Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

EFRACEA 40 mg modified-release hard capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 40 mg doxycycline (as monohydrate).

Excipients with known effect: 102 – 150 mg of sucrose and 26.6 - 29.4 microgram of Allura red AC aluminium lake (E129).

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Modified-release hard capsule

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

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

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

4.2 Posology and method of administration

Posology
Adults, including older people:
Oral use.

The daily dose is 40 mg (1 capsule). It can be taken as monotherapy or as part of combination treatment (see section 5.1).

Patients with renal impairment
No dosage adjustment is necessary in patients with renal impairment.

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

Paediatric population
Efracea is contraindicated in children below 12 years of age (see section 4.3).

Method of administration
The capsule should be taken in the morning, on an empty stomach, preferably at least one hour prior to or two hours after the meal.
The capsule should be taken with adequate amounts of water in order to reduce the risk of oesophageal irritation and ulceration (see section 4.4).

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

4.3 Contraindications

Hypersensitivity to the active substance, to other tetracyclines or to any of the excipients listed in section 6.1.

Infants and children up to 12 years of age.

Second and third trimesters of pregnancy (see section 4.6).
Concomitant treatment with oral retinoids (see section 4.5).

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

4.4 Special warnings and precautions for use

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

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

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

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

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

The bioavailability of doxycycline is reported to be reduced at high pH (also see section 4.5).

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

All patients receiving doxycycline, including Efracea, should be advised to avoid excessive sunlight or artificial ultraviolet light whilst receiving doxycycline and to discontinue therapy if phototoxicity (eg skin eruption etc) occurs. Use of sunscreen or sunblock should beconsidered. Treatment should cease at the first sign of photosensitivity.
In common with the use of antimicrobial medicinal products in general, there is a risk of the developmentof pseudomembranous colitis with doxycycline treatment. In the event of the development of diarrhoea during treatment with Efracea, the possibility of pseudomembranous colitis should be considered and appropriate therapy instituted. This may include the discontinuation of doxycycline and the institution of specific antibiotic therapy. Agents inhibiting peristalsis should not be employed in this situation.

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

In humans, the use of tetracyclines during tooth development may cause permanent discolouration of the teeth (yellow-grey-brown). This reaction is more common during long-term use of the medicinal product but has been observed following repeated short-term courses. Enamel hypoplasia has also been reported. As for other tetracyclines, doxycycline forms a stable calcium complex in any bone-forming tissue. A decrease in fibula growth has been observed in premature

infants given oral tetracycline in doses of 25 mg/kg every 6 hours. This reaction was shown to be reversible when the medicinal product was discontinued.

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

Some patients with spirochete infections may experience a Jarisch-Herxheimer reaction shortly after doxycycline treatment iss tarted. Patients should be reassured that this is a usually self-limiting consequence of antibiotic treatment of spirochete infections.

Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicinal product.
Capsule printing ink contains Allura red AC aluminium lake (E129) which may cause allergic reactions.

4.5 Interaction with other medicinal products and other forms of interaction

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

Interactions affecting doxycycline:

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

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

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

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

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

Interactions affecting other medicinal products:

Concomitant use not recommended:

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

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

Other interactions:

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

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

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

4.6 Fertility, pregnancy and lactation

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

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

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

Fertility
Oral administration of doxycycline to male and female Sprague-Dawley rats adversely affected fertility and reproductive performance (see section 5.3).
The effect of Efracea on human fertility is unknown.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

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

Tabulated list of adversereactions
The table below lists adverse reactions on Efracea in the pivotal clinical trials, ie adverse reactions for which the frequency on Efracea was greater than the frequency on placebo (by ³ 1%).
Adverse reactions reported for tetracycline antibiotics as a class are listed following the table. The adverse reactions are classified by System Organ Class and frequency, using the following convention: very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to <1/1,000),very rare (< 1/10,000), not known (cannot be estimated from the available data) and were reported with Efracea in clinical studies (see Table 1).

Table 1 - Adverse reactions[a] on Efracea inpivotal placebo-controlled studies in rosacea:

MedDRA system organ class	Common: Frequency ³ 1/100, < 1/10
Infections and infestations	Nasopharyngitis Sinusitis Fungal infection
Psychiatric disorders	Anxiety
Nervous system disorders	Sinus headache
Vascular disorders	Hypertension
Gastrointestinal disorders	Diarrhoea Abdominal pain, upper Dry mouth

Musculoskeletal and connective tissue disorders	Back pain
General disorders and administration site conditions	Pain
Investigations	ASAT increased Blood pressure increased Blood LDH increased Blood glucose increased

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

Benign intracranial hypertension and headache (unknown frequency: cannot be estimated from the available data) have been reported during EFRACEA postmarketing surveillance.

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

Infections and infestations:
Very rare: Anogenital candidiasis

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

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

Endocrine disorders:
Very rare: Brown-black microscopic discolouration of thyroid tissue has been reported with long-termuse of tetracyclines. Thyroid functionis normal.

Nervous system disorders:
Rare: Benign intracranial hypertension
Very rare: Bulging fontanelle in infants

Treatment should cease if evidence of raised intracranial pressure develops. These conditions disappeared rapidly when the drug was discontinued.

Cardiac disorders:
Rare: Pericarditis

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

Hepatobiliary disorders:
Rare: Hepatotoxicity

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

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

Renal and urinary disorders:
Rare: Increased blood urea.

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

The following adverse reaction has been observed in patients receiving doxycycline:-
Immune system disorders:
Unknown frequency: Jarisch-Herxheimer reaction (see section 4.4)

Reporting of suspected adversereactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactionsvia HPRA Pharmacovigilance Website:www.hpra.ie

4.9 Overdose

Symptoms

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

Treatment

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

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

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

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

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

Pharmacodynamic effects
The plasma concentration of doxycycline following administration of Efracea is well below the level required to inhibit mircoorganisms commonly associated with bacterial diseases.
In vivo microbiological studies using similar exposure to the active substance for 6 to 18 months could not demonstrate any effect on the dominating bacterial flora sampled from the oral cavity, skin, intestinal tract and vagina. However, it cannot be excluded that long-term use of Efracea can lead to emergence of resistant intestinal bacteria such as Enterobacteriaceae and enterococci, as well as to enrichment of resistance genes.

Clinical efficacy and safety
Efracea has been evaluated in two pivotal randomised, double-blind, placebo-controlled, 16-week studies in 537 patients with rosacea (10 to 40 papules and pustules, and two or fewer nodules). In both studies, the mean reduction in the total inflammatory lesion count was significantly greater in the Efracea group than in the placebo group:

Table 2 - Mean change from baseline to Week 16 in total inflammatory lesion count:

	Study 1		Study 2	

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

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

Treatment with doxycycline 40 mg modified release capsules plus ivermectin
The ANSWER study evaluated the relative efficacy of doxycycline 40 mg modified release capsules (DMR) in combination with Soolantra (IVM) vs IVM plus DMR placebo (PBO) in the treatment of severe rosacea. It was a 12-week, randomized, investigator-blind, controlled, parallel-group study of 273 male and female subjects aged ≥18 years with 20-70 inflammatory lesions (papules and pustules) on the face and a baseline Investigator's Global Assessment (IGA) score of 4.

The primary efficacy endpoint was the percentage change from baseline in inflammatory lesion counts at Week 12. A significantly greater mean percentage reduction in inflammatory lesion count was seen for IVM + DMR compared to IVM + PBO (mean ± standard deviation: -80.29 ± 21.65 % vs -73.56 ± 30.52 %; p=0.032).

5.2 Pharmacokinetic properties

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

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

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

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

Other special populations
The half-life of doxycycline is not significantly altered in patients with severely impaired renal function. Doxycycline is not eliminated to any great extent during haemodialysis.

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

5.3 Preclinical safety data

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

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

In rats, doses of 50 mg/kg/day doxycycline caused a decrease in the straight-line velocity of sperm but did not affect male or female fertility or sperm morphology. At this dose systemic exposure experienced by rats is likely to have been approximately 4 times that seen in humans taking the recommended dose of Efracea. At doses greater than 50 mg/kg/day fertility and

reproductive performance were adversely affected in rats. A peri/postnatal toxicity study in rats revealed no significant effects at therapeutically relevant doses. Doxycycline is known to cross the placenta and literature data indicate that tetracyclines can have toxic effects on the developing foetus.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

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

Printing inks
Shellac
Propylene glycol
Black iron oxide
Indigo Carmine aluminium lake
Allura Red AC aluminium lake (E129)
Brilliant Blue FCF aluminium lake
D & C Yellow No. 10 aluminium lake

Capsule contents
Hypromellose
Methacrylic acid-ethyl acrylate copolymer (1:1)
Triethyl citrate
Talc
Hypromellose, Titanium dioxide, Macrogol 400, Yellow iron oxide, Red iron oxide, Polysorbate 80
Sugar spheres (Maize starch, Sucrose)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

6.4 Special precautions for storage

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

6.5 Nature and contents of container

Aluminium/PVC/Aclar blister

Pack size: 56 capsules in 4 strips of 14 each
28 capsules in 2 strips of 14 each
14 capsules in 1 strip of 14
Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements

7 MARKETING AUTHORISATION HOLDER

Galderma International
La Défense 4 Tour Europlaza
20 Avenue André Prothin
Paris La Défense Cedex
92927
France

8 MARKETING AUTHORISATION NUMBER

PA22743/006/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10 DATE OF REVISION OF THE TEXT

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