacea.

Important Safety Information *ORACEA*® (doxycycline, USP) 40 mg* Capsules

Indication: *ORACEA*® (doxycycline, USP) 40 mg* Capsules are indicated for the treatment of only inflammatory lesions (papules and pustules) of rosacea in adult patients. *ORACEA* Capsules do not lessen the facial redness caused by rosacea. **Adverse Events**: In controlled clinical studies, the most commonly reported adverse events (>2%) in patients treated with *ORACEA* Capsules were nasopharyngitis, sinusitis, diarrhea, hypertension, and aspartate aminotransferase increase. **Warnings/Precautions**: *ORACEA* Capsules should not be used to treat or prevent infections. *ORACEA* Capsules should not be taken by patients who have a known hypersensitivity to doxycycline or other tetracyclines. *ORACEA* Capsules should not be taken during pregnancy, by nursing mothers, or during tooth development (up to the age of 8 years). Although photosensitivity was not observed in clinical trials, *ORACEA* Capsules patients should minimize or avoid exposure to natural or artificial sunlight. The efficacy of *ORACEA* Capsules treatment beyond 16 weeks and safety beyond 9 months have not been established.

You are encouraged to report negative side effects of prescription drugs to the FDA. Visit www.fda.gov/medwatch or call 1-800-FDA-1088.

*30-mg immediate-release and 10-mg delayed-release beads.

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