Safeguarding public health

MHRA

Public Assessment Report

Decentralised Procedure

EFRACEA 40 mg modified-release hard capsules

PL 10590/0056

UK/H/892/01/DC

Galderma (UK) Ltd

Medicines and Healthcare products Regulatory Agency

Lay summary

The Medicines and Healthcare products Regulatory Agency (MHRA) granted Galderma (UK) Ltd a Marketing Authorisation (licence) for the medicinal product EFRACEA 40 mg modified-release hard capsules (Product Licence number: 10590/0056). This medicine is available on prescription only.

EFRACEA 40 mg modified-release hard capsules contain doxycycline monohydrate. The capsules are for use in adults to reduce pimples and red bumps on the face when caused by a condition called rosacea.

The data submitted in support of this application for EFRACEA 40 mg modified-release hard capsules raised no clinically significant safety concerns and it was therefore judged that the benefits of using this product outweigh the risks; hence a Marketing Authorisation has been granted.

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Module 1

Information about decentralised procedure

Name of the product in the Reference Member State	EFRACEA 40 mg modified-release hard capsules
Type of application (Eudratrack details)	Level 1 Abridged Level 2 Initial Level 3 8.3 Level 4 Chemical substance Level 5 Prescription only
Name of the active substance (INN)	Doxycycline monohydrate
Pharmacotherapeutic classification (ATC code)	Tetracyclines (J01AA02)
Pharmaceutical form and strength	Modified-release hard capsule, 40 mg
Reference numbers for the Mutual Recognition Procedure	UK/H/892/01/DC
Reference Member State	United Kingdom
Member States concerned	AT, DE, FI, IE, IT, LU, NL, SE
Date of start of the procedure	12 April 2006
End date of decentralised procedure	27 March 2009
Marketing Authorisation Number	PL 10590/0056
Name and address of the authorisation holder	Galderma (UK) Ltd Meridien House 69-71 Clarendon Road Watford Herts WD17 1DS UK

Module 2

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).

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

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Modified-release hard capsule

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

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

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

4.2 Posology and method of administration

Adults, including the elderly:

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

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

Renal impairment

No dosage adjustment is necessary in patients with renal impairment.

Hepatic impairment

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

Children and adolescents

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

4.3 Contraindications

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

Infants and children up to 12 years of age.

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

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

4.4 Special warnings and precautions for use

EFRACEA contains doxycycline in a formulation designed to yield 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 of vaginal candidiasis. EFRACEA should be used with caution in patients with a history of predisposition to candidiasis overgrowth. If superinfection is suspected, appropriate measures should be taken, including consideration of discontinuing EFRACEA.

Treatment with higher doses of tetracyclines is associated with emergence of resistant intestinal bacteria, such as enterococci and enterobacteria. Although not observed during clinical studies with low dose doxycycline (40 mg/day), the risk for development of resistance in the normal microflora cannot be excluded in patients treated with 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 medicinal products. The antianabolic action of tetracyclines may cause an increase in BUN. Studies to date indicate that this does not occur with the use of doxycycline in patients with impaired renal function.

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

All patients receiving doxycycline, including 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 be considered. Treatment should cease at the first sign of photosensitivity.

In common with the use of antimicrobial medicinal products in general, there is a risk of the development of pseudomembranous colitis with doxycycline treatment. In the event of the development of diarrhoea during treatment with 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 acute hypersensitivity 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).

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

4.5 Interaction with other medicinal products and other forms of interaction

The recommendations below regarding the potential interactions between doxycycline and other medicinal products are based upon experience with the larger doses generally used in antimicrobial formulations of doxycycline rather than with 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 (pseudotumour cerebri). Concomitant administration should therefore be avoided.

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

Other interactions:

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

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

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

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

4.6 Pregnancy and lactation

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

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

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

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

In the pivotal placebo-controlled studies with EFRACEA in rosacea, 269 patients were treated with EFRACEA 40 mg once daily and 268 patients were treated with placebo for 16 weeks. Gastrointestinal adverse reactions overall occurred in a higher proportion of patients on 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.

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

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

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

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

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

Infections and infestations:
Very rare: Anogenital candidiasis

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

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

Endocrine disorders:

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

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

Cardiac disorders:
Rare: Pericarditis

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

Hepatobiliary disorders:
Rare: Hepatotoxicity

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

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

Renal and urinary disorders:
Rare: Increased blood urea.

Adverse reactions typical of the tetracycline class of medicinal products are less likely to occur during medication with 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.

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.

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 can not 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.

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:

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 (95% confidence limits)	-5.9 (-8.9, -2.9)		-5.2 (-7.7, -2.7)	
p-Value[a]	0.0001		< 0.0001	

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

5.2 Pharmacokinetic properties

Absorption:

Doxycycline is almost completely absorbed after oral administration. Following oral administration of 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, metabolism and elimination:

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

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

Pharmacokinetics in special populations:

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

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

5.3 Preclinical safety data

Adverse reactions seen in repeat dose studies in animals include hyperpigmentation of the thyroid and tubular degeneration in the kidney. These effects were seen at exposure levels of 1.5 to 2 times those seen in

humans administered 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
Brilliant Blue FCF aluminium lake
D & C Yellow No. 10 aluminium lake
Opacode Black S-1-8115
Opacode Black S-1-8114

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

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
2 years

6.4 Special precautions for storage
Store in the original package in order to protect from light.

6.5 Nature and contents of container
Aluminium/PVC/Aclar blister

Pack size: 56 capsules in 4 strips of 14 each

6.6 Special precautions for disposal
No special requirements

7 MARKETING AUTHORISATION HOLDER

Galderma (UK) Ltd
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69-71 Clarendon Road
Watford
Herts
WD17 1DS
UK

8 MARKETING AUTHORISATION NUMBER(S)

PL 10590/0056

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

27/03/2009

10 DATE OF REVISION OF THE TEXT

27/03/2009

Module 3

Product Information Leaflet

EFRACEA® 40 mg modified release hard capsules

PACKAGE LEAFLET: INFORMATION FOR THE USER
EFRACEA 40 mg modified release hard capsules
Doxycycline

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

In this leaflet:

1. WHAT *EFRACEA* IS AND WHAT IT IS USED FOR

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

2. BEFORE YOU TAKE *EFRACEA*

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

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

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

Taking other medicines
Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.
EFRACEA and certain other medications may not work properly when taken together. Tell your doctor about medications that you are taking or plan to take whilst you are taking *EFRACEA* .
- *EFRACEA* should not be used at the same time as the medicine isotretinoin because of the risk of increased pressure in the brain. Isotretinoin is prescribed to patients with a severe case of acne.
- Do not take antacids, multi-vitamins or other products that contain calcium (such as milk and dairy products and calcium-containing fruit juices), aluminium, magnesium (including quinapril tablets, which are taken for high blood pressure), iron or bismuth, or cholestyramine, activated charcoal or sucralfate until 2 to 3 hours after taking *EFRACEA*. These medicines may reduce the effectiveness of *EFRACEA* if taken at the same time.
- Other treatments for ulcers or heartburn may also reduce the effectiveness of *EFRACEA* and should not be taken until at least 2 hours after *EFRACEA*.
- If you are taking blood thinners, your doctor may need to make changes to the dose of your blood thinner.
- If you are taking certain treatments for diabetes, your doctor may need to check whether the dose of the diabetes treatment has to be changed.
- There is a possibility that *EFRACEA* reduces the effectiveness of oral contraceptives, resulting in pregnancy.
- *EFRACEA* may make certain antibiotics, including penicillins, less effective.
- Taking barbiturates (sleeping pills or short-term pain-killers), rifampicin (tuberculosis), carbamazepine (epilepsy), diphenylhydantoin and phenytoin (seizures of the brain), primidone (anti-convulsant) or cyclosporin (organ transplant) may reduce the time that *EFRACEA* stays active in your system.
- Using *EFRACEA* with the general anaesthetic methoxyfluorane may cause serious harm to the kidneys.

Taking *EFRACEA* with food and drink
Always take *EFRACEA* with an adequate amount of water to wash down the capsule, since this reduces the risk of irritation or ulcer in the throat or gullet.
Do not take milk or dairy products at the same time as *EFRACEA* since these products contain calcium which may reduce the effectiveness of *EFRACEA*. Leave 2 to 3 hours after your daily dose of *EFRACEA* before drinking or eating dairy products.

Pregnancy and breast-feeding
EFRACEA must not be used ***during pregnancy since it may cause permanent discolouration of the teeth in the unborn child.***
EFRACEA should not be used for long periods by breastfeeding mothers since it may cause tooth discolouration and reduced bone growth in the suckling child.
Ask your doctor or pharmacist for advice before taking any medicine.

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

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

3. HOW TO TAKE *EFRACEA*

Always take EFRACEA exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.
You should take one capsule *EFRACEA* each day in the morning. Swallow the capsule whole and do not chew it.
You should take *EFRACEA* with a full glass of water whilst sitting or standing to avoid any irritation to the throat.

If you take more *EFRACEA* than you should
If you take an overdose of *EFRACEA*, there is a risk of damage to the liver, kidneys or pancreas.
If you take more *EFRACEA* capsules than you should, ask your doctor immediately for advice.

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

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

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

4. POSSIBLE SIDE EFFECTS

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

Common side effects
The following side effects may occur commonly (affects 1 to 10 users in 100) during treatment with *EFRACEA*:
- Inflammation of the nose and throat
- Inflammation of the sinuses
- Fungal infection
- Anxiety
- Sinus headache
- High or increased blood pressure
- Diarrhoea
- Pain in the upper part of the abdomen
- Dry mouth
- Back pain
- Pain
- Changes in some blood tests (amount of glucose in blood or tests of liver function).

Rare side effects
The following side effects may occur rarely (affects 1 to 10 users in 10,000) during treatment with the class of medicines to which *EFRACEA* belongs (the tetracyclines):
- Allergic (hypersensitivity) reaction throughout the body*
- Changes in the number or type of certain blood cells
- Increased pressure in the brain
- Inflammation of the membrane surrounding the heart
- Nausea, vomiting, anorexia
- Liver damage
- Skin rashes or hives
- Abnormal reaction of the skin to sunlight
- Increased level of urea in the blood

Very rare side effects
The following side effects may occur very rarely (affects less than 1 user in 10,000) during treatment with the class of medicines to which *EFRACEA* belongs (the tetracyclines):
- Allergic reaction causing swelling of the eyes, lips or tongue*
- Yeast infection around the anus or genitals
- Damage to red blood cells (haemolytic anaemia)
- Inflammation of the tongue
- Difficulty in swallowing
- Inflammation of the intestine
- Inflammation or ulceration of the gullet
- Inflammation of the skin causing flakiness
- Worsening of the immune system disease known as systemic lupus erythematosus (SLE)

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

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

5. HOW TO STORE *EFRACEA*

Keep out of the reach and sight of children.

Do not use *EFRACEA* after the expiry date which is stated on the outer pack and blister after EXP. The expiry date refers to the last day of that month.

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

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

6. FURTHER INFORMATION

What *EFRACEA* contains
- The active substance is doxycycline. Each capsule contains 40 mg doxycycline (as monohydrate).
- The other ingredients are:
  hypromellose, methacrylic acid-ethyl acrylate copolymer (1:1), triethyl citrate, talc, opadry beige YS-1-17274-A (hypromellose 3cP/6cP, titanium dioxide, macrogol 400, yellow iron oxide, red iron oxide, polysorbate 80), sugar spheres (maize starch, sucrose).
  Capsules: gelatin, black iron oxide, red iron oxide, yellow iron oxide, titanium dioxide.
  Printing ink: shellac, propylene glycol, black iron oxide, indigo carmine aluminium lake, allura red AC aluminium lake, brilliant blue FCF aluminium lake, D & C yellow no. 10 aluminium lake, Opacode black S-1-8115, Opacode black S-1-8114.

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

Marketing Authorisation Holder and Manufacturer
Galderma (UK) Ltd
Meridien House
69-71 Clarendon Road
Watford
Herts.
WD17 1DS
UK

Product Licence Number: PL 10590/0056 (UK) & PA 590/25/1 (IRE)

The manufacturer responsible for batch release is:
Cardinal Health UK 417 Ltd, Great Oakley, Corby,
Northamptonshire NN18 8HS, UK.

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

This leaflet was last approved in 11/2008.

GALDERMA

P2XXXX-X

Module 4

Labelling

Foil:

Carton:


P2XXXX-X
EFRACEA
40 mg modified-release hard capsules
doxycycline
EFRACEA
40 mg modified-release hard capsules
doxycycline
PHARMACY-DISPENSED LABEL
56 modified-release hard capsules
GALDERMA
40 mg modified-release hard capsules
doxycycline
GALDERMA
EFRACEA
Each capsule contains 40 mg doxycycline (as monohydrate).
Contains also sucrose.
See leaflet for further information.
Use only as directed by a doctor/physician.
Oral use.
Read the package leaflet before use.
Swallow whole, do not crush or chew.
Take with water.
Store in the original package in order to protect from light.
Keep out of the reach and sight of children.
Galderma (UK) Ltd
Meridien House
69-71 Clarendon Road
Watford
Herts
WD17 1DS
UK
POM
PL 10590/0056 (UK)
PA 590/25/1 (IRE)
5 020465 200277
Batch No.:
EXP:

Module 5

Scientific discussion during initial procedure

RECOMMENDATION

Based on the review of the data on quality, safety and efficacy, the Reference Member State (RMS) considers that the application for EFRACEA 40 mg modified-release hard capsules for the reduction of papulopustular lesions in adult patients with facial rosacea could be approved.

EXECUTIVE SUMMARY

Problem statement

This marketing authorisation application was made through the decentralised procedure under Article 8.3 of Directive 2001/83/EC. Doxycycline was first approved in the UK in 1973 for the treatment of infection. The applicant has submitted an application for the use of doxycycline in treating papulopustular lesions in adult patients with facial rosacea, claiming that it has anti-inflammatory properties at sub anti-microbial doses. Formulations that contain doxycycline have been developed for use in treating periodontitis (Periostat® 20mg film-coated tablets). Pilot studies with these formulations indicated that this type of formulation is effective in treating rosacea.

The objective of the clinical trial programme discussed in this assessment was the development of a once daily oral preparation to provide steady state doxycycline plasma concentrations at the anti-inflammatory level but not at the antimicrobial level. Pharmacokinetic trials comparing Periostat® with EFRACEA were also performed to argue for the extrapolation of immediate release data from Periostat® to the modified release formulation of EFRACEA.

General comments on the submitted dossier

The dossier contains cross references to the active substance (doxycycline) where appropriate and to Periostat®, which is a low-dose, immediate release formulation of doxycycline approved in the UK as an adjuvant therapy to scaling in adult periodontitis (inflammation caused by microbes that infect the roots of teeth and surrounding gums).

General comments on compliance with GMP, GLP, GCP and agreed ethical principles.

The RMS has been assured that acceptable standards of GMP are in place for these product types at all sites responsible for the manufacture and assembly of this product. No new nonclinical data have been submitted with the current application. The original toxicology studies listed in the toxicology section of this report are reported to have been performed in accordance with GLP standards and requirements. The clinical studies carried out in support of this application are in line with GCP guidelines.

SCIENTIFIC OVERVIEW AND DISCUSSION

QUALITY ASPECTS

Drug substance

Doxycycline monohydrate is a semi-synthetic tetracycline antibiotic, first synthesised in the 1960s. However, in EFRACEA it is not used for its antibacterial and antiprotozoal activities, but for papulopustular lesions in adult patients with facial rosacea (a disorder due to chronic inflammation of facial skin, often giving increased redness or acne-like eruptions on the face).

The drug substance supplied is supported by a Certificate of Suitability issued by the European Directorate for the Quality of Medicines. The drug substance used in this product meets the requirements of the Ph Eur monograph.

Drug Product

This application is for a single strength, modified-release capsule, containing 40mg of doxycycline (as monohydrate). The choice of excipients is justified. Filled capsules are sealed in PVC / aluminium foil blisters.

The drug substance is incorporated into two types of beads that are enclosed in the capsule. These are immediate release beads and delayed release beads that have an outer enteric coating which prevents dissolution of active ingredient until the beads enter the small intestine. Hence, a slightly slower rate of release from EFRACEA compared to conventional doxycycline capsules is achieved.

The manufacturing method has been satisfactorily validated. The finished product specification is based on relevant development and stability studies. Appropriate validation data has been provided for the analytical methods. Batch analyses data support the proposed finished product specification. Stability studies have been carried out in accordance with ICH guidelines. Updated stability data support the proposed two year shelf-life when the storage precaution ‘Store in the original package in order to protect from light’ is met.

NON CLINICAL ASPECTS

The pharmacodynamic, pharmacokinetic and toxicological properties of doxycycline are well known. As doxycycline is a widely used, well-known active substance, no further studies are required. An overview based on a literature review is, thus, appropriate.

CLINICAL ASPECTS

PHARMACOKINETICS

The applicant has conducted five clinical trials in healthy volunteers to study different aspects of the pharmacokinetics of the proposed modified release (MR) formulation and a series of trials on efficacy in rosacea.

The EFRACEA formulation has been shown to have similar rate and extent of absorption at steady state to the IR tablet at doses of 40 mg, as AUC and C_{max} fell within the acceptable limits. However, the 90% CI of C_{min} in one study did not fall within the acceptable range. In principle, EFRACEA capsules can not be considered to be bioequivalent to Doxycycline IR tablets at similar doses. The implications of this difference must be analysed in the context of clinical efficacy. Provided that well controlled clinical trials show efficacy of the MR formulation, differences in the C_{min} at steady state would be of less importance. A food effect has been demonstrated, but is probably not clinically relevant. All other pharmacokinetic aspects have been properly addressed.

PHARMACODYNAMICS

The applicant has not performed any pharmacodynamics trials and has addressed the pharmacodynamics of the product using published literature. This is satisfactory.

Mechanism of action

Research has shown that doxycycline inhibits mediators such as reactive oxygen species, interleukin-6, phospholipase A_2 and nitric oxide, all of which contribute to the inflammatory lesions present in rosacea. It is also thought that it may stimulate the production of the anti-inflammatory cytokine IL-10.

Antibiotics such as doxycycline have been used in the past for treatment of rosacea, in some countries, such as the UK, as an "off label" use. No pharmacodynamic human studies are specifically required for this type of application provided that pharmacodynamics can be properly addressed by other means.

Primary pharmacology

As stated above, sub-antimicrobial doses of doxycycline may down-regulate inflammation.

This principle has been accepted in the past and formed the basis for the use of low doses of doxycycline in periodontitis (Periostat® capsules).

Secondary pharmacology

In order to minimise any potential effect on the normal bacterial flora, plasma levels of doxycycline should remain under the antimicrobial threshold. Microbiological studies have been conducted to evaluate the effects of Doxycycline 20mg administered bid on the micro flora of the skin, intestine, vagina and oral cavity:

- A 6-month, randomised, double blind, placebo controlled study to determine the effects of 20 mg of doxycycline bid on the skin micro flora in 51 subjects with acne showed no differences between or within groups from baseline to 6 months in microbial colony counts and antibiotic susceptibility (Skidmore et al, 2003)
- A 9-month, randomised, double blind, placebo controlled study to determine the effects of 20 mg of doxycycline bid on the intestinal and vaginal micro flora in 69 subjects showed: a) no shift in normal flora, b) no overgrowth or colonisation by opportunistic pathogens, c) no increase in resistance, and d) no development of multi-antibiotic resistance (Walker et al, 2005)
- Three randomised, placebo-controlled studies on the long term use (up to 18 months) of sub-antimicrobial doses of doxycycline in 251 adults with periodontitis showed no effect in the antibiotic susceptibility of the subgingival flora, and no

antimicrobial effect on the periodontal flora (Thomas et al, 2000; Thomas et al, 1998; Walker et al, 2000).

Chronic use of antibiotics leads to unwanted selection of resistant strains and misbalance of the micro flora. These concerns are addressed by referring to published reports and, hence, full study reports are not available for a comprehensive analysis. The scientific literature indicates that the chronic use of 20 mg of doxycycline bid dose not appear to disturb the micro flora of the skin, intestine, vagina and oral cavity. It must be noted that these trials used doxycycline 20 mg bid as the test product, a formulation which is different to the product under assessment. The antimicrobial threshold is said to be 1.0 μg/ml, below which there is no disturbance to the micro flora but there are anti-inflammatory effects. Review of mean plasma concentrations over time show that levels below this limit were achieved consistently by both IR and MR formulations. In addition, it has been demonstrated that C_{max} for both formulations at steady state are equivalent. Therefore, it is acceptable to extrapolate the results of the microbiology studies to the MR formulation.

Relationship between plasma concentration and effect
The expert report states that sub microbial doses of doxycycline that exert anti-inflammatory effects are below the plasma concentration of 1.0 μg/ml. The applicant has presented an appropriate argument to differentiate the evidence for anti-inflammatory activity from antimicrobial efficacy in terms of plasma levels of doxycycline and this level is acceptable.

It has been accepted in the past that low doses of doxycycline have beneficial anti-inflammatory effects (i.e. Periostat®). Although there are no PK/PD studies in humans in the dossier to support this view, PK data in phase one showed that the MR formulation consistently achieved plasma levels below the 1.0 μg/ml threshold in healthy volunteers. This limit is supported by the SPC of doxycycline approved in the USA. No differences in the PK profile are expected between healthy volunteers and patients with rosacea and so it is acceptable to extrapolate these plasma levels to the phase three population. As phase three trials show a significant difference between doxycycline MR capsules and placebo in treating inflammatory lesions, the results of the clinical program support the claim that plasma levels should be below 1.0μg/ml in order to obtain anti-inflammatory effects.

Pharmacodynamic interactions with other medicinal products or substances
No interaction studies have been performed for this application. This is acceptable since doxycycline is a well-known substance

Genetic differences in PD response
No studies to this regard have been conducted. This is acceptable since doxycycline is a well-known substance

Overall conclusions on pharmacodynamics
The basic principles of the pharmacodynamic properties of doxycycline 40mg MR capsules can be accepted based on the literature provided and on previous experience with similar products. The proposed plasma levels have been substantiated in the expert report and the validity of using 40 mg of doxycycline daily can be accepted as

long as well-design, well-conducted trials show enough evidence of clinical efficacy in favour of the product with an acceptable safety profile.

CLINICAL EFFICACY

Introduction

Table: Efficacy trials

Design	Study Posology	Study Objective	Subjs by arm enterered/ compl.	Duration	Gender M/F Median Age	Diagnosis Incl. criteria	Primary Endpoint
Double blind, randomised, placebo-controlled, parallel group	Periostat 20mg capsules bid for 16 weeks	Evaluate safety and efficacy of study drug in rosacea	Active: 67/53 Placebo: 67/55	From 11/7/2002 to 5/1/2004	40M/94F Mean age: 46	Rosacea with 10-30 papules and pustules, ≤ 2 nodules and score of 2-4 on the clinician's global severity score	Change from baseline to endpoint (week 16) in total lesion count and clinician's erythema score
Double blind, randomised, placebo-controlled, parallel group	Doxycycline 40mg MR capsule	Evaluate safety and efficacy of study drug in rosacea	251/127 (active) and 124 (placebo)	From 22/6/2004 to 1/4/2005	65M/186 F Median age: 47	Rosacea with 10-40 papules and pustules, ≤ 2 nodules and score of 2-4 on the investigators global assessment score	Change from baseline to endpoint (week 16) in total inflammatory lesion count
Double blind, randomised, placebo-controlled, parallel group	Doxycycline 40mg MR capsule	Evaluate safety and efficacy of study drug in rosacea and evaluate longevity of the effect	286/142 (active) and 144 (placebo)	From 24/6/2004 to 4/4/2005	97M/189 F Median age: 46	Rosacea with 10-40 papules and pustules, ≤ 2 nodules and score of 2-4 on the investigators global assessment score	Change from baseline to endpoint (week 16) in total inflammatory lesion count

Overall conclusions on clinical efficacy

The studies consistently showed a reduction in papule and pustule count in patients with rosacea. Doxycycline did not have any effect in other features which are common in rosacea such as erythema or nodules.

CLINICAL SAFETY

Introduction

Safety information contained in the dossier includes data from two phase three studies and four PK studies, plus data from three ongoing trials in rosacea and acne and an additional trial in adult periodontitis. Post marketing experience is provided in the form of Periodic Safety Update Reports (PSURs) from 1999 to 2005 for Periostat®.

Doxycycline is the active ingredient in Periostat®, and experience with this formulation can be extrapolated to the MR capsule which has the same active. The extent of the data base presented in the dossier is acceptable. The adverse effect (AE) profile reveals no patterns of concern. The analysis of the serious adverse effects (SAE) database does not reveal any new trends of concern.

The review of the laboratory findings does not reveal any significant trends. Doxycycline is known to have the potential for immunological events. The safety database does not reveal any patterns for new concerns.

The AEs that led to discontinuation are known, undesirable side effects of doxycycline, although the percentage of patients that withdrew due to AEs was higher for the doxycycline group this number is not of great concern. The MR capsule seems to be well tolerated.

The post marketing safety experience presented is considered adequate. There are no previously unknown trends identified. Although this experience refers to a different formulation it is still relevant since the active substance is the same.

A satisfactory Risk Management Plan has been submitted with this application.

BENEFIT RISK ASSESSMENT

The risk: benefit ratio is satisfactory.

Overall conclusion

QUALITY
The important quality characteristics of EFRACEA 40 mg modified-release hard capsules are well defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

PRECLINICAL
No preclinical data is needed for this application. No new or unexpected safety concerns arise from this application.

EFFICACY
Clinical studies have demonstrated the efficacy of EFRACEA 40 mg modified-release hard capsules in reducing papulopustular lesions in adult patients with facial rosacea.

The SPC, PIL and labelling are satisfactory and consistent with that for the innovator product.

RISK BENEFIT ASSESSMENT
The quality of the product is acceptable and no new preclinical or clinical safety concerns have been identified.