



Australian Government

Department of Health and Ageing
Therapeutic Goods Administration

Australian Public Assessment Report for Doxycycline monohydrate

Proprietary Product Name: Oracea

Sponsor: Galderma Australia Pty Ltd

June 2013

TGA Health Safety
Regulation

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- An AusPAR is a static document, in that it will provide information that relates to a submission at a particular point in time.
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List of abbreviations used in this AusPAR

Abbreviation	Meaning
AAN	Australian approved name
AE	Adverse event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
BMI	Body mass index
CEA	Clinician's Erythema Assessment
CER	Clinical evaluation report
COPD	Chronic obstructive pulmonary disease
CSR	Clinical study report
GCP	Good clinical (research) practice
GGT	Gamma glutamyl transferase
HPLC	High performance liquid chromatography
IGA	Investigator's Global Assessment
ITT	Intention to treat
LC-MS/MS	Liquid chromatography–tandem mass spectrometry
LLQ	Lower limit of quantitation
LSM	Geometric least square mean
PI	Product information
PK	Pharmacokinetic

Abbreviation	Meaning
PP	Per protocol
SAE	Serious adverse event
SOC	System organ class
SRP	Scaling and root planing
TIL	Total inflammatory lesions (papules + pustules + nodules)

I. Introduction to product submission

Submission details

Type of Submission: Extension of indications and New presentation

Decision: Rejected

Date of Decision: 10 May 2012

Active ingredient: Doxycycline monohydrate

Product Name: Oracea

Sponsor's Name: Galderma Australia Pty Ltd
138 Narabang Way
Belrose NSW 2085

Dose form: Modified release capsules

Strength: 40 mg

Container: Blister pack

Pack sizes: 28 and 56 capsules

Approved Therapeutic use: Not applicable

Route of administration: Oral

Dosage: 40 mg once daily

ARTG Number: Not applicable

Product background

Doxycycline is a tetracycline antimicrobial agent which is currently registered in Australia by several sponsors for the treatment of various infectious diseases and the treatment of severe acne, including Mayne Pharma's *Doryx* capsules and Pfizer's *Vibramycin* tablets. All registered formulations are immediate release (IR) tablets or capsules which are available in 50 and 100 mg strengths, containing either doxycycline hydrochloride or doxycycline monohydrate.

The current application seeks approval for a new presentation of doxycycline monohydrate (40 mg modified release capsule) for a new indication

To reduce papulopustular lesions in adult patients with facial rosacea.

The proposed dose is 40 mg once daily.

Doxycycline immediate release products are currently used 'off-label' for the treatment of rosacea. Typical recommended doses are 50 – 100 mg per day.^{1,2} The mechanism of action of doxycycline in rosacea is thought to be unrelated to its antimicrobial effect.

The sponsor's formulation development was intended to provide a capsule allowing for once daily oral administration:

"to provide an extended release profile in vivo of doxycycline concentrations that at steady state are high enough to have a beneficial [anti-inflammatory] effect but not high enough to exert an antibacterial effect. It was also planned that the Oracea formulation be equivalent to doxycycline 20 mg immediate release tablet twice a day (bd) in terms of area under the concentration-time curve (AUC), whilst maintaining the maximum plasma level (C_{max}) below the antimicrobial threshold of 1.0 µg/mL."

Regulatory status

The following table summarises the overseas regulatory status of this product.

Table 1. International regulatory status of Oracea. Table continued across 2 pages.

Country	Local Name	Regulatory status and approved Indication
Austria	Oraycea 40 mg Hartkapseln mit veränderter Wirkstoffresistenz	Approved. Oraycea is indicated to reduce papulopustular lesions in adult patients with facial rosacea.
Belgium	Oracea 40 mg capsules	Approved. Oracea is indicated to reduce papulopustular lesions in adult patients with facial rosacea.
Canada	Efracea 40 mg capsules	Approved. Efracea (doxycycline) modified release capsule is indicated for the treatment of only inflammatory lesions (papules and pustules) of rosacea in adult patients. No meaningful effect was demonstrated for generalized erythema (redness) of rosacea.
Czech Republic	Oracea 40 mg	Approved. Oracea is indicated to reduce papulopustular lesions in

¹ Therapeutic Guidelines: Dermatology – Version 2, 2004; Therapeutic Guidelines Ltd

² Powell FC. Rosacea. NEJM 2005; 352: 793 – 803

Country	Local Name	Regulatory status and approved Indication
	capsules	adult patients with facia rosacea.
Denmark	Oracea 40 mg capsules	Approved. Oracea is indicated to reduce papulopustular lesions in adult patients with facia rosacea.
Finland	Oracea 40 mg deportskapseli, kova	Approved. Oracea is indicated to reduce papulopustular lesions in adult patients with facia rosacea.
France	Oracea 40 mg capsules	Approved. Oracea is indicated to reduce papulopustular lesions in adult patients with facia rosacea.
Germany	Oraycea 40 mg Hartkapseln mit veranderter Wirkstoffresistenz	Approved. Oraycea is indicated to reduce papulopustular lesions in adult patients with facia rosacea.
Greece	Oracea 40 mg capsules	Approved. Proposed: Oracea is indicated to reduce papulopustular lesions in adult patients with facia rosacea..
Hungary	Oracea 40 mg capsules	Approved. Oracea is indicated to reduce papulopustular lesions in adult patients with facia rosacea.
Iceland	Oracea 40 mg Modified release capsules, hard	Approved. Oracea is indicated to reduce papulopustular lesions in adult patients with facia rosacea.
Ireland	Efracea 40 mg modified release hard capsules	Approved. Efracea is indicated to reduce papulopustular lesions in adult patients with facia rosacea.
Italy	Efracea 40 mg rigide a rilascio modificato	Approved. Efracea is indicated to reduce papulopustular lesions in adult patients with facia rosacea.
Luxembourg	Oraycea 40 mg capsules	Approved. Oraycea is indicated to reduce papulopustular lesions in adult patients with facia rosacea.
Netherlands	Efracea capsules met geregleerde afgifte, hard 40 mg	Approved. Efracea is indicated to reduce papulopustular lesions in adult patients with facia rosacea.
Norway	Oracea 40 mg Modified release hard capsules	Approved. Oracea is indicated to reduce papulopustular lesions in adult patients with facia rosacea.
Poland	Efracea 40 mg capsules	Approved. Efracea is indicated to reduce papulopustular lesions in adult patients with facia rosacea.

Country	Local Name	Regulatory status and approved Indication
Portugal	Oracea 40 mg capsules	Approved. Oracea is indicated to reduce papulopustular lesions in adult patients with facia rosacea.
Russian Federation	Oracea	Rejected (the dossier for registration was rejected at submission for to administrative reasons)
Slovakia	Oracea 40 mg capsules	Approved. Oracea is indicated to reduce papulopustular lesions in adult patients with facia rosacea.
South Africa	Oracea 40 mg capsules	Pending approval. Proposed Oracea is indicated to reduce papulopustular lesions in adult patients with facia rosacea
Spain	Oracea 40 mg capsules	Approved. Oracea is indicated to reduce papulopustular lesions in adult patients with facia rosacea
Sweden	Oracea, 40 mg kapsel med modifierad frisattning, hard.	Approved. Oracea is indicated to reduce papulopustular lesions in adult patients with facia rosacea
Switzerland	Oracea	Approved. Oracea is indicated to reduce papulopustular lesions in adult patients with facia rosacea.
United Kingdom	Efracea 40 mg modified release hard capsules	Approved. Efracea is indicated to reduce papulopustular lesions in adult patients with facia rosacea.
United States of America	Oracea (doxycycline, USP) Capsules 40 mg	<p>Approved. Oracea is indicated for the treatment of only inflammatory lesions (papules and pustules) of rosacea in adult patients. No meaningful effect was demonstrated for generalized erythema (redness) of rosacea.</p> <p><i>Limitations of Use:</i> This formulation of doxycycline has not been evaluated in the treatment or prevention of infections. Oracea should not be used for treating bacterial infections, providing bacterial prophylaxis, or reducing the numbers or eliminating microorganism associated with any bacterial disease. To reduce the development of drug-resistant bacteria as well as to maintain the effectiveness of other antibacterial drugs, Oracea should be used only as indicated.</p> <p>Efficacy of Oracea beyond 16 weeks and safety beyond 9 months have not been established.</p> <p>Oracea has not been evaluated for the treatment of erythematous, telangiectatic, or ocular components of rosacea.</p>

Product Information

This application was rejected therefore no Product Information was approved.

safety & efficacy of a doxycycline product with a new indication". (See comment from PSC below.)

Not all of the studies comparing Periostat and Oracea showed bioequivalence, but bioequivalence has not been reviewed in detail.

Pharmacokinetic studies

It is claimed that the preferred blood level of doxycycline is between about 0.1 µg/mL and 1.0 µg/mL at steady state in order that the anti-collagenase effect is retained but to avoid antibacterial side effects on intestinal flora.

The sponsor undertook a pharmacokinetic study in which the drug was remotely delivered to specific regions of the gastrointestinal tract (GIT). It was concluded that the extent of doxycycline absorption varies along the GIT, indicating that absorption of the drug may be rate limited.

Four other pharmacokinetics studies were submitted:

Study COL-101-SDPK-105 was a single-dose, food effect study. Food decreased C_{max} and AUC by about 45% and ~20% respectively and delayed the time to C_{max} (T_{max}) by about 1 hour.

Study PERIO-DOXYSR-104 was a fasting, multidose, crossover comparison of Oracea capsules and Periostat tablets (20 mg twice daily: 12 h apart) for seven days (n=14). The study provides a comparison of first dose and seventh day pharmacokinetics with Oracea.

Study COL-101-SSPK-106 was a larger, fasting, multidose, crossover comparison of Oracea capsules and Periostat tablets (20 mg twice daily: 12 h apart) for seven days (n=32), but without pharmacokinetic analysis on Day 1.

Study PERIO-DOXYSR-103 was 3-way, single dose comparison of Oracea capsules and Periostat tablets (2x20 mg) as well as Periostat tablets (20 mg twice daily: 12 h apart).

Study 103 provides the only direct, **single dose** comparison of 40 mg doxycycline doses from Oracea and an immediate release product (2x20 mg Periostat tablets) (as well as 20 mg tablets bd) in healthy volunteers. Thus, this study should show the pharmacokinetic effect of the modified release formulation used in Oracea.

Three individual patient plasma profiles (Figures 2A-C) and the mean profiles (Figure 3) are shown in the graphs below. Individual profiles following Oracea dosing (Treatment A: ● in graph) show two clear peaks, at about 4 hours and a smaller peak at approximately 16 hours. The mean profiles are also shown at the end; the second peak is less evident in the average graph. Twice a day tablet dosing (Treatment B: ■) gives two main peaks per day as expected:

Figure 2A. Sample individual pharmacokinetic profiles

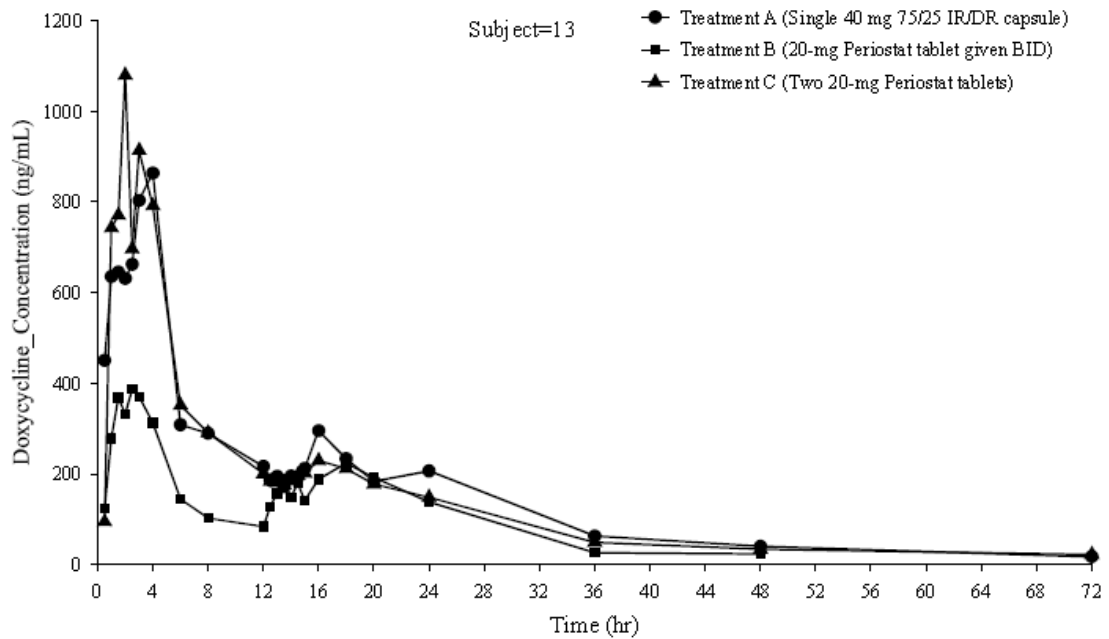


Figure 2B. Sample individual pharmacokinetic profiles

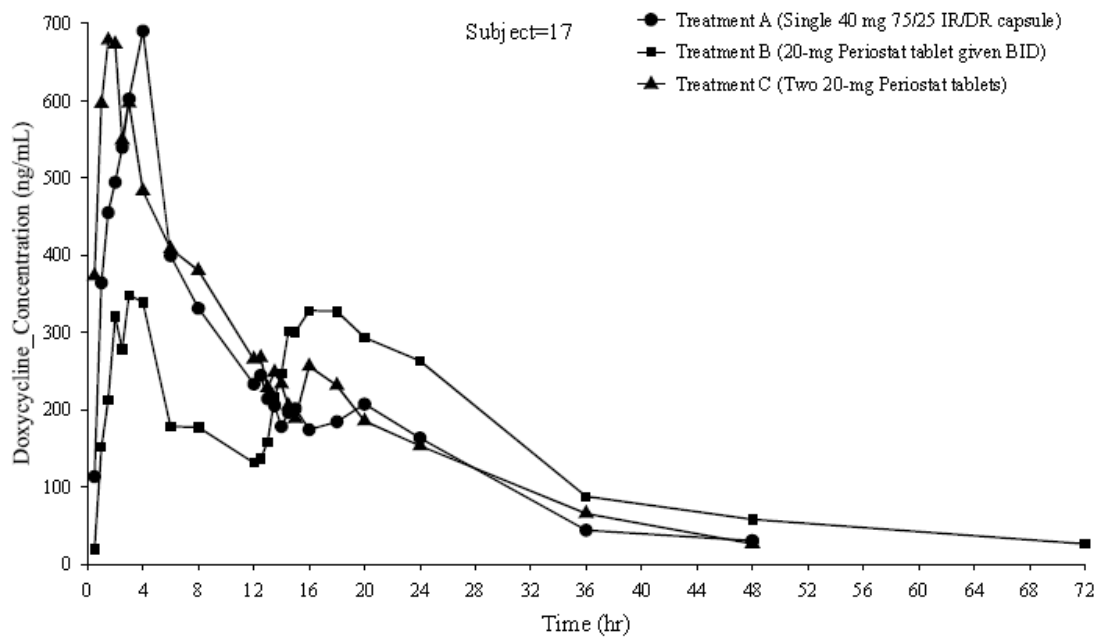


Figure 2C. Sample individual pharmacokinetic profiles

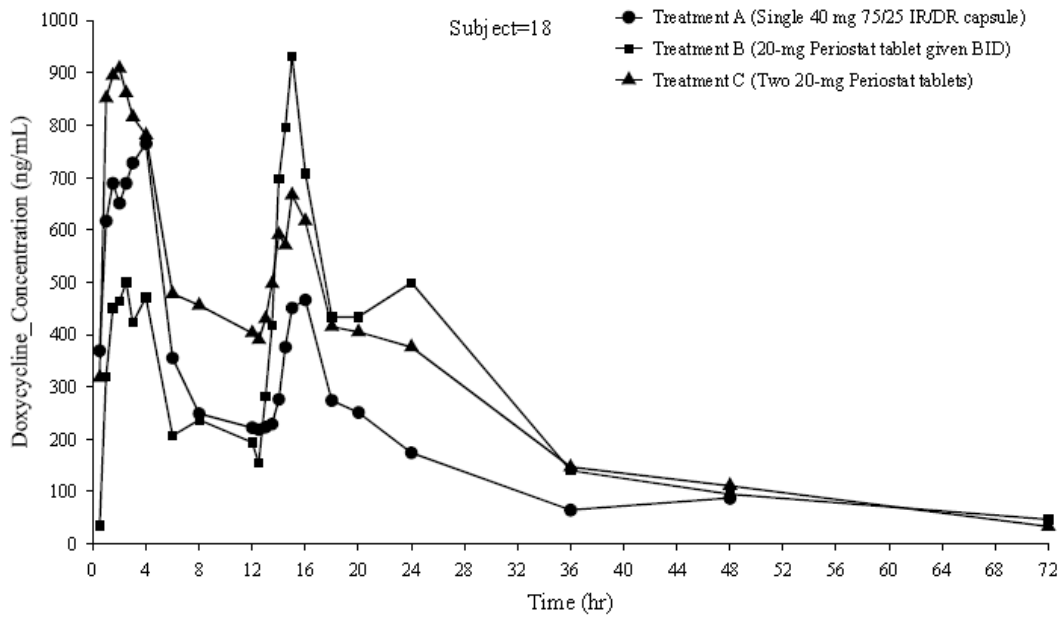


Figure 3. Mean profiles:

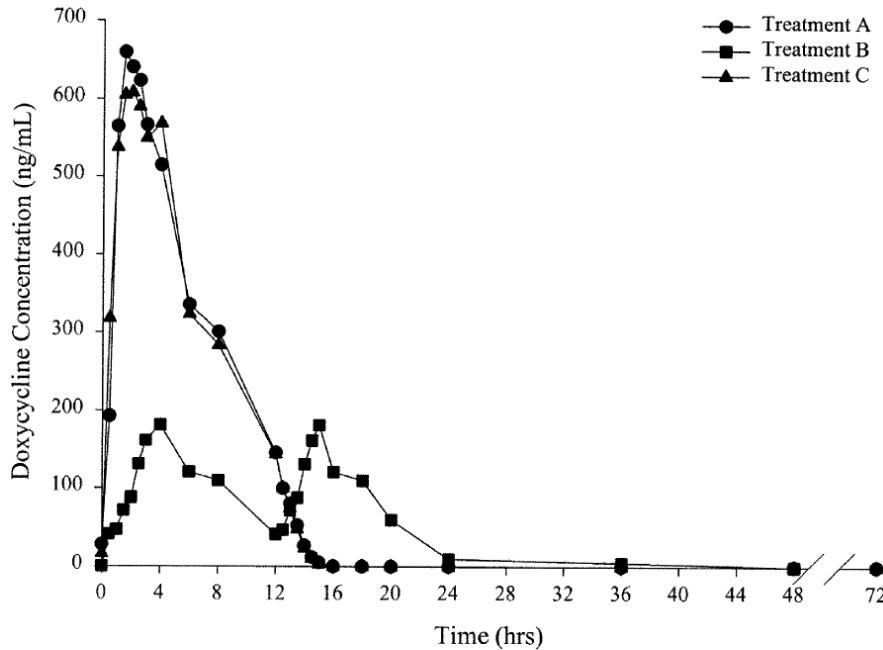


Figure 14.2.1-1. Mean Plasma Doxycycline Concentration versus Time Profile for Treatments A, B, and C in the Normal Scale.

It is notable that the 2x20 mg immediate release Periostat tablet dosing (▲ in graphs above) gives **very** similar profiles to Oracea dosing (●), that is, including the second peak. No pharmacokinetic result of including the delayed release beads in Oracea is evident in this study. The observed dissolution characteristics for the Oracea capsules are not evident *in vivo*. Either form of once daily dosing gives greater variability in plasma levels than the bd dosing.

(The intended C_{max} threshold for the product, 1.0 µg/mL, is equivalent to 1000 ng/mL as used on the above graph scales.)

Advisory committee considerations

Pharmaceutical SubCommittee (PSC) consideration

The initial evaluation was considered at the 140th (2011/5) meeting of the Pharmaceutical Subcommittee of the Advisory Committee on Prescription Medicines (ACPM):

The Committee considered that the lack of a bioavailability comparison to an Australian sourced doxycycline product was acceptable if appropriate clinical data had been submitted for the modified-release capsules.

The Committee did not consider that modified release characteristics had been established *in vivo*.

Recommendation no. 2224

1. The PSC endorsed all the questions raised by the TGA in relation to pharmaceutical and biopharmaceutical aspects of the submission by Galderma Australia Pty Ltd to register Oracea modified release capsule containing 40 mg of doxycycline (as monohydrate).
2. The Committee considered that all outstanding issues should be addressed to the satisfaction of the TGA.
3. The Committee did not consider that modified release characteristics had been established *in vivo*.
4. The Committee considered that the lack of a bioavailability comparison to an Australian sourced doxycycline product was acceptable if appropriate clinical data had been submitted for the modified-release capsules.

There is no requirement for this submission to be reviewed again by the PSC before it is presented for consideration by the Advisory Committee on Prescription Medicines (ACPM).

Quality summary and conclusions

Recommendation

A number of issues were raised with the sponsor following evaluation. The sponsor has chosen not to respond to questions, or has given incomplete or inadequate responses. The information about manufacturing and specifications and controls are not considered adequate to ensure consistent product quality.

Registration is not recommended with respect to chemistry and quality control aspects.

The similarity in pharmacokinetic profiles after single 2x20 mg immediate release Periostat tablet doses and 1x40 mg Oracea capsule doses is drawn to the attention of the committee.

III. Nonclinical findings

Introduction

Published references referred to in the nonclinical section of this AusPAR have been listed at the end of this section (under *Nonclinical references*).

General comments

The nonclinical dossier was a combination of literature data and a set of toxicology studies that were generated in the mid to late 1990s to support an application, in some overseas countries, for doxycycline hyclate capsules for the treatment of periodontal disease in adults (Periostat). Thus, they were not performed specifically to support the current application for Oracea. Oracea is a different pharmaceutical form with a different dosing regimen (20 mg twice daily). Oracea was developed as a slower release formulation enabling the convenience of once daily dosing. All studies were conducted with doxycycline as the hyclate rather than the monohydrate as in Oracea. Whilst it would not be expected that there would be any major differences in the effects of doxycycline hyclate and doxycycline monohydrate, some small differences are possible. However, it should be noted that doxycycline is currently registered as either the monohydrate or the hydrochloride. The studies conducted were limited, but were all Good laboratory practice (GLP)-compliant. The package included a single dose toxicity study in rats, repeat dose toxicity studies (2, 13 and 26 weeks in rats and 4 and 52 weeks in Cynomolgus monkeys, all supported by toxicokinetic data), an *in vivo* and 2 *in vitro* genotoxicity studies, a 2 year rat carcinogenicity study and reproductive toxicity studies (fertility and early embryonic development study and a peri/postnatal study, both in rats), with all *in vivo* studies using the oral route (the proposed clinical route). The relevance and quality of the individual studies are discussed further under the sections below. Overall, the nonclinical dossier was surprisingly large given the extensive clinical experience with doxycycline.

The duration of intended human dosing is unclear but is assumed to be at least 16 weeks, based on clinical trial data.

Pharmacology

Primary pharmacology

Rosacea is a chronic and recurrent inflammatory skin disease characterised by erythema, papules, pustules, telangiectasia, and occasionally sebaceous hyperplasia, which primarily affects the central face. The exact aetiology of rosacea is unknown but is probably multifactorial.³ Hypotheses include involvement of an antioxidant defect⁴ and the cutaneous over-production of a cathelicidin peptide.⁵ Various immune factors such as eicosanoids, pro-inflammatory cytokines and polymorphonuclear leukocytes appear to be involved in this disorder.⁶ The sponsor reported that animal models do not exist for rosacea. Some published studies refer to a murine model of rosacea in which intradermal injection of LL-37 (human cathelicidin) into Balb/c mice at 12 hour intervals for 48 hours produces cutaneous erythema, prominent intradermal neutrophil infiltration and myeloperoxidase (MPO) activity.^{5,7} However, this model does not appear to be widely used.

It appears unlikely that doxycycline at the recommended dose of 40 mg daily exerts its effect on the papulopustular lesions of rosacea via its anti-microbial activity. A clinical

³ McDonnell, J.K. and Tomecki, K.J. (2000) Rosacea: an update. *Cleveland Clinic J. Med.* 67: 587-590.

⁴ Öztas, M.O., Balk, M., Ögüs, E., Bozkurt, M., Ögüs, I.H. and Özer, N. (2003) The role of free oxygen radicals in the aetiopathogenesis of rosacea. *Clin. and Exper. Dermatol.* 28: 188-192.

⁵ Yamasaki, K., Di Nardo, A., Bardan, A., Murakami, M., Ohtake, T *et al.*, (2007) Increased serine protease activity and cathelicidin promotes skin inflammation in rosacea. *Nat. Med.* 13: 975-980.

⁶ Millikan, L.E. (2004) Rosacea as an inflammatory disorder: a unifying theory? *Cutis* 73: 5-8.

⁷ Zhang, J., Xu, X., Rao, N.V., Argyle, B., McCoard, L.J., Rusho, W.J., Kennedy, T.P., Prestwich, G.D. and Krueger, G. (2011) Novel sulfated polysaccharides disrupt cathelicidins, inhibit RAGE and reduce cutaneous inflammation in a mouse model of rosacea. *PLoS ONE* 6(2): e16658. doi: 10.1371/journal.pone.0016658

study (6 month regimen of 20 mg doxycycline BID) found no effect of treatment on the cultivable microflora of the skin (Skidmore *et al.*, 2003; submitted for evaluation to the clinical evaluator, full paper not sighted by this evaluator). The current Product Information and the Clinical and Nonclinical Experts reported that doxycycline plasma concentrations above 1 µg/mL are generally required to exert an antimicrobial effect, while the recommended dose of Oracea gives a C_{max} of 0.6 µg/mL.

The efficacy of doxycycline in rosacea is believed to be due to its anti-inflammatory activity. To support the use of doxycycline in the treatment of rosacea, the sponsor submitted literature publications relating to the effect of doxycycline on inflammatory processes *in vitro* and on various inflammatory disease models in laboratory animals *in vivo*. *In vitro* anti-inflammatory effects included inhibition of phagocytosis by neutrophils, inhibition of nitric oxide production and influencing the arachidonic acid cascade by inhibition of extracellular phospholipase A2 and augmentation of cyclooxygenase-2 expression and prostaglandin-E2 production. Doxycycline also inhibited the activities of a number of matrix metalloproteinases involved in collagen, cartilage and elastin degradation. Anti-inflammatory effects in *in vivo* models included inhibition of osteoarthritis in dogs and alveolar bone loss in a rat model of periodontitis, inhibition of pathological findings (airway inflammation, inflammatory cells in bronchoalveolar lavage (BAL) fluid, airway hyperresponsiveness and/or increased lung and BAL fluid MMP-9) in respiratory inflammation in mice and guinea pigs, protection from lethal IP injections of lipopolysaccharide (LPS) in mice, inhibition of inflammation in a croton-oil induced pouch in rats and inhibition of brain MMP-9 and angiogenesis in vascular endothelial growth factor-induced cerebral angiogenesis in mice. Whilst it is possible that some of these findings may have relevance to rosacea, due to the unknown aetiology of rosacea, the exact relevance cannot be determined. Further, in all of the *in vitro* studies, the concentrations at which doxycycline showed activity were greater than the plasma C_{max} achieved at the recommended clinical dose for the treatment of rosacea (0.6 µg/mL) and, except for the study by Milano *et al.* (1997)⁸ (LPS-induced shock in mice; single dose of 1.5 mg/kg IP), the doses used in the *in vivo* studies were greater than the recommended clinical dose (calculations on a mg/m² basis).

In conclusion, the nonclinical data were insufficient to demonstrate the efficacy of doxycycline in the treatment of rosacea and therefore the efficacy for the proposed indication will have to rely on clinical data.

Secondary pharmacodynamics and safety pharmacology

The main secondary pharmacological effects of doxycycline are its antimicrobial effects which are well known. No safety pharmacology studies were submitted and none are required given the extensive clinical experience with this drug. No abnormalities were detected in electrocardiogram (ECG) examinations conducted in the 4 week monkey study (exposure ratio (ER) based on C_{max} [$ER_{C_{max}}$] ≤10).

Pharmacokinetics

No new pharmacokinetic studies were submitted. The nonclinical overview summarised some of the main pharmacokinetic characteristics of doxycycline (derived from the published literature). Doxycycline was reported to be rapidly and almost completely absorbed after oral administration, have excellent tissue penetration, limited metabolism

⁸ Milano, S., Arcoleo, F., D'Agostino, P. and Cillari, E. (1997) Intraperitoneal injection of tetracyclines protects mice from lethal endotoxemia downregulating inducible nitric oxide synthase in various organs and cytokine and nitrate secretion in blood. *Antimicrob. Agents and Chemother.* 41: 117-121.

and be excreted in both faeces and urine. Available data suggested similar pharmacokinetics in humans and laboratory animal species.

Of relevance to the current indication is distribution of the drug to the skin, the site of action in the treatment of rosacea. Whilst there were no specific data relating directly to distribution to skin, Banning and Heard (2002)⁹ demonstrated the uptake of doxycycline by human epidermis *in vitro*. Available data on tissue distribution suggest that doxycycline is widely distributed to tissues, consistent with its high lipid solubility. Tissues that were associated with excretion of the drug (intestine, liver and kidney) generally had high tissue: serum ratios (7–40), brain and blood cells had low ratios (0.1–0.4), while other tissues had ratios in the range 2–15, and skin might be expected to have a ratio in this vicinity.

No nonclinical pharmacokinetic studies were submitted that investigated the oral absorption of doxycycline from Oracea capsules which contain delayed-release, as well as immediate-release, beads. No nonclinical pharmacokinetic studies were submitted that examined interactions with other drugs.

All repeat dose toxicity studies were supported by toxicokinetic data which are summarised in the table below.

Table 2. Plasma AUC and C_{max} values and animal: human exposure ratios

Species	Duration (weeks)	Sample day/week	Dose mg/kg/day	AUC µg.h/mL*	C _{max} µg/mL	AUC exposure ratio (ER) [^]	C _{max} exposure ratio (ER) [^]
Rat	2	day 14	400	154	9.02	20	15
Rat	13	day 91	25	15.4	1.83	2.0	3
			100	45.0	3.49	6	6
			400	142	9.96	19	17
			600	134	8.42	18	14
Rat	26	day during 6 th month	20	12.9	1.89	1.7	3
			75	40.8	3.73	5	6
			200	80.4	6.90	11	12
Cynomolgus monkey	4	mean days 1, 5 and 28	5	17.2	1.71	2.3	3
			25	48.6	3.97	6	7
			50	72.4	6.03	10	10
Cynomolgus monkey	52	week 52	5	5.71	1.27	0.8	2.1
			15	11.5	2.59	1.5	4
			30	19.2	4.56	2.5	8

* AUC_{0-last} or AUC_T; [^] AUC relative to a human steady state value of 7.543 µg.h/mL, and C_{max} relative to a human value of 0.6 µg/mL with a dose of 40 mg Oracea.

Animal:human exposure ratios (based on AUC; ER_{AUC}) achieved in the repeat dose toxicity studies were adequate in rats, reaching up to 11 in the 6 month study but somewhat low in Cynomolgus monkeys (up to 2.5 in the 1 year study). It is unclear why AUC values in the

⁹ Banning, T.P. and Heard, C.M. (2002) Binding of doxycycline to keratin, melanin and human epidermal tissue. *Int. J. Pharmaceutics* 235: 219-227.

1 year monkey study were considerably lower than those at the same or similar doses in the 4 week study. Plasma samples from both studies were analysed by the same laboratory using the same (or closely similar) methodology, but inter-animal variability was high.

Toxicology

Repeat dose toxicity studies were conducted in rats and Cynomolgus monkeys. Based on the broad similarity of the pharmacokinetic characteristics of doxycycline in laboratory animals and humans, they are considered acceptable models. The submitted toxicity studies add to the available nonclinical information on doxycycline. In general, the studies were adequately conducted, with sufficient animals. Repeat dose toxicity studies were of adequate duration but the high dose levels used in the longest studies could have been higher based on minimal effects on body weight gain, particularly in females in both species. The lack of statistical analyses for data in the 4 week monkey study was disappointing.

Organs affected by doxycycline administration in both rats and Cynomolgus monkeys were the stomach and thyroid. In rats, both the glandular and non-glandular stomachs were affected. Effects in the rat non-glandular stomach included spongiosis at the limiting ridge, submucosal inflammation, hyperkeratosis and increased incidence of epithelial hyperplasia but these findings are not discussed further here as the non-glandular stomach does not have a counterpart in humans. From clinical experience, doxycycline is known to be irritant to the gastric and oesophageal mucosae. At 600 mg/kg/day in the 13 week rat study, focal erosion in the glandular stomach was of sufficient severity to cause or contribute to death in 2 animals but it was not observed at lower doses. Other changes in the glandular stomach included increased mucus producing cells/mucus production, observed in both rats and monkeys, and submucosal inflammation and eosinophilic chief cells, observed only in rats. In rats, other parts of the gastrointestinal tract (small and large intestines) were also affected, which may have been due to changes in intestinal flora. At doses ≥ 400 mg/kg/day (13 week study), diffuse mucosal hyperplasia was observed in both the duodenum and caecum and, additionally, villus hypertrophy was observed in the caecum. The NOEL for gastrointestinal lesions was 25 mg/kg/day in rats (ER_{AUC} 2) and 30 mg/kg/day in monkeys (ER_{AUC} 2.5 based on the 1 year study).

Brown pigment deposits in the thyroid epithelium (often seen macroscopically as discoloured/dark thyroids) were observed histologically in both rats and monkeys. While the severity was minimal to slight in monkeys, it ranged from minimal to severe in rats. A No observable effect level (NOEL) was not established in rats (the lowest tested dose was 20 mg/kg/day; ER_{AUC} 1.7), while the NOEL was 15 mg/kg/day in the 1 year monkey study (ER_{AUC} 1.5). The pigmentation was not seen after 4 weeks of treatment in Cynomolgus monkeys at up to 50 mg/kg/day (ER_{AUC} 10), suggesting a longer duration of dosing would be required for the finding to be seen. Given the high incidence of the thyroid pigment, even at the lowest tested dose in rats (10/20 males and 4/20 females affected), as well as the low safety margin, deposition of pigment in the thyroid might occur in patients treated for long periods with doxycycline. Such pigment deposition has been observed in patients treated with other tetracyclines such as minocycline.¹⁰ As the thyroid discolouration was not apparently associated with any other microscopic changes in the thyroid (such as proliferative lesions), it is considered of limited toxicological significance.

¹⁰ Gordon, G., Sparano, B.M., Kramer, A.W., Kelly, R.G. and Iatropoulos, M.J. (1984) Thyroid gland pigmentation and minocycline therapy. *Am. J. Path.* 117, 98-109.

Kidney weights were increased in both species but histological correlates were only observed in monkeys (tubular degeneration/regeneration [mainly diffuse], and interstitial oedema in the medulla were observed in both studies; there was no evidence of tubular necrosis). Increases in blood urea were observed in the 4 week monkey study which may have been associated with effects on the kidney and/or an anti-anabolic effect (due to a reduction in protein synthesis). The NOEL for kidney lesions was 5 mg/kg/day orally (PO) (ER_{AUC} 0.8). Given the low safety margin, there is a potential for renal effects in patients treated for rosacea at the proposed dose.

In rats, additional organs affected by doxycycline treatment include the adrenals (increased incidence of minimal cortical lipidosis) and, in the 6 month study only, the pharynx (minimal inflammatory cell infiltrate), while the spleen (reduction in the incidence of extramedullary haematopoiesis) was only affected at 600 mg/kg/day PO. Red blood cells were also affected in both studies in rats, with reductions in red cell numbers, and associated parameters (haemoglobin and haematocrit). The reduction in the incidence of extramedullary haematopoiesis in the spleen may have contributed to this finding at 600 mg/kg/day but red cell parameters were also reduced at lower doses (≥ 200 mg/kg/day). The NOEL for all of these effects was 20 mg/kg/day (ER_{AUC} 1.7).

The extensive clinical experience with the use of doxycycline for the treatment of various infections needs to be taken into account when considering the use of this drug for rosacea. Doxycycline has been used as an antibiotic since the 1960s and its safety profile is well documented. Doses used for the treatment of microbial infections are ≥ 100 mg/day, that is, at least 2.5 times the daily dose proposed for the treatment of rosacea. Doses used for the treatment of acne (50 mg/day) also exceed (1.25 fold) the daily dose proposed for the treatment of rosacea. The duration of dosing proposed for the treatment of rosacea is open-ended but with clinical trials lasting 16 weeks. As lesions tend to return after a treatment-free of about 4 weeks, it might be expected that treatment cycles of 16 weeks followed by treatment-free periods of 4 weeks might be common. Thus, the duration of treatment for rosacea is considerably longer than the duration of treatment for microbial infections (generally up to about 10 days); it is also longer than the duration of treatment for acne (12 weeks). Increases in the duration of dosing in the repeat dose rat and monkey studies did not reveal any new effects of toxicological significance. No new target organs were identified for non-neoplastic changes in the rat carcinogenicity study (thyroid, stomach and pharynx were affected).

There may be a risk of induction of bacterial resistance following prolonged treatment with doxycycline. In the nonclinical overview, literature data on the antimicrobial effects of doxycycline were summarised and MIC values from the various studies were in the range 0.015-14 $\mu\text{g}/\text{mL}$. The plasma C_{max} achieved in humans at the recommended dose is 0.6 $\mu\text{g}/\text{mL}$, although the total drug concentration may not be available for antimicrobial activity. If plasma protein binding is taken into account and only free drug is available for antimicrobial activity, then the active concentration might be only ~ 0.06 $\mu\text{g}/\text{mL}$. However, plasma C_{max} values for both total and free doxycycline lie above the lowest MIC values in the range noted above, suggesting that there are some organisms which are susceptible at the doxycycline concentrations achieved at the recommended dose for treatment of rosacea. A major route of excretion of doxycycline is via the faeces, so intestinal microflora may be particularly at risk. The issue of potential development of resistance has been addressed by clinical studies, including investigation of effects on intestinal flora and statements are included in the proposed Product Information noting that it cannot be excluded that long-term use of Oracea could lead to the emergence of resistant intestinal bacteria such as enterobacteriaceae and enterococci, as well as the enrichment of resistance genes.

Genotoxicity

Genotoxicity studies submitted were forward gene mutation (at the HGPRT locus) and chromosome aberration studies, both in Chinese Hamster Ovary (CHO) cells, and an *in vivo* mouse micronucleus test (at doses up to 3 times the proposed clinical dose on a mg/m² basis¹¹). For an antibiotic it is generally not appropriate to conduct gene mutation studies in bacteria. All the studies were adequately conducted, with appropriate concentrations/doses selected following dose range-finding tests. Doxycycline was weakly clastogenic *in vitro*; however, the response was not always consistent and there was no clear concentration-related effect. Based on negative findings in other genotoxicity assays, the weight of evidence indicates that doxycycline has a low genotoxic risk to humans.

Carcinogenicity

A 2 year rat carcinogenicity study was submitted. The guidelines (ICH S1A)¹² recommend that carcinogenicity studies be conducted for any pharmaceutical whose expected clinical use is continuous for at least 6 months. As the duration of dosing in the proposed Product Information is open-ended, it is appropriate that a carcinogenicity study has been conducted. Whilst carcinogenicity studies are normally conducted in two species, investigation in a single species in this instance is considered adequate, given the extensive clinical experience with doxycycline and the lack of any clear positive genotoxicity findings. Group sizes were appropriate and dual control groups were used, as recommended in the European Union (EU) guideline on carcinogenic potential.¹³ At termination, the number of surviving females was low across all groups (≤ 25 /group), including the controls. As sufficient numbers survived to Week 90, this is not considered to have adversely affected the adequacy of the study to reveal potential carcinogenic effects. Exposure at the highest tested dose was low, 11 times the anticipated clinical exposure, and given there was no appreciable drug-related effects on survival and body weight, higher doses should have been considered. Exposures at least 25 times the anticipated clinical exposure are recommended.¹⁴

At the highest dose in females, there was an increase in the incidence of uterine polyps (35% compared to 17% in controls), an increase in the severity (but not incidence) of mammary gland fibroadenomas and an increase in the severity of cystic endometrial hyperplasia. All of these findings are consistent with alterations in hormone levels, although these were not directly measured. Both uterine polyps and mammary gland fibroadenomas are common tumours in ageing female rats. As there was no evidence of carcinogenic changes in the uterus and exposures at the highest tested dose were modest, and there was no overall increase in mammary tumours, the findings are not a major cause for concern in clinical use.

An increase in the incidence of thyroid C-cell adenomas was observed in all drug-treated female groups. However, there was no clear relationship with dose and no apparent increase in thyroid C-cell hyperplasia or thyroid C-cell carcinoma, suggesting the increase in adenoma incidence may be incidental.

¹¹ The highest dose in the main study was 1250 mg/kg PO or 3750 mg/m² using a mg/kg to mg/m² conversion factor of 3 for mice.

¹² ICH Harmonised Tripartite Guideline (S1A). Guideline on the need for carcinogenicity studies for pharmaceuticals.

¹³ CPMP/SWP/2877/00. Note for guidance on carcinogenic potential. <<http://www.tga.gov.au/pdf/euguide/swp287700en.pdf>>

¹⁴ EMEA/CHMP/ICH/383/1995. Note for guidance on dose selection for carcinogenicity studies of pharmaceuticals. <<http://www.tga.gov.au/pdf/euguide/ich038395final.pdf>>

Reproductive toxicity

Submitted reproductive toxicity studies included a fertility/early embryonic development study and a peri-postnatal study (both in rats). Doses in both reproductive toxicity studies were ≤ 500 mg/kg/day. Toxicokinetic data were not generated for the reproductive toxicity studies but extrapolation from the toxicokinetic data from non-pregnant rats in the repeat dose toxicity studies suggested that exposure ratios (based on plasma AUC) of about 18 might have been achieved at the high dose in these studies. Literature publications examining embryofetal toxicity in the mouse, rat and rabbit were also submitted.

The fertility study involved mating of treated males and treated females from the same dose groups. After adverse effects were observed following the first mating, rather than initiating a second study, males were mated again (after 46 days of dosing), this time to untreated females. For both matings, there was a tendency for an increased time to mating in the treated groups. Mating index was not affected but the fertility index was significantly decreased at 500 mg/kg/day in the second mating. This was associated with adverse effects on sperm: dose-related reductions in straight line velocity (significant at all doses) and, additionally at 500 mg/kg/day, significant reductions in sperm concentration, motility and actual path velocity, and significant increases in the numbers of abnormal sperm. A no-effect dose was not established for adverse effects on male fertility. Estimated exposure at the lowest dose would be 3–4 times the clinical AUC. There also appeared to be an effect of doxycycline treatment on females, as a significant reduction in corpora lutea was observed at 500 mg/kg/day (NOEL 250 mg/kg/day; estimated ER_{AUC} 14). Increases in pre-implantation loss were observed at ≥ 250 mg/kg/day (at both matings, although not significant for the first mating), suggesting that this may have been due to an effect on males. Although not reaching statistical significance, post-implantation loss was also higher than controls at 500 mg/kg/day.

The published papers on embryofetal toxicity were not particularly useful, due to non-standard techniques or limited investigations, but the study in rabbits was suggestive of teratogenic potential, while the study in rats was suggestive of delayed skeletal development. Other tetracyclines (tetracycline, minocycline and tigecycline) have been shown to cross the placenta in animals, and as a result of their affinity for calcium ions, they can have adverse effects on the developing fetus (Achromycin®, Tygacil® and Minomycin® Product Information documents). During the period of mineralisation of teeth (the second and third trimesters of pregnancy, the neonatal period and the first 8 years of life), tetracyclines may induce hypoplasia of the enamel and discolouration of the teeth. Tetracyclines also accumulate in the growing skeleton. Tetracyclines are generally contraindicated beyond the fifteenth week of gestation. These findings support classification of doxycycline in Pregnancy Category D, rather than the Category B1 proposed by the Sponsor. Given the extensive clinical use of doxycycline, some clinical data regarding potential teratogenicity of doxycycline may also be available and should be included when evaluating adverse embryofetal effects.

Doxycycline was shown to be excreted into human breast milk with milk: plasma ratios determined at 3 and 24 h to be 0.3 and 0.4, respectively.¹⁵ There is a theoretical risk of dental staining and inhibition of bone growth in breast-fed infants following maternal administration. In rats, treatment of females from gestational day (GD) 18 to postpartum day (PPD) 20 had no effect on the viability of the F₁ generation¹⁶ and only a relatively

¹⁵ Morganti, G., Ceccarelli, G., and Ciaffi, E.G. (1968) Comparative concentrations of a tetracycline antibiotic in serum and maternal milk. *Antibiotica* 6: 216-223

¹⁶ F1 generation: offspring of the F0 generation (parents). F (Filial) generation numbers indicate the numbers of generations that its members are removed from the original parent generation.

minor effect on their growth and development (most notably, small reductions in body weights/weight gains during lactation at 500 mg/kg/day) which occurred in the context of maternotoxicity. There were small but significant increases in duration of gestation in F₀ dams at ≥250 mg/kg/day, which may have been incidental, although an effect of treatment cannot be ruled out. The lack of mating of the F₁ generation in the peri-postnatal study was disappointing.

Phototoxicity

A published paper¹⁷ revealed that doxycycline has phototoxic potential, and phototoxicity has been observed to be induced by doxycycline in humans.¹⁸ However, a warning statement is included in the proposed Product Information, noting that an exaggerated sunburn reaction can occur in individuals taking tetracyclines and that treatment should be discontinued in the event of such a reaction. This should be considered given the proposed indication (rosacea) and the intended long duration of treatment.

Use in children

Doxycycline is generally not recommended for use in children under 8 years of age, due to adverse effects such as teeth discolouration and enamel hypoplasia and delays in bone development in premature infants. It is noted that the Product Information contraindicates use in infants and children up to 12 years of age.

Nonclinical summary and conclusions

- The nonclinical dossier was a combination of literature data and a limited set of toxicology studies (all GLP, with *in vivo* studies using the oral route) conducted in the mid to late 1990s. Studies were conducted with doxycycline hyclate rather than the monohydrate but this is unlikely to have any major implications.
- There is extensive clinical experience with doxycycline. It is currently approved in Australia for the treatment of a variety of infections generally at doses of 100–300 mg daily for periods of up to about 10 days, for prophylaxis of malaria (100 mg daily for 8 weeks) and as an adjunct in the treatment of acne (50 mg daily for 12 weeks).
- Rosacea is an inflammatory skin disease but its exact aetiology is unknown. The efficacy of doxycycline in this indication appears to be due to its anti-inflammatory activity rather than its antimicrobial activity. To support the new indication, the sponsor submitted published studies which revealed a range of *in vitro* and *in vivo* anti-inflammatory activities of doxycycline. However, given the unknown aetiology of rosacea, the role that these activities play in the proposed indication is unclear. Further, the concentrations/doses used in the majority of these studies were greater than the clinical C_{max}/dose. Thus, the efficacy of doxycycline for the proposed new indication will have to rely on clinical data.
- No secondary or safety pharmacology studies were submitted. This is acceptable given that the main secondary pharmacological effects of doxycycline are its antimicrobial effects and that there is extensive clinical experience with this drug.

¹⁷ Kersten, B., Zhang, J., Brendler-Schwaab, S.Y., Kasper, P. and Müller, L. (1999) The application of the micronucleus test in Chinese hamster V79 cells to detect drug-induced photogenotoxicity. *Mutation Res.* 445: 55-71.

¹⁸ Habif, T.P. (2006) Doxycycline-induced phototoxicity. *N. Engl. J. Med.* 355, 182

- No new nonclinical pharmacokinetic studies were conducted. No pharmacokinetic data on the absorption of the drug from the modified-release capsules (which contain 30 mg doxycycline as immediate-release beads and 10 mg doxycycline as delayed-release beads) were submitted. No data on distribution to skin are available but doxycycline is widely distributed to tissues and most tissues have tissue: serum ratios >1. All repeat dose toxicity studies were supported by toxicokinetic data.
- Toxicity was examined in an acute toxicity study in rats, and in repeat dose studies in rats (2, 13 and 26 weeks) and Cynomolgus monkeys (4 and 52 weeks). Maximum animal: human exposure ratios (based on plasma AUC) in the longest duration studies were 11 in rats and 2.5 in monkeys. Doxycycline is a known irritant to the stomach mucosa and effects on the stomach were observed in both species, but were minor at exposure ratios ≤5. Pigment deposition in thyroid epithelial cells was also observed in both species, at an exposure ratio of 1.7 in the 6 month rat study and 2.5 in the 1 year monkey study. It is a known effect of tetracyclines and might occur in patients dosed for prolonged periods at the recommended dose for treatment of rosacea but it is considered to be of limited toxicological concern. In monkeys, findings in the kidney (tubular degeneration/regeneration and interstitial oedema in the medulla) at a low exposure ratio (1.5) suggest a potential for mild renal changes in patients. Other findings in rats (a reduction in red cell parameters, cortical lipidosis in the adrenals, inflammatory cell infiltrate in the pharynx and mucosal hyperplasia in the duodenum and caecum), were generally of minor severity and/or occurred at doses giving exposure ratios ≥5.
- There may be a risk of induction of bacterial resistance following prolonged treatment. This issue has been addressed by a number of clinical studies, including investigation of effects on intestinal flora which may be a particular concern.
- An acceptable package of genotoxicity studies was submitted, comprising a forward mutation study at the HGPRT locus in CHO cells and an *in vivo* mouse micronucleus test which both gave negative results, and a chromosome aberration study in CHO cells, in which doxycycline showed weak clastogenicity. The weight of evidence indicates a low genotoxic concern.
- A 2 year rat carcinogenicity study was conducted (exposure ratio 11 at the high dose (HD)). An increased incidence of uterine polyps and fatal¹⁹ mammary gland fibroadenomas (no increase in total mammary gland fibroadenomas), both benign tumours, was observed in HD females. These findings are not considered of particular concern for the clinical use of doxycycline for the proposed indication.
- Reproductive toxicity studies comprised a fertility/early embryonic development study and a peri-postnatal study (dosing from GD 18 to PPD 20), both in rats at doses from 50 to 500 mg/kg/day (estimated exposure ratios approximately 3–18, based on plasma AUC for non-pregnant rats). Embryofetal development studies were not submitted and literature data were poor. The fertility study included a first mating in which both males and females were treated, followed by a second mating of treated males to untreated females. The main finding in this study was an adverse effect on sperm (including decreases in straight line velocity at all doses) associated with a reduced fertility index at the HD (second mating). Other findings observed at estimated exposure ratios >10 included decreases in corpora lutea (first mating) and trends for increases in time to mating and pre-implantation and post-implantation losses (both matings). In the peri-postnatal study, treatment of F₀ dams had little effect

¹⁹ Fatal or probably fatal (when the size and/or position of the mass resulted in early sacrifice of the animal)

on the F₁ generation (mainly reductions in body weight gain over the lactation period). Tetracyclines cross the placenta and can have adverse effects on fetal development, including teeth discolouration and delayed bone development.

- In a published paper, doxycycline was shown to have phototoxic potential.

Conclusions and recommendations

The efficacy of doxycycline for the proposed new indication, rosacea, will have to rely on clinical data. The sponsor submitted published studies which revealed a range of *in vitro* and *in vivo* anti-inflammatory activities of doxycycline, but given the unknown aetiology of rosacea, the role these activities play in the proposed indication is unclear.

Although the proposed dose is lower than the doses recommended for currently approved indications, the duration of dosing is longer. Maximum animal: human exposure ratios in the long term repeat dose toxicity studies were moderate in rats and low in Cynomolgus monkeys. The main findings of potential clinical relevance include mild renal effects, hyperpigmentation of the thyroid, minor stomach and oesophageal mucosal irritation, the potential for skin erythema associated with phototoxicity, and the emergence of bacterial resistance. These are all known effects of doxycycline. Doxycycline poses a low genotoxic and carcinogenic risk at the proposed dose. Reproductive studies and published papers indicate a risk to male fertility and adverse effects on embryofetal and neonatal development. Doxycycline should not be used during pregnancy or lactation or in paediatric patients (<15 years).

There were no nonclinical objections to the registration of Oracea for the proposed indication. Revisions to the draft Product Information document were also recommended but these are beyond the scope of this AusPAR.

IV. Clinical findings

Introduction

A summary of the clinical findings is presented in this section. Further details of these clinical findings can be found in Attachment 1.

Clinical rationale

The mode of action in rosacea is thought to be *via* properties of the drug other than its antimicrobial activity. Nonclinical studies and also some clinical pharmacodynamic results (such as Skidmore *et al.* 2003²⁰), suggest that the drug has effects in certain dermatologic conditions at concentrations generally below the antimicrobial level.

Formulation

The FDA approved product Periostat (doxycycline hydrochloride 20 mg tablets) had been developed for use twice daily in periodontitis. Preliminary studies suggesting that the same dosage may be effective in treating rosacea led the sponsor to aim at developing a once-daily product for rosacea which would "*achieve bioequivalence to Periostat in terms of the area under the concentration-by-time curve (AUC) while keeping the maximum*

²⁰Skidmore R, Kovach R, Walker C, Thomas J, Bradshaw M, Leyden J, Powala C and Ashley R. 2003. Effects of submicrobial-dose doxycycline in the treatment of moderate acne. *Arch Dermatol* 139: 459-464.

plasma level (C_{max}) below 1.0 µg/mL so as not to exceed the threshold for antimicrobial activity in vivo."

Australian regulatory history

Guidance

TGA had advised as follows:

"TGA advises that the pharmacokinetic studies include comparisons with Periostat tablets. As this product is not registered in Australia, the sponsor is required to provide either a comparison with relevant Australian registered formulation, or a justification/comparative data etc for not doing so."

The sponsor's response was:

"The comparative PK studies with Periostat, PERIO-DOXYSR-103 (Mod 5, Vol 1), PERIODOXYSR-104 (Mod 5, Vol 3) & COL-101-SSPK-106 (Mod 5, Vol 4), submitted in Module 5.3.1.2 of the registration dossier are included in the dossier to demonstrate the PK parameters of doxycycline monohydrate (Oracea) which is the subject of this registration application.

The dossier is not intended to be comparative and the studies are included as the available PK data for Oracea. These PK studies in comparison with Periostat have been provided to show the bioequivalence with Oracea. Therefore, Galderma used the existing animal safety data performed with the product Periostat in this registration application.

Oracea dossier is a stand-alone application with a full package of clinical data to demonstrate the safety & efficacy of a doxycycline product with a new indication."

Contents of the clinical dossier

The submission contained the following clinical information:

- Five pharmacokinetic/bioavailability studies (nos. 110801, COL-101-SDPK-105, PERIO-DOXYSR-103, PERIO-DOXYSR-104 and COL-101-SSPK-106).
- Five published clinical studies (in which the effect of chronic administration of low doses of doxycycline on antimicrobial resistance was examined: Thomas et al. (1998)²¹, Walker et al. (2000)²², Thomas et al. (2000)²³, Skidmore et al. (2003)²⁴ and Walker et al. (2005)²⁵).

²¹ Thomas JG, Metheny RJ, Karakiozis JM, Wetzel JM and Crout RJ. 1998. Long-term sub-antimicrobial doxycycline (Periostat) as adjunctive management in adult periodontitis: Effects on subgingival bacterial population dynamics. *Adv Dent Res* 12: 32-39.

²² Walker C, Thomas J, Nango S, Lennon J, Wetzel J and Powala C. 2000. Long-term treatment with subantimicrobial dose doxycycline exerts no antibacterial effect on the subgingival microflora associated with adult periodontitis. *J Periodontol* 71: 1465-1471.

²³ Thomas J, Walker C and Bradshaw M. 2000. Long-term use of subantimicrobial dose doxycycline does not lead to changes in antimicrobial susceptibility. *J Periodontol* 71: 1472-1483.

²⁴ Skidmore R, Kovach R, Walker C, Thomas J, Bradshaw M, Leyden J, Powala C and Ashley R. 2003. Effects of submicrobial-dose doxycycline in the treatment of moderate acne. *Arch Dermatol* 139: 459-464.

²⁵ Walker C, Preshaw PM, Novak J, Hefti AF, Bradshaw M and Powala C. 2000. Long-term treatment with sub-antimicrobial dose doxycycline has no antibacterial effect on intestinal flora. *J Clin Periodontol* 32: 1163-1169.

- Three Phase III, placebo-controlled studies in patients with rosacea: 2 with Oracea (COL-101-ROSE-301 and COL-101-ROSE-302) and 1 with a different product (DERM-303).
- The level of detail provided in these study reports was as follows:
- 110801: A brief report only, lacking protocol and individual subject measurements. The document was not indexed, and referred extensively to documentation which was not presented. The evaluator considered it unevaluable.
- COL-101-SDPK-105, PERIO-DOXYSR-103, PERIO-DOXYSR-104 and COL-101-SSPK-106: Full reports.
- Thomas *et al.* (1998), Walker *et al.* (2000), Thomas *et al.* (2000) and Walker *et al.* (2005): Brief published reports including data from apparently overlapping studies. The evaluator considered this material unevaluable.
- Skidmore *et al.* (2003): A brief published report.
- COL-101-ROSE-301 and COL-101-ROSE-302: Full reports.
- DERM-303: A brief report.

Note. For brevity, study numbers will often be abbreviated to the last 3 digits.

Good Clinical Practice (GCP)

Routine GCP certification was presented for the following studies: COL-101-SDPK-105, PERIO-DOXYSR-103, PERIO-DOXYSR-104, COL-101-SSPK-106, COL-101-ROSE-301, COL-101-ROSE-302 and DERM-303.

GCP was not mentioned in any of the published reports or in the report of Study 110801.

Pharmacokinetics

Studies providing pharmacokinetic data

Table 3 shows the studies relating to each pharmacokinetic topic and the location of each study summary.

Table 3. Submitted pharmacokinetic studies.

PK topic	Subtopic	Study ID
PK in healthy adults	General PK - Single dose	110801 COL-101-SDPK-105 PERIO-DOXYSR-103
	- Multi-dose	PERIO-DOXYSR-104 COL-101-SSPK-106
	Bioequivalence† - Single dose	
	- Multi-dose	
	Food effect	COL-101-SDPK-105

* Indicates the primary aim of the study. † Bioequivalence of different formulations.

Table 4 lists pharmacokinetic results that were excluded from consideration due to study deficiencies.

Table 4. Pharmacokinetic results excluded from consideration.

Study ID	Subtopic(s)	PK results excluded
110801	Absorption at different levels of the intestine.	All
PERIO-DOXYSR-104	Comparison of PK parameters for Oracea 40 mg/day and Periostat 20 mg bd.	C_{max} and T_{max} for Periostat on Day 1, and AUC_{0-24} for Periostat on Day 7.

Summary of pharmacokinetics

The information in the following summary is derived from conventional pharmacokinetic studies unless otherwise stated.

Pharmacokinetics in healthy subjects

Absorption

In single dose studies (103 and 105), under fasting conditions, Oracea mean C_{max} was 510-523 ng/mL; median T_{max} was 2-3 h, and mean AUC from time 0 to infinity ($AUC_{0-\infty}$) was 7962-9227 h.ng/mL. The effect of food was to reduce rate and extent of absorption.

Both multiple-dose studies (104 and 106) were done under quasi-fasting conditions and compared Oracea 40 mg daily to an immediate-release US product (Periostat) 20 mg bd. In Study 104, the mean C_{max} measurements were comparable, as were the median T_{max} values. A valid comparison of AUC_{0-24} during chronic dosing was not available. In Study 106, the mean C_{max} measurements were comparable, as were the mean AUC_{SS} values.

In Study 103, in which Oracea 40 mg was compared to 40 mg of Periostat, the mean C_{max} measurements were 523 and 623 ng/mL for the two treatments, respectively. Corresponding measurements of median T_{max} were 2 and 1.5 h and of mean $AUC_{0-\infty}$ were 7962 and 9570 h.ng/mL. These results raise the question of the extent to which Oracea is in fact a modified-release product.

Evaluator's overall conclusions on pharmacokinetics

The evaluator did not consider the values of C_{max} and T_{max} derived from the pharmacokinetic studies to be accurate, in view of the paucity of sampling points in the relevant time intervals.

The argument purporting to justify the introduction of a controlled-release doxycycline product for the treatment of rosacea is questionable. Even if the rationale described at *Formulation Development* above is accepted, the pharmacokinetic data from Study 103 suggest that if 40 mg daily of an immediate-release product is used, C_{max} values will generally remain below the target maximum of 1.0 µg/mL. The principle that the absorption characteristics of a pharmaceutical should not be unnecessarily complex relates to quality, as does the point in the next paragraph below.

It is questionable whether Oracea has meaningful controlled-release properties. Further study would be required, to elucidate differences from immediate-release products. Preferably, such comparisons should be with a product having the same active (doxycycline monohydrate).

Pharmacodynamics

Studies providing pharmacodynamic data

Table 5 shows the studies relating to each pharmacodynamic topic. Note that none of these studies used Oracea.

Table 5. Submitted pharmacodynamic studies.

PD Topic	Subtopic	Study ID
Primary Pharmacology	Effect on subgingival microflora	Thomas <i>et al.</i> (1998) Walker <i>et al.</i> (2000) Thomas <i>et al.</i> (2000)
	Effect on skin microflora	Skidmore <i>et al.</i> (2003)
	Effect on intestinal and vaginal microflora	Walker <i>et al.</i> (2005)

Skidmore R, Kovach R, Walker C, Thomas J, Bradshaw M, Leyden J, Powala C and Ashley R. 2003. Effects of submicrobial-dose doxycycline in the treatment of moderate acne. *Arch Dermatol* 139: 459-464.

Thomas JG, Metheny RJ, Karakiozis JM, Wetzel JM and Crout RJ. 1998. Long-term sub-antimicrobial doxycycline (Periostat) as adjunctive management in adult periodontitis: Effects on subgingival bacterial population dynamics. *Adv Dent Res* 12: 32-39.

Thomas J, Walker C and Bradshaw M. 2000. Long-term use of subantimicrobial dose doxycycline does not lead to changes in antimicrobial susceptibility. *J Periodontol* 71: 1472-1483.

Walker C, Thomas J, Nango S, Lennon J, Wetzel J and Powala C. 2000. Long-term treatment with subantimicrobial dose doxycycline exerts no antibacterial effect on the subgingival microflora associated with adult periodontitis. *J Periodontol* 71: 1465-1471.

Walker C, Preshaw PM, Novak J, Hefti AF, Bradshaw M and Powala C. 2000. Long-term treatment with sub-antimicrobial dose doxycycline has no antibacterial effect on intestinal flora. *J Clin Periodontol* 32: 1163-1169.

Table 6 lists pharmacodynamic results that were excluded from consideration due to study or presentational deficiencies.

Table 6. Pharmacodynamic results excluded from consideration.

Study ID	Subtopic(s)	PD results excluded
Thomas <i>et al.</i> (1998)	Effect on subgingival microflora	All
Walker <i>et al.</i> (2000)	Effect on subgingival microflora	All
Thomas <i>et al.</i> (2000)	Effect on subgingival microflora	All
Walker <i>et al.</i> (2005)	Effect on intestinal and vaginal microflora	All

Summary of pharmacodynamics

The sponsor's *Clinical Overview* explains that the pharmacodynamic studies presented (all in the form of published papers) are included in the dossier to provide information on whether there is likely to be a risk of resistance induction with Oracea. One of the studies presented (Skidmore *et al.* 2003) provides preliminary reassurance on this point.

Evaluator's overall conclusions on pharmacodynamics

All the pharmacodynamic studies presented were aimed at demonstrating the absence of certain unwanted effects, and thus were related to safety rather than efficacy. The sponsor sought to show that although doxycycline is a known broad-spectrum antibiotic, it lacks (at the dosage used for the claimed indication) a measurable effect in respect of

- antibacterial potency, and
- induction of resistance—specifically in intestinal flora.

In view of the deficiencies noted, regarding the papers Thomas *et al.* (1998), Walker *et al.* (2000), Thomas *et al.* (2000) and Walker *et al.* (2005), the evaluator found proper evaluation of these papers impossible. If the sponsor believes the findings of the studies reported in these papers are important to the application, it should have provided separate, adequately detailed reports of the studies.

In addition to the confusion over exactly which studies are covered by some of the papers presented, there is the question of the extent to which this small selection of published papers provides an objective and unbiased survey of the literature relevant to the antibacterial effect and extent of induction of resistance resulting from treatment with low dose doxycycline. This section of the dossier amounts to a literature-based submission, yet no attempt has been made to comply with the guidelines for such submissions. (See TGA 2003.²⁶)

Thus, in the evaluator's opinion, all that can be derived from the pharmacodynamic studies presented is the preliminary reassurance described *at Summary of Pharmacodynamics* above.

Dosage selection for the pivotal studies

The rationale for the dose used (Oracea 40 mg once daily) was:

- An expectation (based on previous studies) that it would produce plasma doxycycline levels not exceeding 1 µg/mL over the 24 hours in chronic treatment. This concentration was considered to be below that required for an antimicrobial effect on many common micro-organisms.
- Study DERM-303, which demonstrated some efficacy in rosacea of doxycycline 20 mg (as hydrochloride) bd.

Efficacy

Indication: facial rosacea

Pivotal efficacy studies

The evaluator has used the term "pivotal" when referring to Studies 301 and 302 for convenience, because the studies are so designated by the sponsor. However, for the reason given under *Effect of food* (Attachment 1), the evaluator believes that the studies are in fact of little assistance to the application.

²⁶ TGA. 2003. Literature-Based Submissions. *Points to Consider*. www.tga.gov.au

Studies COL-101-ROSE-301 and COL-101-ROSE-302

The designs of these two studies were identical except that a 4 week extension was added to Study 302 to assess the longevity of the treatment effects. In that study, double-blind treatment ceased at 16 weeks and in the period between Week 16 and Week 20 visits, patients were instructed to refrain from taking the study drug or any systemic or topical rosacea or acne medication or any prohibited Concomitant Medication.

Evaluator's conclusions on clinical efficacy

The aetiology of rosacea is not known and the mode of action of doxycycline in this condition is uncertain. The sponsor suggests, largely on the basis of published nonclinical studies, that low dose doxycycline has an anti-inflammatory effect, at dosage below that required for a significant antimicrobial effect. This is a matter for the nonclinical evaluator, or for possible future clinical studies, preferably in conditions of known aetiology in which microorganisms are not thought to play any role. The evaluator did not consider that approval of the present application need depend upon elucidation of the mode of action.

Major problems

Modified-release property

A fundamental problem with the present application is lack of evidence that the modified-release property of Oracea is necessary to its use in rosacea. See *Evaluator's Overall Conclusion on Pharmacokinetics*, above. The relevant guideline (EMA 2000)²⁷ states, at section 2.1 (of guideline):

"The development of a prolonged or delayed release formulation has to be based on a well-defined clinical need and on an integration of physiological, pharmacodynamic and pharmacokinetic considerations."

Speculation about the mode of action, or about a possible advantage over immediate release preparations regarding resident microflora, cannot in my opinion take the place of clinical testing, aimed at establishing whether Oracea has any efficacy or safety advantage over a once daily dose of an immediate release preparation.

Effect of food

An unusual feature of this application is that the main efficacy and safety studies have been done with a modified-release preparation. Although those studies have demonstrated some efficacy and provided safety data, we do not know (because the study protocols were silent on the matter) exactly how the patients were treated: that is, with Oracea taken in fasting conditions, or Oracea taken with food. This point is important, because food has been shown (in Study 105) to have a significant effect on absorption, particularly on C_{max} , and the fundamental rationale for the product's development (see *Clinical Rationale* above) relates particularly to the C_{max} which it produces. It is the clinical evaluator's opinion therefore that Studies 301 and 302 contribute no valid efficacy data to the application. The sponsor argues:

"In the single-dose food-effect study involving healthy volunteers ... concomitant administration of Oracea with a 1000 calorie, high-fat, high protein meal that included dairy products resulted in a decrease in peak plasma levels of 43.4% and a decrease in overall doxycycline exposure of 20.3% compared to fasted conditions."

²⁷ European Agency for the Evaluation of Medical Products (EMA). 1999. *Note for Guidance on Modified Release Oral and Transdermal Dosage Forms: Section II (Pharmacokinetic and Clinical Evaluation)*. Document CPMP/EWP/280/96.

Thus, the decrease in overall exposure to doxycycline following a high-fat meal (arguably the worst case situation) was modest and is smaller than the variability between the genders observed in the same study Patients in the Phase 3 clinical studies were advised to take Oracea capsules once daily in the morning, with no specific instruction with respect to ingestion before or after food. In view of the limited effect of food on doxycycline bioavailability from Oracea and in view of the efficacy observed in Phase 3 studies where timing of dose in relation to meals was not restricted, it is considered that Oracea may be administered with or without food in clinical practice."

The evaluator rejected every part of this argument. The decrease in overall exposure resulting from food is significant and the decrease in peak level is substantial. The sponsor has implied elsewhere (other parts of the sponsor's submission) that the latter is of particular relevance in the present application. The argument in the last sentence lacks logic. The fact that some efficacy was demonstrated in a trial with unrestricted dosing conditions leaves open the possibility that efficacy or safety might have been different in patients who dosed (say) 2 hours before breakfast, compared to efficacy or safety in patients who dosed after breakfast. (The data on "responders" above are also relevant to this point.)

Dose-finding

As no dose-finding studies were presented, it is not known whether the dosage proposed is optimal.

Other problems

As rosacea is a clinical diagnosis, some patients with other diagnoses may have been enrolled in the clinical trials. The exclusion criterion relating to topical corticosteroid use would have excluded patients with steroid-induced acne, and the requirement for telangiectasia would have reduced the risk of including adult-onset acne patients in the studies. However, the possibility exists that some of the responses in the pivotal studies may have been in patients who in fact suffered from adult-onset acne rather than rosacea.

From the outcome of the pivotal studies, the benefit of Oracea treatment in rosacea appears to be modest, and confined to certain aspects of the condition. Erythema is a principal feature but benefit was not consistent across the studies. Telangiectasia is often a prominent aspect of rosacea and presence of this feature was an inclusion criterion in the pivotal studies. However, telangiectasia was not considered in any of the efficacy measures (presumably because it was thought unlikely to respond).

As symptoms in rosacea are principally concerned with its appearance, it would have been of interest to include patient self-assessments in the pivotal studies. This is particularly relevant in the present application, where one of the principal features of the condition is regarded as refractory to the treatment studied (see previous paragraph).

There were no studies comparing Oracea with any other active treatment such as topical metronidazole or azelaic acid. Studies with active comparators are of particular interest where the first Phase III studies show only a small benefit.

Safety

Studies providing evaluable safety data

The following studies provided evaluable safety data:

Pivotal efficacy studies

In the pivotal efficacy studies, the following safety data were collected:

- General adverse events (AEs) were assessed by open-ended questioning at each study visit (Weeks 3, 6, 12 and 16).
- Routine haematology and clinical chemistry laboratory tests at baseline and study end (Week 16).

Dose-response and non-pivotal efficacy studies

Safety data from Study DERM-303 not included, as Oracea was not administered in that study.

Clinical pharmacology studies

Of the clinical pharmacology studies presented, only the following used Oracea: COL-101-SDPK-105, PERIO-DOXYSR-103, PERIO-DOXYSR-104 and COL-101-SSPK-106. Adverse events (AEs), vital signs, haematology and clinical chemistry were recorded in these studies, all of which enrolled participants who were not in the target population and who received Oracea for periods of a week or less.

Pivotal studies that assessed safety as a primary outcome

None presented.

Patient exposure

Table 7. Exposure to Oracea and comparators in clinical studies. Numbers of subjects.

Study type	Controlled studies			Uncontrolled studies	Total Oracea
	Oracea	Placebo	Periostat	Oracea	
Clinical pharmacology¹	93	0	63	0	93
Phase III					
Pivotal	269	268		0	269
Other	0	67	67	0	0
TOTAL	362	335	130	0	362

¹ Studies COL-101-SDPK-105, PERIO-DOXYSR-103, PERIO-DOXYSR-104 and COL-101-SSPK-106.

Table 8. Exposure to Oracea in clinical studies according to dose and duration.

Study type	Proposed dose range			
	≥ 3 mo.	≥ 6 mo.	≥ 12 mo.	Any duration
Clinical pharmacology	0	0	0	93
Phase III				
Placebo-controlled	269	0	0	269
Active-controlled	0	0	0	0
Uncontrolled	0	0	0	0
TOTAL	269	0	0	362

Evaluator's overall conclusions on clinical safety

The safety data from Studies 301 and 302 are of only ancillary value, for the reason given under *Effect of food* in *Evaluator's Conclusions on Clinical Efficacy*.

The safety data from the pivotal studies suggest that use of Oracea is associated with gastrointestinal AEs, and that the possibility of an effect on blood pressure (BP) should remain under review although currently they do not raise any major concern. Also, safety should be considered in the context of the long history of doxycycline use at dosages of 100 mg daily, often for months at a time (as an anti-malarial), a fact which provides useful general safety reassurance.

Studies like that of Skidmore *et al.* (2003) can provide some reassurance in relation to the point described. But

- the concept of attempting to identify a particular plasma concentration of an antibiotic, below which micro-organisms, wherever they occur in the body, are not expected to be affected is, in the evaluator's opinion, fundamentally flawed; and
- any study which focuses on examination of the microflora in small patient groups leaves open the possibility that some unrecognised or unstudied microorganism may be affected by prolonged treatment with low-dose doxycycline which may result in adverse results for the patient.

In principle, this aspect of safety should involve use of the actual product proposed for registration. Ultimately, Phase III clinical studies of adequate size and duration must be relied upon for safety reassurance, including reassurance on the question of possible effects of low dose doxycycline on microflora. Thus, the evaluator had doubts that there would be much to gain from the submission of further studies of the kind considered under *Pharmacodynamics* above. The question of co-morbidities, which may require periodic antibiotic treatment, should also be given some consideration. For example, Chronic obstructive pulmonary disease (COPD) affects > 1 million Australians, and for initial treatment of exacerbations therapeutic guidelines recommend amoxicillin or doxycycline²⁸. It would be of interest to study if exacerbations in patients with COPD taking long-term low-dose doxycycline for rosacea are more difficult to treat. The

²⁸ Therapeutic Guidelines Limited. 2010. *Therapeutic Guidelines: Antibiotic*. 14th ed.

guideline for the assessment of clinical safety for populations exposed to medicines intended for long-term treatment of non-life-threatening conditions²⁹ recommends 300-600 patients over 6 months, with perhaps 100 patients exposed for 1 year. In view of the point made in the first paragraph in this section, in the evaluator's opinion further Phase III trials need to include at least 300 patients studied over 6 months, with specific attention being given to problems which may result from an effect on resident microflora.

List of questions

The evaluator considered that there was no point in pursuing this application further unless the sponsor can provide a justification to support the pivotal studies. If the sponsor is able to provide this, then the sponsor might be invited to

- address the problem raised under Modified-release property under Evaluator's Overall Conclusions on Clinical Efficacy, Major Problems; and
- respond to the question of whether Oracea has meaningful modified-release properties (see Summary of Pharmacokinetics, Absorption above).

Clinical summary and conclusions

Preliminary benefit-risk assessment and recommendations

Preliminary assessment of benefits

In view of the evaluator's opinion on the flaws in the pivotal studies, the evaluator makes the assessment that there is no valid efficacy data and no benefits have been established.

The reported benefits of the treatment proposed are modest but these have not been subjected to patient self-assessment or compared to benefits offered by other treatment (see *Evaluator's Overall Conclusions on Clinical Efficacy, Major Problems*, above).

Preliminary assessment of risks

The evaluator believed that the safety has not been adequately studied (see *Evaluator's Overall Conclusions on Clinical Safety*).

Preliminary assessment of benefit-risk balance

In view of the preliminary assessments detailed in *Preliminary Assessment of Benefit-Risk Balance* above, the evaluator considered that the benefit-risk balance is unfavourable. Also, the evaluator has recorded that assessment of the benefit-risk balance requires dose-finding studies, which have not been done.

Preliminary recommendation regarding authorisation

The evaluator recommended rejection, on the grounds of

- inadequate evidence of quality (see Evaluator's Overall Conclusions on Clinical Pharmacokinetics above); and
- an unfavourable benefit-risk balance (see Preliminary Assessment of Benefit-Risk Balance above).

²⁹ European Union (EU). 1998. The extent of population exposure to assess clinical safety for medicines intended for long-term treatment of non-life-threatening conditions. *Rules 3(c) - 3cc5a*, pages 121-125.

V. Pharmacovigilance findings

The TGA's Office of Product Review did not require an RMP evaluation for this product.

VI. Overall conclusion and risk/benefit assessment

The submission was summarised in the following Delegate's overview and recommendations:

Quality

A number of issues were raised during the quality evaluation and the sponsor has not adequately addressed these. The evaluator has commented that specifications and controls are not adequate to ensure consistent quality of the drug product. The evaluator has therefore recommended rejection of the application.

The application had been considered at the August 2011 meeting of the PSC. No objections to registration were raised (provided that issues outstanding at that time were resolved by the TGA). The Committee considered that modified release characteristics had not been demonstrated for the product.

Nonclinical

There were no preclinical objections to registration.

Toxicity was studied in rats and monkeys. Toxic effects in the stomach were observed in the animal studies but were minor at the exposure levels likely to be achieved in humans. Irritation of the stomach is a known adverse event of doxycycline. Pigment deposition in the thyroid, a known effect of tetracyclines, was also observed but was considered to be of limited toxicological concern. Mild renal changes were also observed in monkeys. Fertility studies in rats indicated an adverse effect on sperm.

Clinical

The clinical evaluator has recommended rejection of the application on a number of grounds. The sponsor has provided a response to the questions raised by the evaluator (see *Response from Sponsor* below).

Pharmacokinetics (PK)

The product was developed with a view to obtaining C_{max} values below a level of 1.0 µg/mL, as it was considered that doxycycline would not have antimicrobial effects at this concentration and would therefore not be associated with the risk of the development of antimicrobial resistance.

The submission included a study (Study 103) which compared the PK of a single dose of the Oracea 40 mg formulation with a single dose of 40 mg of an IR formulation of doxycycline hydrochloride ('Periostat', not registered in Australia). The Oracea product (treatment A) was associated with a lower mean C_{max} value compared to 40 mg of the IR formulation (523 versus 623 ng/mL). However, the product did not display any other characteristics normally associated with a modified or 'slow' release product in that T_{max} was only slightly delayed (2.0 versus 1.5 hours) and half-life was not prolonged (15.1 versus 20.8 hours).

The submission also included two studies (Studies 104 and 106) which compared the PK of 40 mg Oracea with 20 mg bd of the IR formulation over 7 days. The C_{max} and AUC values at Day 7 were comparable for the two products, suggesting that the Oracea product does produce reduced C_{max} compared to this IR formulation, without a reduction in bioavailability.

There were no PK data comparing the Oracea product with the doses of an IR formulation currently used in the treatment of rosacea (such as 50–100 mg per day).

A study examining the effect of food on the absorption of the product was also provided (Study 105). Administration with food resulted in a 44% reduction in C_{max} and a 20% reduction in AUC.

Pharmacodynamics (PD)

The sponsor included five published papers which described placebo-controlled clinical studies which examined the ability of a low dose of IR doxycycline (Periostat 20 mg bd) to cause antibiotic resistance in human bacterial flora (gingival, skin, intestinal and vaginal). The evaluator considered four of these papers to be unevaluable. In one remaining paper (Skidmore *et al*, 2003) treatment with doxycycline for 6 months was not associated with significant differences in skin flora microbial colony counts or the development of antibiotic resistance, compared to placebo.

Efficacy

Evidence for efficacy comes from two pivotal, randomised, double-blind, placebo-controlled, parallel group design trials (Studies 301 and 302) which had essentially an identical design. Subjects enrolled had:

- a clinical diagnosis of rosacea;
- 10-40 inflammatory lesions;
- an Investigator's Global Assessment (IGA) score of 2-4 (possible range = 0-4);
- an erythema score of 5-20 (possible range = 0-20);
- telangiectasia.

Subjects were randomised to receive either Oracea 40 mg or placebo once daily in the morning. Treatment was continued for 16 weeks.

The primary efficacy outcome was the change in total inflammatory lesion (TIL) count. In both trials, active treatment was associated with a statistically significant reduction in TIL count.

A number of secondary endpoints were also studied. Oracea reduced erythema in Study 301 to statistically significant but clinically modest, extent. However, erythema was not significantly improved in Study 302. The IGA score was improved significantly in both studies as was the proportion of patients who achieved an IGA score of 0 (clear) or 1 (near clear).

In Study 302, after treatment was discontinued at 16 weeks, an additional follow-up visit was conducted at Week 20. Benefit in terms of TIL count was maintained at Week 20. There was one supportive efficacy study (DERM-303) which was conducted with the IR Periostat formulation given at a dose of 20 mg bd for 16 weeks. Active treatment was associated with a significant reduction in TIL count, but no benefit in terms of erythema.

Safety

A total of 269 patients with rosacea received the Oracea product in the submitted pivotal studies. A total of 216 completed the planned 16 weeks of treatment.

Compared to placebo, Oracea treatment was associated with an increased incidence of gastrointestinal adverse events (AEs) such as diarrhoea and abdominal pain. There was also an increased incidence of aspartate aminotransferase (AST) elevations (2.2% versus 0.7%) and hypertension (3.0% versus 0.7%). Overall the evaluator considered that the safety data from the pivotal studies did not raise any major concerns. The long history of doxycycline use also provides reassurance regarding the safety of the product.

The evaluator considered that the major safety issue associated with the product was the potential for long term use of low doses of doxycycline to be associated with the development of microbial resistance in resident microflora, or the development of opportunistic infections. In the evaluator's view the submitted data did not provide adequate reassurance on this issue.

Risk management plan

The TGA's Office of Product Review did not require an RMP evaluation for this product.

Risk-benefit analysis

Delegate considerations

Issues

1. Clinical evaluator's concerns

The clinical evaluator has recommended rejection of the application on multiple grounds. The specific issues raised are discussed below:

A. Need for a modified release (MR) formulation.

The rationale given by the sponsor for developing the product as an MR formulation was to keep C_{max} levels below a certain level (1.0 µg/mL) so as to avoid the product producing antimicrobial effects and therefore reduce the likelihood of development antimicrobial resistance. The evaluator noted that levels below 1.0 µg/mL were achieved with a 40 mg IR formulation (Study 103) and therefore questioned the need for the modified release formulation.

Study 103 suggests that the MR formulation does produce *lower* C_{max} values than 40 mg of an IR formulation (523 versus 623 ng/mL). Studies 104 and 106 indicated that the 40 mg MR formulation produces comparable C_{max} values to a 20 mg bd regimen of an IR formulation. If the development of antimicrobial resistance is a significant issue, then the low C_{max} produced by the product would be a desirable characteristic, regardless of the pre-specified level of 1.0 µg/mL.

B. Is the product a modified release formulation?

The evaluator noted that although the product had a reduced C_{max} compared to 40 mg of an IR formulation, it did not display other characteristics usually associated with an MR formulation, such as delayed T_{max} and prolonged half-life. Also there were no data comparing the product to an IR formulation of doxycycline *monohydrate* or an IR formulation marketed in Australia.

If a reduction in C_{max} is the desired outcome of modifying the formulation, then the submitted data suggest that this has been achieved. Prolongation of T_{max} or half-life would not add any further benefit. The Delegate did not consider that this issue should preclude registration.

C. Effect of administration with food.

Co-administration with food resulted in a 43% reduction in C_{max} and a 20% reduction in AUC (Study 105). Reduction in C_{max} is unlikely to be clinically significant and may have some theoretical advantage in terms of prevention of antimicrobial resistance. The evaluator considered that the decrease in AUC was significant.

In the pivotal studies, patients were able to take the product with or without food. Although statistically significant efficacy was established in the trials, the concern would be that the product was only effective in those subjects who took it in the fasting state and that it would have been rendered ineffective in those who took it with food. In the absence of efficacy data for doses lower than 40 mg, it is not possible to determine the effect on efficacy of a 20% reduction in AUC.

A possibility would be to approve the product but only with administration in the fasted state. However, tetracyclines are normally taken with food, to avoid gastro intestinal tract (GIT) irritation and hence this approach would be associated with some safety concerns. In retrospect it would have been prudent for the sponsor to have recommended that the product be taken with food in the pivotal studies.

The Delegate is therefore inclined to agree with the evaluator that the effect of food on the efficacy of the product has not been adequately defined.

D. Development of antimicrobial resistance.

As indicated above, the rationale given by the sponsor for developing the product as an MR formulation was to keep C_{max} levels below a certain level (1.0 $\mu\text{g}/\text{mL}$) so as to avoid the product producing antimicrobial effects and therefore reduce the likelihood of development antimicrobial resistance. The evaluator did not accept that avoidance of antimicrobial resistance had been established, or that the product has any advantage over IR formulations of doxycycline.

According to a review of the literature included in the submission, minimum inhibitory concentration (MIC) values for doxycycline were in the range 0.015 to 14 $\mu\text{g}/\text{mL}$ (nonclinical evaluation report [NER]). The nonclinical evaluator noted that the C_{max} values for the product (0.6 $\mu\text{g}/\text{mL}$ for total drug and \sim 0.06 $\mu\text{g}/\text{mL}$ for free doxycycline) lie *above* the lower MIC values in this range. Also, doxycycline is extensively distributed to tissues (NER) and doxycycline concentrations in tissues with resident microflora may be higher than the C_{max} . The drug is also excreted in faeces so that intestinal microflora may be at particular risk.

The clinical data provided on the development of antimicrobial resistance were limited to five published papers. The clinical evaluator considered four of these to be not evaluable. The fifth (Skidmore *et al* 2003) provided some reassurance that long term treatment with doxycycline did not result in the development of resistance in skin microflora.

Overall, the Delegate would agree with the evaluator that it cannot be concluded that the product will not be associated with the development of antimicrobial resistance. If the product were to be approved, all claims to this effect should be removed from the product information. However, the Delegate does not consider this issue should preclude registration. Currently marketed IR formulations (containing 50 mg of doxycycline) are approved and used for the long term treatment of acne. A 40 mg presentation, with a low C_{max} , would appear to present less of a risk for the development of antimicrobial resistance. Also, the National Health and Medical Research Council's (NHMRC's) Expert Advisory Group on Antimicrobial Resistance (EAGAR) in 2003 considered the impact of doxycycline resistant bacteria would be low (copy of document included in agenda papers but not in this AusPAR).

E. Clinical significance of the efficacy benefit.

Although a significant benefit in terms of reduction in the number of inflammatory lesions was demonstrated, the evaluator considered efficacy to be modest, in that it had no consistent effect on erythema and no demonstrated effect on telangectasia. There were also no patient assessments of efficacy.

The Committee's advice is sought as to the clinical significance of the efficacy benefit.

F. Lack of dose finding studies.

The application seeks approval for a 40 mg daily dose. Current clinical practice in the treatment of rosacea typically involves the use of doses of 50 mg per day. The Delegate therefore does not consider the absence of data on doses below 40 mg per day to be a significant deficiency in the application.

G. Lack of comparative data.

The submission did not include any studies comparing the product with registered topical therapies for rosacea (such as metronidazole cream, azelaic acid). Such studies would have been valuable. However, systemic therapy such as doxycycline is usually used in situations where topical therapy has failed.³⁰ The Delegate did therefore consider that use of a placebo control in the pivotal studies was acceptable.

2. Product Information

Changes were recommended to the draft PI but these are beyond the scope of this AusPAR.

Proposed action

The Delegate proposed to reject the application due to the unresolved quality issues, and on the grounds that the effect of food on efficacy has not been adequately defined.

The advice of the Committee (ACPM) is requested, especially as to whether any of the other issues identified by the clinical evaluator should be grounds for rejection.

Response from sponsor

General statement

Galderma wished to remind the ACPM that Oracea was approved in the USA on 26 May 2006. Oracea has been approved through a Decentralised Procedure in Austria, Finland, Germany, Ireland, Italy, Luxemburg, the Netherlands, Sweden and the United Kingdom (UK) after a positive opinion of the Committee for Medicinal Products for Human Use

³⁰Therapeutic Guidelines: Dermatology – Version 2, 2004; Therapeutic Guidelines Ltd

(CHMP) on July 2008, and through a Mutual Recognition Procedure in Belgium, Czech Republic, Denmark, Greece, Spain, France, Hungary, Iceland, Poland, Portugal, Norway and Slovakia on October 2010. UK was acting as the Reference Member State (RMS) in these procedures.

Oracea has also been approved in Canada on 14 December 2011.

Oracea is currently marketed in the USA, Finland, Germany, the Netherlands, Sweden and the UK.

Events of pseudomembranous colitis, colitis/gastritis/gastric ulcerations/esophagitis/oesophageal ulcerations and photosensitivity reactions are closely monitored. During the period mentioned above, no new safety concern has been identified regarding these events which could change the benefit/risk ratio of Oracea. These events will continue to be closely monitored.

During the same period, there were no major findings bearing on the established overall safety profile of the product. The overall risk profile remains stable.

Pharmaceutical chemistry data

The Company refers to the August 2011 meeting of the PSC when it found that there were no objections to registration provided that issues outstanding at that time were resolved.

Galderma provided assurance that all issues raised by the TGA would be addressed should the registration approval be granted.

Question 1

Regarding the drug substance, reference is made to Galderma's response to the TGA quality evaluator's comments on 20 January 2012. Doxycycline hyclate used as starting material is covered by a Certificate of Conformity to the European Pharmacopeia (CEP) and therefore the adequacy between the quality control and the synthesis process has been validated by the European Directorate for the quality of Medicines & HealthCare (EDQM).

Questions 2, 10, 24, 25, 27

Galderma wishes to provide assurance that revised controlled documentation from the drug product manufacturer (including specifications and methods of control) according to the evaluator's request would be provided to the TGA once available.

Questions 15, 17, 18

Galderma wished to provide assurance that additional information concerning the dissolution specification for IR and DR beads, the holding time for IR and DR beads, the in-process controls for fill weight (IR and DR beads) would be provided to the TGA.

Question 19

Galderma wished to provide assurance that a retrospective analysis of the drug product batches already manufactured to confirm the effective validation of the manufacturing process would be provided to the TGA.

Question 23

Galderma wished to provide assurance that compliance with the TGA guideline *Supplementary Requirements for minimising the risk of transmitting transmissible spongiform encephalopathy* (TSEs), including record keeping, will be undertaken.

Question 35

The company refers to the response to the TGA chemistry evaluator's comments on 20 January 2012 where an answer was provided.

Question 42

Stability data from the ongoing stability studies will be provided to the TGA once available.

Clinical data:

The main issues concerns of the clinical evaluator raised in the TGA Delegate's report are addressed as follows:

*Issues A and B (Pharmacokinetic)**A. Need for a modified release (MR) formulation**B. Is the product a modified release formulation?*

Galderma wishes to confirm that a reduction in C_{max} is the desired outcome for Oracea. The reduction of the C_{max} is achieved as demonstrated by the PK studies provided and as noted by the clinical evaluator.

Issue C (Effect of administration with food):

Regarding the efficacy in the pivotal studies the conditions of drug administration were not established precisely. In particular it was not stated if the drug was to be taken in a fasting state. It can reasonably be excluded that all the patients were in the same state (either fasting or fed). More reasonably, it can be anticipated that some patients took the drug concomitantly with food. Therefore, in the pivotal studies the level of efficacy observed is probably inferior to the efficacy which would have been observed if the drug was taken as proposed in the amended Product Information which is to avoid the effect of food on the bioavailability of doxycycline monohydrate. Please refer to the amended Product Information in Appendix C which states under "*Dosage and Administration*" that "*The capsule should be taken in the morning on an empty stomach with adequate amounts of water*".

Issue D (Development of antimicrobial resistance):

Galderma agreed to remove all claims that Oracea will not be associated with antimicrobial resistance from the Product Information, although Oracea would be expected to present a lower risk for the development of antimicrobial resistance than currently marketed 50 mg formulations.

Issue E (Clinical significance of the efficacy benefits):

Rosacea is a chronic inflammatory disorder primarily affecting the face and has the potential to cause major emotional and psychological consequences. The key goals of treatment are to alleviate the signs and symptoms of the condition to improve appearance and to delay or prevent disease progression. The treatment of rosacea with doxycycline at doses of 50-100 mg/day is well established in clinical practice and results in plasma concentrations that may increase the risk of developing resistant microorganisms. The efficacy benefit of treatment with doxycycline resulting in a reduction of papules and pustules is thought to be exerted via multiple anti-inflammatory mechanisms.

The efficacy of an anti-inflammatory dose of doxycycline 40 mg, modified-release, (Oracea) administered once daily for the treatment of adults with papulopustular rosacea has been shown to offer a statistically significant therapeutic benefit in terms of a reduction in total inflammatory lesions and Investigator Global Assessment (IGA). This benefit also includes a lower risk of adverse events, especially gastrointestinal side effects. Plasma concentrations of doxycycline observed during Oracea treatment are maintained

at levels below those required to exert an antimicrobial effect. This is expected to be associated with a lower risk of the development of antimicrobial resistance.

Treatment with Oracea provides patients with an improvement in their symptoms and physical appearance and offers relief from the psychological and social consequences of the condition.

The availability of Oracea in Australia as a treatment option is supported by an Australian dermatologist who frequently prescribes doxycycline to alleviate the symptoms of rosacea.

Advisory committee considerations

The Advisory Committee on Prescription Medicines (ACPM), having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, advised the following:

The ACPM, taking into account the submitted evidence of quality, safety and efficacy agreed with the Delegate that this product has an overall **negative benefit-risk profile** for the new presentation for the proposed indication.

In making this recommendation the ACPM noted the unresolved quality issues; however, the committee was of the view that these matters might be addressed through further discussions between the sponsor and the TGA.

The ACPM considered that the clinical relevance of the outcome measures assessed was doubtful; the lack of dose finding studies in relation to the currently acceptable dosing of 50-100 mg and the lack of pharmacokinetic data supporting the label of "*modified release*".

The long term safety, in terms of risk of antibiotic resistance for the proposed modified release formulation remained inadequately addressed and of concern.

The ACPM advised that the potential for resistance may indeed be increased with bacterial exposure to low levels of doxycycline below the MIC.

Further, the ACPM did not believe the advice to use this product on an empty stomach was safe in view of the dosage and administration requirements for this drug substance in an immediate release formulation and the effect of food on clinical efficacy was poorly defined in the pivotal trials.

Outcome

Based on a review of quality, safety and efficacy, TGA rejected the application for registration of Oracea (doxycycline monohydrate).

Findings on material questions of fact and evidence relied upon

Section 25 (1) (d) of the Act requires that applications made under section 25 of the Act are to be evaluated having regard to whether the quality, safety and efficacy of the goods, for the purposes for which they are to be used, have been satisfactorily established.

The Delegate's findings with regard to quality, safety and efficacy are as follows:

Quality

There are multiple unresolved issues relating to the chemistry, manufacturing and quality control of Oracea capsules.

Evidence: the quality evaluations.***Efficacy***

The two pivotal studies submitted with the application (301 and 302) demonstrated that in patients with facial rosacea, treatment with Oracea was associated with statistically significant improvements in the following parameters, compared to placebo treatment:

- The total inflammatory lesion count (papules plus pustules plus nodules);
- The investigators' global assessment (IGA) score;
- The proportion of patients who achieved an IGS score of 0 (clear) or 1 (near clear).

Evidence: data from the application, the clinical evaluation.

The two pivotal studies submitted with the application did not consistently demonstrate statistically significant improvements in erythema.

Evidence: data from the application, the clinical evaluation.

Independent expert opinion indicated that the clinical relevance of the demonstrated efficacy benefits was doubtful.

Evidence: The ACPM minutes.

Co-administration of Oracea with food results in a significant reduction in systemic absorption of the active ingredient doxycycline.

Evidence: data from the application, the clinical evaluation.

In the pivotal studies, patients were instructed to take Oracea with or without food. From the submitted data it was not possible to determine the effect of co-administration with food on efficacy outcomes.

Evidence: data from the application, the clinical evaluation.***Safety***

Administration of doxycycline without food has been associated with gastrointestinal adverse effects such as gastric irritation and oesophagitis. It is generally recommended that doxycycline should be taken with food to avoid such effects.

Evidence: The Vibramycin PI, the Therapeutic Guidelines,

In the pivotal studies, patients were instructed to take Oracea with or without food. From the submitted data it was not possible to determine the safety profile of Oracea if taken in the fasted state.

Evidence: data from the application, the clinical evaluation.

The sponsor has agreed to remove any claims for the product to the effect that it is not associated with the development of antimicrobial resistance.

Evidence: the pre-ACPM Response.***Reasons for the decision***

As there are multiple unresolved issues relating to the chemistry, manufacturing and quality control of Oracea capsules, the Delegate concluded that the quality of the product has not been satisfactorily established.

Administration of Oracea with food results in a significant reduction in the systemic absorption of the active ingredient doxycycline. This may translate into a reduction in efficacy. From the submitted data it was not possible to determine what proportion of patients in the pivotal studies had taken Oracea with food. It was therefore not possible to

determine whether Oracea would be effective when taken with food. As the clinical relevance of the efficacy benefits of the product in the pivotal studies were doubtful, any potential reduction in that efficacy caused by co-administration with food would be of concern. The Delegate therefore concluded that the efficacy of the product, when taken with food, has not been satisfactorily established.

Administration of a doxycycline product such as Oracea in the fasted state has the potential to cause significant gastrointestinal adverse effects. From the submitted data it was not possible to determine what proportion of patients in the pivotal studies had taken Oracea without food. It was therefore not possible to determine whether Oracea would be safe when taken without food. The Delegate therefore concluded that the safety of the product, when taken without food, has not been satisfactorily established.

The Delegate therefore decided to reject the application.

Attachment 1. Extract from the Clinical Evaluation Report

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