ANNEX I

LIST OF THE NAME, PHARMACEUTICAL FORM, STRENGTH OF THE MEDICINAL PRODUCT, ROUTE OF ADMINISTRATION, APPLICANT(S) IN THE MEMBER STATES

Member State	Marketing Authorisation Holder	Applicant	Invented name	Strength	Pharmaceutical Form	Route of administration
Austria		FGK Representative Service GmbH Heimeranstrasse 35 80339 München, Germany	ORACEA	40 mg	Modified-release capsule, hard	Oral
Finland		FGK Representative Service GmbH Heimeranstrasse 35 80339 München, Germany	ORACEA	40 mg	Prolonged-release capsule, hard	Oral
Germany		FGK Representative Service GmbH Heimeranstrasse 35 80339 München, Germany	ORACEA	40 mg	Prolonged-release capsule, hard	Oral
Ireland		FGK Representative Service GmbH Heimeranstrasse 35 80339 München, Germany	ORACEA[1]	40 mg	Modified-release capsule, hard	Oral
Italy		FGK Representative Service GmbH Heimeranstrasse 35 80339 München, Germany	ORACEA	40 mg	Prolonged-release capsule, hard	Oral
Luxembourg		FGK Representative Service GmbH Heimeranstrasse 35 80339 München, Germany	ORACEA	40 mg	Prolonged-release capsule, hard	Oral
Netherlands		FGK Representative Service GmbH Heimeranstrasse 35 80339 München, Germany	ORACEA[2]	40 mg	Prolonged-release capsule, hard	Oral
Sweden		FGK Representative Service GmbH Heimeranstrasse 35 80339 München, Germany	ORACEA	40 mg	Modified-release capsule, hard	Oral
United Kingdom		FGK Representative Service GmbH Heimeranstrasse 35 80339 München, Germany	ORACEA	40 mg	Prolonged-release capsule, hard	Oral

[1] Name approval pending
[2] Name approval pending

ANNEX II

SCIENTIFIC CONCLUSIONS AND GROUNDS FOR AMENDMENT OF THE SUMMARY OF PRODUCT CHARACTERISTICS, LABELLING AND PACKAGE LEAFLET PRESENTED BY THE EMEA

SCIENTIFIC CONCLUSIONS

OVERALL SUMMARY OF THE SCIENTIFIC EVALUATION OF ORACEA

Rosacea is a well-recognized chronic cutaneous disorder, often characterized by remissions and exacerbations, that primarily affects the face causing significant psychological problems in addition to the physical discomfort. Treatment of rosacea is mainly aimed at reducing the papulopustular lesions while the erythema and telangiectasia components are difficult to alleviate. The only treatments currently widely authorized in the EU are topical therapies containing metronidazole or azelaic acid, which require twice daily administration and may give rise to local adverse events such as skin irritation or worsening of rosacea. Doxycycline, generally in the dose of 100-200 mg daily, has been widely used in clinical practice for the treatment of various infectious diseases for more than 25 years, with a well documented safety profile. According to several international guidelines, doxycycline is also commonly recommended for the treatment of rosacea but is only approved in a few EU countries; consequently the off-label use of doxycycline is widely prescribed in clinical practice for long-term treatment (months to up to several years) of *acne vulgaris*, with dosages generally higher (100 mg daily) than the proposed dosage for Oracea (40 mg daily). This probably leading to a higher risk for adverse reactions, such as development of resistance in the commensal microflora. Thus, the present application for Oracea (doxycycline 40 mg tablets) is not for a New Chemical Entity but aims to develop a formulation designed for once a day oral administration that could provide steady state doxycycline plasma concentrations at the anti-inflammatory level but not at the antimicrobial level.

The procedure was referred to the CHMP, who raised a number of issues through a List of Questions and a subsequent List of Outstanding Issues, which were addressed by the Applicant.

The CHMP considered that the safety of doxycycline (100-200 mg daily) has been established over many decades of clinical use, providing re-assurance on the tolerability of the lower dose of Oracea. The clinical studies showed no treatment-related serious AEs and tolerability seems to be unaffected by gender, age or disease severity. In contrast to higher, antimicrobial doses of doxycycline that may lead to the development of resistance and opportunistic overgrowth, long-term clinical trial experience with doxycycline 40 mg/day confirms the good tolerability of doxycycline at this dose level during prolonged treatment. Post-marketing experience has not identified any new safety concerns. Overall it is estimated that, since authorization, more than 400,000 prescriptions for Oracea were filled at pharmacies in the USA up to November 2007 and the post-marketing experience identified no new safety concerns.

Regarding efficacy, the Applicant demonstrated the clinical efficacy of Oracea as monotherapy in reducing the papulo-pustular lesion count, through two Phase III double-blinded, randomized, placebo-controlled studies, including over 530 patients. Both studies showed significant superiority of Oracea compared with placebo. Since no formal dose-response studies have been conducted, Phase III data were analyzed to investigate the existence of a dose–efficacy relationship. The applicant concluded that higher mg/kg doses led to higher plasma concentrations, but did not lead to increased clinical efficacy and that anti-inflammatory–dose doxycycline (40-mg formulation) conferred peak anti-inflammatory efficacy in the treatment of rosacea. In addition, the preliminary results of a study comparing Oracea (40 mg doxycycline) to 100 mg doxycycline daily, both in conjunction with topical metronidazole, support the non-inferiority hypothesis of the Oracea dosing regimen. Provided that the proposed indication mirrors the primary endpoint in the pivotal studies, as currently suggested, the CHMP considered that efficacy could be regarded as sufficiently demonstrated in the presently studied populations in the submitted phase 3 studies.

The Applicant addressed the concern that no comparator study was provided by arguing that a controlled clinical trial using an active comparator such as systemic doxycycline was not required, as the development program was in line with a number of ICH guidelines CPMP/ICH/291/95 and CPMP/ICH/135/95 which do not require an active comparator and with the E10 Guidance for the choice of control group in clinical trials (CPMP/ICH/364/96), which supports the use of a placebo control group as the most appropriate design where ethically and practically feasible. The Applicant

considered that studies against other active treatments were not practical or warranted, in the case of Oracea. In addition, there is a lack of well-characterized comparator as very few EU countries have the indication rosacea approved for doxycycline (100 mg daily), which would present additional challenges studying two unapproved drugs (100 mg doxycycline and Oracea) in one clinical trial. However, studies were conducted to evaluate the efficacy and safety of Oracea in conjunction to active treatment such as metronidazole, showing that Oracea, given as an adjunct to metronidazole, is far superior to metronidazole alone and that no difference in efficacy was found between low and high doses of doxycycline. The CHMP agreed with the ICH guidelines, stating that an active comparator is not required if it is considered ethically and practically feasible to use placebo in the control group. The indication rosacea as defined by the study inclusion criteria was regarded to fulfil these criteria. Consequently, the CHMP considered the clinical efficacy of Oracea to be sufficiently demonstrated in the two placebo-controlled phase 3 studies and the issue to be resolved.

Regarding the risk of resistance induction, the Applicant provided data from several studies demonstrating that the 100 mg doxycycline dose leads to marked emergence of resistant strains in the oral and intestinal micro flora. Six studies addressed the emergence issue in low dose doxycycline (40 mg daily), focusing on the effects on the intestinal microflora, on subgingival microflora and saliva and on the skin flora. A double-blind, placebo controlled study by Walker et al, 2005 studying the effect of 20 mg doxycycline bid did not show any statistically significant differences between the active group and the placebo group in terms of emergence of doxycycline- or multidrug-resistant bacteria in faecal or vaginal samples. With regard to target site exposure of bacteria to doxycycline, the Applicant referred to several publications stating that the resulting concentrations of antibacterially-active drug will be very low, leading to a very low risk of resistance pressure. Following the administration of the 40 mg modified release formulation of doxycycline, the maximum excreted concentrations of doxycycline will be between 0.03 – 0.16 mg/L for all excretion mechanisms. The binding of doxycycline to plasma proteins, epidermal tissue and faeces must be taken into account as only the free fraction (10%) of doxycycline is antibacterially active following the oral administration of 40 mg doxycycline. The Applicant also presented data from six placebo-controlled studies conducted in over 400 patients, showing no evidence of increase in resistance of the microbiological flora of the gastrointestinal tract (faeces), vagina, skin, saliva or dental plaque after long-term treatment with doxycycline 40 mg/day for 6 to 18 months, which is in line with pharmacokinetic investigations on target site exposure. Based on these findings it is scientifically reasonable to conclude that the effect of low dose doxycycline on the normal residential flora including *E coli*, Enterococci, Staphylococci and Streptococci to be almost non-existent and concluded that the risk of inducing resistance development is negligible.

The CHMP acknowledges that available studies and pharmacokinetic data indicate that Oracea (40 mg doxycycline daily) is less likely to induce resistance in the normal micro biota than 100 mg doxycycline daily, and thus does not consider this issue to be a major objection that should preclude an approval of the product. However, increased knowledge of the ecological effects of long-term administration of low-dose doxycycline is highly desirable, and the Applicant is requested to commit to submitting a study protocol for a well designed post-marketing clinical study investigating emergence of resistance in relevant bacterial groups in the intestinal and upper respiratory tract for validation and to carry out a study accordingly within 3 months of approval. The data resulting from this study should be provided to the relevant national competent authorities for assessment. The Applicant was also requested to reflect information on this issue in sections 4.4 and 5.1 of the SPC.

Finally, the CHMP also acknowledged the difficulty in breaking down the different subgroups of rosacea since symptoms often overlap between the different subtypes and recognised that Oracea is aimed towards the treatment of papules and pustules rather than treatment of rosacea as a whole or treatment of a specific subtype. The CHMP was also satisfied with the explanation on the exclusion criteria of nodule numbers, as no effect on nodules is claimed in the proposed indication. Regarding erythema, the CHMP considered that despite the absence of evidence of a positive effect on erythema, there are no indications of any risk of worsening of erythema during Oracea therapy. Furthermore, the CHMP was of the opinion that although the efficacy of doxycycline 40mg daily has not been demonstrated in patients with ocular rosacea, the literature data combined with the results from the

two placebo-controlled studies submitted indicated no specific safety concerns in this subgroup. The CHMP proposed the amendment of section 4.4 of the SPC, in order to minimise the risk for withholding treatment from patients with ocular rosacea. The CHMP also considered that the survey referred to by the Applicant, showing that papulopustular lesions are readily recognized and rated by dermatologists providing a qualitative as well as quantitative measurement, was relevant; therefore the currently proposed indication was considered clinically applicable and practical.

In conclusion, the CHMP considers the efficacy of Oracea to reduce papulopustular lesions in adult patients with facial rosacea to be sufficiently demonstrated. The extensive clinical experience of long-term treatment with doxycycline at higher dosages (100-200 mg daily) and the fact that all Phase 3 studies indicate that Oracea is well tolerated and demonstrates a safety profile comparable to placebo was considered reassuring. However, the studies submitted concerning the absence of risk for selection of antibiotic resistance in the normal microbiota were not considered as fully convincing, due to limitations in the methods used. Consequently, the CHMP required a commitment from the Applicant to perform an appropriate post-marketing study in order to further elucidate the risk for emergence of resistance in the intestinal and upper respiratory microflora associated with the long-term use of Oracea. The scope, design and endpoints of the study should be in line with similar trials published in the literature and the study protocol should be validated by and submitted to the National Competent Authority of the Reference Member State within three months of approval. The Applicant should complete this study and file a report within a reasonable period of time (e.g. 2 years) from the date of approval. The Applicant was also requested to revise the SPC for Oracea, in sections 4.4 and 5.1 due to the lack of experience in patients with ocular rosacea, as seen in the adopted revised Product Information.

In assessing the benefit/risk of Oracea, the current situation of limited treatment options for rosacea was taken into consideration, as well as the fact that Oracea is expected to provide an alternative to the international guidelines recommending off-label use of doxycycline (or other tetracycline derivates) for the treatment of rosacea, with the associated decrease in risk for adverse events. Thus, the CHMP considers that the benefits of marketing a systemic drug such as Oracea in the present indication outweighs the risk for potential harmful effects related to resistance development and therefore consider the benefit-risk ratio to be positive.

GROUNDS FOR AMENDMENT OF THE SUMMARY OF PRODUCT CHARACTERISTICS, LABELLING AND PACKAGE LEAFLET

Whereas

- The CHMP considers the efficacy of Oracea to reduce papulopustular lesions in adult patients with facial rosacea to be sufficiently demonstrated,

- The CHMP considers that Oracea is well tolerated and is satisfied with the safety profile when in conjunction with the commitment to carry out a post-marketing study as set out in Annex IV and the revision of the Summary of Product Characteristics as set out in Annex III,

- The CHMP considers that the benefits of marketing a systemic drug such as Oracea in the present indication outweigh the risk for potential harmful effects related to resistance development and therefore considers the benefit-risk ratio to be positive,

the CHMP has recommended the granting of the Marketing Authorisations for which the Summary of Product Characteristics, labelling and package leaflet are set out in Annex III for Oracea. The conditions of the Marketing Authorisation are set out in Annex IV.

ANNEX III

SUMMARY OF PRODUCT CHARACTERISTICS, LABELLING AND PACKAGE LEAFLET

A. SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

ORACEA 40 mg modified-release hard capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 40 mg doxycycline (as monohydrate).

Excipient: Each hard capsule contains 102 – 150 mg of sucrose.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Modified-release hard capsule

Beige capsule, No. 2 size, bear the marking "CGPI 40".

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

ORACEA is indicated to reduce papulopustular lesions in adult patients with facial rosacea.

4.2 Posology and method of administration

Adults, including the elderly:

The daily dose is 40 mg (1 capsule). The capsule should be taken in the morning with adequate amounts of water in order to reduce the risk of oesophageal irritation and ulceration (see section 4.4).

Patients should be evaluated after 6 weeks and, if no effect is seen, consideration should be given to stopping treatment. In clinical trials patients were treated for 16 weeks. Upon discontinuation, lesions tended to reappear at 4 weeks follow-up. Therefore it is recommended that patients should be assessed 4 weeks after stopping treatment.

Renal impairment

No dosage adjustment is necessary in patients with renal impairment.

Hepatic impairment
ORACEA should be administered with caution to patients with hepatic impairment or to those receiving potentially hepatotoxic medicinal products (see section 4.4)

Children and adolescents

Doxycycline is contraindicated in children below age 12 (see section 4.3).

4.3 Contraindications

Hypersensitivity to the active substance, to other tetracyclines or to any of the excipients.

Infants and children up to 12 years of age.

Second and third trimesters of pregnancy (see section 4.6).

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.

4.4 Special warnings and precautions for use

ORACEA contains doxycycline in a formulation designed to yield plasma levels below the antimicrobial threshold. ORACEA must not be used to treat infections caused by organisms susceptible (or suspected to be susceptible) to doxycycline.

Solid dosage forms of the tetracyclines may cause oesophageal irritation and ulceration. To avoid oesophageal irritation and ulceration, adequate fluids (water) should be taken with this medicinal product (see section 4.2). ORACEA should be swallowed whilst in an upright sitting or standing posture.

Whilst no overgrowth by opportunistic microorganisms such as yeasts were noted during the clinical studies with ORACEA, therapy with tetracyclines at higher doses may result in overgrowth of non-susceptible microorganisms including fungi. Although not observed in clinical trials with ORACEA, the use of tetracyclines at higher doses may increase the incidence of vaginal candidiasis. ORACEA should be used with caution in patients with a history of predisposition to candidiasis overgrowth. If superinfection is suspected, appropriate measures should be taken, including consideration of discontinuing ORACEA.

Treatment with higher doses of tetracyclines is associated with emergence of resistant intestinal bacteria, such as enterococci and enterobacteria. Although not observed during clinical studies with low dose doxycycline (40 mg/day), the risk for development of resistance in the normal microflora cannot be excluded in patients treated with ORACEA.

Doxycycline blood levels in patients treated with ORACEA are lower than in those treated with conventional antimicrobial formulations of doxycycline. However, as there are no data to support safety in hepatic impairment at this lower dose, ORACEA should be administered with caution to patients with hepatic impairment or to those receiving potentially hepatotoxic medicinal products. The antianabolic action of tetracyclines may cause an increase in BUN. Studies to date indicate that this does not occur with the use of doxycycline in patients with impaired renal function.

Caution should be observed in the treatment of patients with myasthenia gravis who may be at risk of worsening of the condition.

All patients receiving doxycycline, including ORACEA, should be advised to avoid excessive sunlight or artificial ultraviolet light whilst 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.

In common with the use of antimicrobial medicinal products in general, there is a risk of the development of pseudomembranous colitis with doxycycline treatment. In the event of the development of diarrhoea during treatment with ORACEA, the possibility of pseudomembranous colitis should be considered and appropriate therapy instituted. This may include the discontinuation

of doxycycline and the institution of specific antibiotic therapy. Agents inhibiting peristalsis should not be employed in this situation.

ORACEA should not be used in patients with ocular manifestations of rosacea (such as ocular rosacea and/or blepharitis/meibomianitis) as there are limited efficacy and safety data in this population. If these manifestations appear during the course of the treatment Oracea should be discontinued and the patient should be referred to an ophthalmologist.

In humans, the use of tetracyclines during tooth development may cause permanent discolouration of the teeth (yellow-grey-brown). This reaction is more common during long-term use of the medicinal product but has been observed following repeated short-term courses. Enamel hypoplasia has also been reported. As for other tetracyclines, doxycycline forms a stable calcium complex in any bone-forming tissue. A decrease in fibula growth has been observed in premature infants given oral tetracycline in doses of 25 mg/kg every 6 hours. This reaction was shown to be reversible when the medicinal product was discontinued.

In the event of a severe acute hypersensitivity reaction (eg anaphylaxis), treatment with ORACEA must be stopped at once and the usual emergency measures taken (eg administration of antihistamines, corticosteroids, sympathomimetics and, if necessary, artificial respiration).

Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicinal product.

4.5 Interaction with other medicinal products and other forms of interaction

The recommendations below regarding the potential interactions between doxycycline and other medicinal products are based upon experience with the larger doses generally used in antimicrobial formulations of doxycycline rather than with ORACEA. However, at the present time, insufficient data exist for reassurance that the interactions described with higher doses of doxycycline will not occur with ORACEA.

Interactions affecting doxycycline:

The absorption of doxycycline from the gastro-intestinal tract may be inhibited by bi- or tri-valent ions such as aluminium, zinc, calcium (found for example in milk, dairy products and calcium-containing fruit juices), by magnesium (found for example in antacids) or by iron preparations, activated charcoal, cholestyramine, bismuth chelates and sucralfate. Therefore such medicinal products or foodstuffs should be taken after a period of 2 to 3 hours following ingestion of doxycycline.

Medicinal products which increase gastric pH may reduce the absorption of doxycycline, and should be taken at least 2 hours after doxycycline.

Quinapril may reduce the absorption of doxycycline due to the high magnesium content in quinapril tablets.

Rifampicin, barbiturates, carbamazepine, diphenylhydantoin, primidone, phenytoin and chronic alcohol abuse may accelerate the decomposition of doxycycline due to enzyme induction in the liver thereby decreasing its half-life. Sub-therapeutic doxycycline concentrations may result.

Concurrent use of cyclosporin has been reported to decrease the half-life of doxycycline.

Interactions affecting other medicinal products:

Concomitant use not recommended:

When doxycycline is administered shortly before, during or after courses of isotretinoin, there is the possibility of potentiation between the medicinal products to cause reversible pressure increase in the intracranial cavity (pseudotumour cerebri). Concomitant administration should therefore be avoided.

Bacteriostatic medicinal products including doxycycline may interfere with the bacteriocidal action of penicillin and beta-lactam antibiotics. It is advisable that doxycycline and beta-lactam antibiotics should not therefore be used in combination.

Other interactions:

Tetracyclines and methoxyflurane used in combination have been reported to result in fatal renal toxicity.

Doxycycline has been shown to potentiate the hypoglycaemic effect of sulphonylurea oral antidiabetic agents. If administered in combination with these medicinal products, blood glucose levels should be monitored and, if necessary, the doses of the sulphonylureas should be reduced.

Doxycycline has been shown to depress plasma prothrombin activity thereby potentiating the effect of anticoagulants of the dicoumarol type. If administered in combination with these agents, coagulation parameters including INR should be monitored and, if necessary, the doses of the anticoagulant medicinal products reduced. The possibility of an increased risk of bleeding events should be borne in mind.

Tetracyclines used concurrently with oral contraceptives have in a few cases resulted in either breakthrough bleeding or pregnancy.

4.6 Pregnancy and lactation

Studies in animals have not demonstrated a teratogenic effect. In humans, the use of tetracyclines during a limited number of pregnancies has not revealed any specific malformation to date.

The administration of tetracyclines during the second and the third trimesters results in permanent discolouration of the deciduous teeth in the offspring. As a consequence, doxycycline is contraindicated during the second and third trimesters of pregnancy (see section 4.3).

Low levels of tetracyclines are secreted into the milk of lactating women. Doxycycline can be used by breast-feeding mothers for short term use only. Long term use of doxycycline may result in significant absorption by the suckling infant and is therefore not recommended because of a theoretical risk of dental discolouration and decreased bone growth of the suckling child.

4.7 Effects on ability to drive and use machines

Doxycycline has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

In the pivotal placebo-controlled studies with ORACEA in rosacea, 269 patients were treated with ORACEA 40 mg once daily and 268 patients were treated with placebo for 16 weeks. Gastrointestinal adverse reactions overall occurred in a higher proportion of patients on ORACEA (13.4%) than on placebo (8.6%). The most commonly reported adverse reactions in patients treated with ORACEA, ie those which occurred with ≥ 3% frequency on ORACEA and with a frequency at least 1% higher than on placebo, were nasopharyngitis, diarrhoea and hypertension.

The table below lists adverse reactions on ORACEA in the pivotal clinical trials, ie adverse reactions for which the frequency on ORACEA was greater than the frequency on placebo (by ≥ 1%).

Adverse reactions reported for tetracycline antibiotics as a class are listed following the table. The frequency categories used are:
Common: ≥ 1/100 to < 1/10
Uncommon: ≥ 1/1,000 to < 1/100
Rare: ≥ 1/10,000 to < 1/1,000
Very rare: < 1/10,000

Adverse reactions[a] on ORACEA in pivotal placebo-controlled studies in rosacea:

MedDRA system organ class	Common: Frequency ≥ 1/100, < 1/10
Infections and infestations	Nasopharyngitis Sinusitis Fungal infection
Psychiatric disorders	Anxiety
Nervous system disorders	Sinus headache
Vascular disorders	Hypertension
Gastrointestinal disorders	Diarrhoea Abdominal pain, upper Dry mouth
Musculoskeletal, connective tissue and bone disorders	Back pain
General disorders and administration site conditions	Pain
Investigations	ASAT increased Blood pressure increased Blood LDH increased Blood glucose increased

[a] Defined as adverse events for which the frequency on ORACEA was higher than on placebo (by at least 1%)

The following adverse reactions have been observed in patients receiving tetracyclines:-

Infections and infestations:
Very rare: Anogenital candidiasis

Blood and lymphatic system disorders:
Rare: Thrombocytopenia, neutropenia, eosinophilia
Very rare: Haemolytic anaemia

Immune system disorders:
Rare: Hypersensitivity reactions including anaphylaxis
There have also been reports of: Anaphylactoid purpura

Endocrine disorders:
Very rare: Brown-black microscopic discolouration of thyroid tissue has been reported with long-term use of tetracyclines. Thyroid function is normal.

Nervous system disorders:
Rare: Benign intracranial hypertension
Very rare: Bulging fontanelle in infants
Treatment should cease if evidence of raised intracranial pressure develops. These conditions disappeared rapidly when the drug was discontinued.

Cardiac disorders:
Rare: Pericarditis

Gastrointestinal disorders:
Rare: Nausea, vomiting, diarrhoea, anorexia
Very rare: Glossitis, dysphagia, enterocolitis. Oesophagitis and oesophageal ulceration have been reported most often in patients administered the hyclate salt in capsule form. Most of these patients took medication just prior to going to bed.

Hepatobiliary disorders:
Rare: Hepatotoxicity

Skin and subcutaneous tissue disorders:
Rare: Maculopapular and erythematous rashes, skin photosensitivity, urticaria
Very rare: Exfoliative dermatitis, angioneurotic oedema

Musculoskeletal, connective tissue and bone disorders:
Very rare: Exacerbation of systemic lupus erythematosus

Renal and urinary disorders:
Rare: Increased blood urea.

Adverse reactions typical of the tetracycline class of medicinal products are less likely to occur during medication with ORACEA, due to the reduced dosage and the relatively low plasma levels involved. However, the clinician should always be aware of the possibility of adverse events occurring and should monitor patients accordingly.

4.9 Overdose

Symptoms:

To date no significant acute toxicity has been described in the case of a single oral intake of a multiple of therapeutic doses of doxycycline. In case of overdose there is, however, a risk of parenchymatous hepatic and renal damage and of pancreatitis.

Treatment:

The usual dose of ORACEA is less than half the usual doses of doxycycline used for antimicrobial therapy. Therefore clinicians should bear in mind that in many cases overdose is likely to produce blood concentrations of doxycycline within the therapeutic range for antimicrobial treatment, for which there is a large quantity of data supporting the safety of the medicinal product. In these cases observation is recommended. In cases of significant overdose, doxycycline therapy should be stopped immediately and symptomatic measures undertaken as required.

Intestinal absorption of unabsorbed doxycycline should be minimised by administering magnesium or calcium salt-containing antacids to produce non-absorbable chelate complexes with doxycycline. Gastric lavage should be considered.

Dialysis does not alter serum doxycycline half-life and thus would not be of benefit in treating cases of overdose.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antibacterials for systemic use, Tetracyclines. ATC code: J01AA02.

Mechanism of Action: The pathophysiology of the inflammatory le*sions of rosacea is, in part, a* manifestation of a neutrophil-mediated process. Doxycycline has been shown to inhibit neutrophil activity and several pro-inflammatory reactions including those associated with phospholipase A_2, endogenous nitric oxide and interleukin-6. The clinical significance of these findings is not known.

The plasma concentration of doxycycline following administration of ORACEA is well below the level required to inhibit mircoorganisms commonly associated with bacterial diseases.

In vivo microbiological studies using similar exposure to the active substance for 6 to 18 months could not demonstrate any effect on the dominating bacterial flora sampled from the oral cavity, skin, intestinal tract and vagina. However, it can not 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 has been evaluated in two pivotal randomised, double-blind, placebo-controlled, 16-week studies in 537 patients with rosacea (10 to 40 papules and pustules, and two or fewer nodules). In both studies, the mean reduction in the total inflammatory lesion count was significantly greater in the ORACEA group than in the placebo group:

Mean change from baseline to Week 16 in total inflammatory lesion count:

	Study 1		Study 2	
	ORACEA 40 mg (N = 127)	Placebo (N = 124)	ORACEA 40 mg (N = 142)	Placebo (N = 144)
Mean (SD) change from baseline	-11.8 (9.8)	-5.9 (13.9)	-9.5 (9.6)	-4.3 (11.6)
Mean between-group difference (95% confidence limits)	-5.9 (-8.9, -2.9)		-5.2 (-7.7, -2.7)	
p-Value[a]	0.0001		< 0.0001	

[a] p-Value for treatment difference in change from baseline (ANOVA)

5.2 Pharmacokinetic properties

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 at 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%.

Distribution, metabolism and elimination:

Doxycycline is greater than 90% bound to plasma proteins and has an apparent volume of distribution of 50 L. Major metabolic pathways of doxycycline have not been identified but enzyme inducers decrease the half-life of doxycycline.

Doxycycline is excreted in the urine and faeces 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 faeces. The terminal elimination half-life of doxycycline after administration of ORACEA was approximately 21 h after a single dose and approximately 23 h at steady state.

Pharmacokinetics in special populations:

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 haemodialysis.

There is no information on the pharmacokinetics of doxycycline in patients with hepatic impairment.

5.3 Preclinical safety data

Adverse reactions seen in repeat dose studies in animals include hyperpigmentation of the thyroid and tubular degeneration in the kidney. These effects were seen at exposure levels of 1.5 to 2 times those seen in humans administered ORACEA at the proposed dose. The clinical relevance of these findings remains unknown.

Doxycycline showed no mutagenic activity and no convincing evidence of clastogenic activity. In a rat carcinogenicity study increases in benign tumours of the mammary gland (fibroadenoma), uterus (polyp) and thyroid (C-cell adenoma) were noted in females.

In rats, doses of 50 mg/kg/day doxycycline caused a decrease in the straight-line velocity of sperm but did not affect male or female fertility or sperm morphology. At this dose systemic exposure experienced by rats is likely to have been approximately 4 times that seen in humans taking the recommended dose of ORACEA. At doses greater than 50 mg/kg/day fertility and reproductive performance were adversely affected in rats. A peri/postnatal toxicity study in rats revealed no significant effects at therapeutically relevant doses. Doxycycline is known to cross the placenta and literature data indicate that tetracyclines can have toxic effects on the developing fetus.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule shell
Gelatin
Black iron oxide
Red iron oxide
Yellow iron oxide
Titanium dioxide

Printing inks
Shellac
Propylene glycol
Black iron oxide
Indigo Carmine aluminium lake
Allura Red AC aluminium lake
Brilliant Blue FCF aluminium lake
D & C Yellow No. 10 aluminium lake
Opacode Black S-1-8115
Opacode Black S-1-8114

Capsule contents

Hypromellose
Methacrylic acid-ethyl acrylate copolymer (1:1)
Triethyl citrate
Talc
Opadry beige YS-1-17274-A (Hypromellose 3cP/6cP, Titanium dioxide, Macrogol 400, Yellow iron oxide, Red iron oxide, Polysorbate 80)
Sugar spheres (Maize starch, Sucrose)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

6.4 Special precautions for storage

Store in the original package in order to protect from light.

6.5 Nature and contents of container

Aluminium/PVC/Aclar blister

Pack size: 56 capsules in 4 strips of 14 each

6.6 Special precautions for disposal

No special requirements

7. MARKETING AUTHORISATION HOLDER

[See Annex I - To be completed nationally]

{Name and address}
<{tel}>
<{fax}>
<{e-mail}>

8. MARKETING AUTHORISATION NUMBERS

[To be completed nationally]

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

[To be completed nationally]

10. DATE OF REVISION OF THE TEXT

[To be completed nationally]

B. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

ORACEA 40 mg modified-release hard capsules
doxycycline

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each capsule contains 40 mg doxycycline (as monohydrate).

3. LIST OF EXCIPIENTS

Contains also sucrose
See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

56 modified-release hard capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Swallow whole, do not crush or chew. Take with water.

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in the original package in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

[See Annex I - To be completed nationally]

{Name and address}
<{tel}>
<{fax}>
<{e-mail}>

12. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

13. BATCH NUMBER

Batch No.:

14. GENERAL CLASSIFICATION FOR SUPPLY

[To be completed nationally]

15. INSTRUCTIONS ON USE

[To be completed nationally]

16. INFORMATION IN BRAILLE

[To be completed nationally]

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

ALUMINIUM/PVC/ACLAR BLISTER

1. NAME OF THE MEDICINAL PRODUCT

ORACEA 40 mg modified-release hard capsules
doxycycline

2. NAME OF THE MARKETING AUTHORISATION HOLDER

[See Annex I - To be completed nationally]

3. EXPIRY DATE

EXP:

4. BATCH NUMBER

Batch No..

5. OTHER

Store in the original package in order to protect from light.

C. PACKAGE LEAFLET

PACKAGE LEAFLET: INFORMATION FOR THE USER

ORACEA 40 mg modified release hard capsules
Doxycycline

Read all of this leaflet carefully before you start taking this medicine.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:

1. WHAT ORACEA IS AND WHAT IT IS USED FOR

ORACEA is a medicine for use in adults to reduce the pimples or red bumps on the face caused by a condition called rosacea.

2. BEFORE YOU TAKE ORACEA

Do not take ORACEA
- if you are allergic (hypersensitive) to any medicinal product in the tetracycline family, including doxycycline or minocycline, or to any of the other ingredients of ORACEA (see section 6.)
- if you are pregnant ORACEA should not be used from the 4th month of because it may harm the unborn child. If you suspect or learn that you are pregnant whilst taking ORACEA, contact your doctor immediately.
- if you have a condition causing absence of acid in the stomach (achlorhydria) or if you have had surgery on the upper part of the gut (called the duodenum).

ORACEA must not be taken by infants or children under the age of 12, because it may cause permanent discolouration of the teeth or problems with tooth development.

Take special care with ORACEA
Inform your physician
- **if you have liver disease**
- **if you have a history of predisposition to candidiasis overgrowth or are currently experiencing an oral or vaginal yeast or fungal infection**
- **if you suffer from the muscle disease called myasthenia gravis**
- **if you suffer from colitis**
- **if you suffer from oesophageal irritation or ulceration**
- **if you have the type of rosacea which affects the eyes**
- **if you expose your skin to strong sunlight or artificial sunlight, because more severe sunburn may occur in some people taking doxycycline. You should consider using a sunscreen or sunblock to reduce the risk of sunburn and you should stop using ORACEA if your skin becomes sunburned.**

Taking other medicines
Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

ORACEA and certain other medications may not work properly when taken together. Tell your doctor about medications that you are taking or plan to take whilst you are taking ORACEA .

- ORACEA should not be used at the same time as the medicine isotretinoin because of the risk of increased pressure in the brain. Isotretinoin is prescribed to patients with a severe case of acne.
- Do not take antacids**,** multi-vitamins or other products that contain calcium (such as milk and dairy products and calcium-containing fruit juices), aluminium, magnesium (including quinapril tablets, which are taken for high blood pressure), iron or bismuth, or cholestyramine, activated charcoal or sucralfate until 2 to 3 hours after taking ORACEA. These medicines may reduce the effectiveness of ORACEA if taken at the same time.
- Other treatments for ulcers or heartburn may also reduce the effectiveness of ORACEA and should not be taken until at least 2 hours after ORACEA.
- If you are taking blood thinners, your doctor may need to make changes to the dose of your blood thinner.
- If you are taking certain treatments for diabetes, your doctor may need to check whether the dose of the diabetes treatment has to be changed.
- There is a possibility that ORACEA reduces the effectiveness of oral contraceptives, resulting in pregnancy.
- ORACEA may make certain antibiotics, including penicillins, less effective.
- Taking barbiturates (sleeping pills or short-term pain-killers), rifampicin (tuberculosis), carbamazepine (epilepsy), diphenylhydantoin and phenytoin (seizures of the brain), primidone (anti-convulsant) or cyclosporin (organ transplant) may reduce the time that ORACEA stays active in your system.
- Using ORACEA with the general anaesthetic methoxyfluorane may cause serious harm to the kidneys.

Taking ORACEA with food and drink
Always take ORACEA with an adequate amount of water to wash down the capsule, since this reduces the risk of irritation or ulcer in the throat or gullet.

Do not take milk or dairy products at the same time as ORACEA since these products contain calcium which may reduce the effectiveness of ORACEA. Leave 2 to 3 hours after your daily dose of ORACEA before drinking or eating dairy products.

Pregnancy and breast-feeding
ORACEA must not be used ***during pregnancy since it may cause permanent discolouration of the teeth in the unborn child.***

ORACEA should not be used for long periods by breastfeeding mothers since it may cause tooth discolouration and reduced bone growth in the suckling child.

Ask your doctor or pharmacist for advice before taking any medicine.

Driving and using machines
ORACEA has no or negligible influence on the ability to drive and use machines.

Important information about some of the ingredients of ORACEA
ORACEA contains sugar (sucrose). If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicine.

3. HOW TO TAKE ORACEA

Always take ORACEA exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.

You should take one capsule ORACEA each day in the morning. Swallow the capsule whole and do not chew it.
You should take ORACEA with a full glass of water whilst sitting or standing to avoid any irritation to the throat.

If you take more ORACEA than you should
If you take an overdose of ORACEA, there is a risk of damage to the liver, kidneys or pancreas.

If you take more ORACEA capsules than you should, ask your doctor immediately for advice.

If you forget to take ORACEA
Do not take a double dose to make up for a forgotten capsule.

If you stop taking ORACEA
You should continue to take ORACEA until your doctor tells you to stop.

If you have any further questions on the use of this product, ask your doctor or pharmacist.

4. POSSIBLE SIDE EFFECTS

Like all medicines, ORACEA can cause side effects, although not everybody gets them.

Common side effects
The following side effects may occur commonly (affects 1 to 10 users in 100) during treatment with ORACEA:

- Inflammation of the nose and throat
- Inflammation of the sinuses
- Fungal infection
- Anxiety
- Sinus headache
- High or increased blood pressure
- Diarrhoea
- Pain in the upper part of the abdomen
- Dry mouth
- Back pain
- Pain
- Changes in some blood tests (amount of glucose in blood or tests of liver function).

Rare side effects
The following side effects may occur rarely (affects 1 to 10 users in 10,000) during treatment with the class of medicines to which ORACEA belongs (the tetracyclines):

- Allergic (hypersensitivity) reaction throughout the body*
- Changes in the number or type of certain blood cells
- Increased pressure in the brain

- Inflammation of the membrane surrounding the heart
- Nausea, vomiting, anorexia
- Liver damage
- Skin rashes or hives
- Abnormal reaction of the skin to sunlight
- Increased level of urea in the blood

Very rare side effects
The following side effects may occur very rarely (affects less than 1 user in 10,000) during treatment with the class of medicines to which ORACEA belongs (the tetracyclines):

- Allergic reaction causing swelling of the eyes, lips or tongue*
- Yeast infection around the anus or genitals
- Damage to red blood cells (haemolytic anaemia)
- Inflammation of the tongue
- Difficulty in swallowing
- Inflammation of the intestine
- Inflammation or ulceration of the gullet
- Inflammation of the skin causing flakiness
- Worsening of the immune system disease known as systemic lupus erythematosus (SLE)

* Tell your doctor immediately or go to casualty if you suffer side effects such as swollen face, lips, tongue and throat, difficulty in breathing, hives or itchy skin and eyes, or rapid heart beat (palpitations) and feeling faint. These effects may be symptoms of a severe allergic (hypersensitivity) reaction.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. HOW TO STORE ORACEA

Keep out of the reach and sight of children.

Do not use ORACEA after the expiry date which is stated on the outer pack and blister after Batch No. The expiry date refers to the last day of that month.

Store in the original package in order to protect from light.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What ORACEA contains

The active substance is doxycycline. Each capsule contains 40 mg doxycycline (as monohydrate).

The other ingredients are:
Hypromellose[piq-qrd1], methacrylic acid-ethyl acrylate copolymer (1:1), triethyl citrate, talc, Opadry beige YS-1-17274-A (hypromellose 3cP/6cP, titanium dioxide, macrogol 400, yellow iron oxide, red iron oxide, polysorbate 80), sugar spheres (maize starch, sucrose).
Capsules: gelatin, black iron oxide, red iron oxide, yellow iron oxide, titanium dioxide

Printing ink: shellac, propylene glycol, black iron oxide, indigo carmine aluminium lake, allura red AC aluminium lake, brilliant blue FCF aluminium lake, D & C yellow no. 10 aluminium lake, Opacode black S-1-8115, Opacode black S-1-8114.

What ORACEA looks like and contents of the pack
ORACEA is a modified-release hard capsule.
The capsules are beige in colour and bear the marking “CGPI 40”.
Each pack contains 56 capsules.

Marketing Authorisation Holder and Manufacturer

[See Annex I - To be completed nationally]

{Name and address}
<{tel}>
<{fax}>
<{e-mail}>

The manufacturer responsible for batch release is:

Cardinal Health UK 417 Ltd, Great Oakley, Corby, Northamptonshire NN18 8HS, UK.

This medicinal product is authorised in the Member States of the EEA under the following names:
SE - ORACEA 40 mg modified release hard capsules
UK - ORACEA 40 mg modified release hard capsules
DE - ORACEA 40 mg modified release hard capsules
IE - ORACEA 40 mg modified release hard capsules
AT - ORACEA 40 mg modified release hard capsules
FI - ORACEA 40 mg modified release hard capsules
LU - ORACEA 40 mg modified release hard capsules
NL - ORACEA 40 mg modified release hard capsules
IT - ORACEA 40 mg modified release hard capsules

This leaflet was last approved in

ANNEX IV

CONDITIONS OF THE MARKETING AUTHORISATION(S)

The National Competent Authorities, coordinated by the Reference Member State, shall ensure that the following conditions are fulfilled by the Marketing Authorisation Holders:

The Applicant should conduct a post-marketing microbiological study in order to further elucidate the risk for emergence of resistance in the intestinal and upper respiratory microflora associated with the long-term use of Oracea, and commit to submitting a study protocol within 3 months of approval. The scope, design and end-points should be in line with similar trials published in the literature. The Applicant should further agree to complete this study and file a report within a reasonable period of time (e.g. 2 years) from the date of approval.