Medicines & Healthcare products Regulatory Agency

MHRA
Regulating Medicines and Medical Devices

Public Assessment Report

Mutual Recognition Procedure

EFRACEA 40 mg modified-release hard capsules

PL 10590/0056

UK/H/0892/001/DC

Galderma (UK) Ltd

Medicines and Healthcare Products Regulatory Agency

LAY SUMMARY

This is a summary of the Public Assessment Report (PAR) for Efracea 40 mg modified-release hard capsules. Efracea 40 mg modified-release hard capsules will be termed Efracea 40 mg modified-release capsules throughout this Lay Summary for ease of reading. This PAR explains how this product was assessed and its authorisation recommended, as well as its conditions of use. It is not intended to provide practical advice on how to use this product.

For practical information about using Efracea 40 mg modified-release capsules, patients should read the Package Leaflet or contact their doctor or pharmacist.

What are Efracea 40 mg modified-release capsules and what are they used for?
Efracea 40 mg modified-release capsules are used in adults to reduce the pimples or red bumps on the face caused by a condition called rosacea.

How do Efracea 40 mg modified-release capsules work?
This product contains 40 mg doxycycline monohydrate and works by utilizing the anti-inflammatory properties of low-dose doxycycline (i.e. below the level required for an antimicrobial activity).

How are Efracea 40 mg modified-release capsules used?
This product is a prescription-only medicines (POM).

It is for oral use. Capsules should be swallowed with a full glass of water whilst sitting or standing to avoid any irritation to the throat.

The recommended dose is one capsule of Efracea 40 mg modified-release capsules each day in the morning, on an empty stomach, preferably at least 1 hour prior to or 2 hours after the meal. Swallow the capsule whole and do not chew it.

Please read Section 3 of the Package Leaflet for detailed information on dosing recommendations, the route of administration and the duration of treatment.

How have Efracea 40 mg modified-release capsules been studied?
Suitable data from clinical studies have been provided to show the suitability of this product in treating the proposed indications.

What are the possible side effects of Efracea 40 mg modified-release capsules?
Like all medicines, this medicine can cause side effects, although not everybody gets them. If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in the Package Leaflet.

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 heartbeat (palpitations) and feeling faint. These effects may be symptoms of a severe allergic (hypersensitivity) reaction.

For a full list of possible side effects, please see Section 4 the Package Leaflet.

Why are Efracea 40 mg modified-release capsules approved?
It was concluded that, based on the data submitted for this medicine, the benefits outweigh the identified risks and it was recommended that Efracea 40 mg modified-release capsules can be approved for use.

What measures are being taken to ensure the safe and effective use of Efracea 40 mg modified-release capsules?
A risk management plan (RMP) has been developed to ensure that Efracea 40 mg modified-release capsules is used as safely as possible. Based on this plan, safety information has been included in the Summary of Product Characteristics and the Package Leaflet for Efracea 40 mg modified-release capsules, including the appropriate precautions to be followed by healthcare professionals and patients.

Known side effects are continuously monitored. Furthermore, new safety signals reported by patients and healthcare professionals will be monitored and reviewed continuously, as well.

Other information about Efracea 40 mg modified-release capsules
Marketing authorisations were granted in the UK to FGK Representative Service GmbH on 23 March 2009 (PL 27682/0001). Following a change of authorisation holder, granted on 02 April 2009, the current marketing authorisation holder is Galderma (UK) Limited (PL 10590/0056).

The full PAR for Efracea 40 mg modified-release capsules follows this summary.

For more information about treatment with Efracea 40 mg modified-release capsules, read the Package Leaflet or contact your doctor or pharmacist.

This summary was last updated in November 2017.

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I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the UK 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.

Efracea 40 mg modified-release hard capsules contains the active substance doxycycline (as doxycycline monohydrate). Doxycycline has been shown to inhibit neutrophil activity and several pro-inflammatory reactions including those associated with phospholipase A2, endogenous nitric oxide and interleukin-6. The pathophysiology of the inflammatory lesions of rosacea is, in part, a manifestation of a neutrophil-mediated process.

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 initial marketing authorisation application was made through the Decentralised Procedure (DCP) under Article 8.3 of Directive 2001/83/EC (UK/H/0892/001/DC), with the UK as Reference Member State (RMS) and Austria, Germany, Finland, Ireland, Italy, Luxembourg, the Netherlands and Sweden as Concerned Member States (CMSs). The DCP concluded successfully on 24 April 2008 and, following a national phase, the UK granted a marketing authorisation for this product to FGK Representative Service GmbH on 23 March 2009 (PL 27682/0001). Following a change of authorisation holder, granted on 02 April 2009, the current marketing authorisation holder is Galderma (UK) Limited (PL 10590/0056). A subsequent repeat-use procedure, with the UK as RMS and Belgium, Czech Republic, Denmark, Greece, Spain, France, Hungary, Norway, Poland, Portugal and the Slovak Republic as CMSs was concluded on 23 October 2010 (UK/H/0892/001/E/01).

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).

The RMS has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for these product types at all sites responsible for the manufacture and assembly of this product.

No new non-clinical data was submitted with this application. The original toxicology studies listed in the non-clinical section of this report are stated to have been performed in accordance with Good Laboratory Practice (GLP) standards and requirements. The clinical studies carried out in support of this application are in line with Good Clinical Practice (GCP) guidelines.

II QUALITY ASPECTS

II.1 Introduction

This application was submitted under Article 8.3, a full-dossier application for a known active substance.

Efracea 40 mg modified-release hard capsules contains 40mg doxycycline, as doxycycline monohydrate. Additionally, it contains the following excipients:

Capsule shell:
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 (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)

With the exception of the printing ink and the gelatin capsule shell, all excipients are controlled to their respective European Pharmacopoeia monograph. The printing ink and the gelatin capsule shell are controlled to suitable in-house specifications. The components of the printing ink and capsule shell (with the exception of gelatin) are all controlled to their respective National Formulary specifications and are in-line with current EU regulations concerning the use of colourants.

The finished product is packaged in aluminium/polyvinylchloride/aclar blisters in pack sizes of 14, 28 and 56 capsules. All packaging complies with current European regulations concerning materials in contact with foodstuff.

II.2 DRUG SUBSTANCES

II.2.1 Doxycycline monohydrate

Pharmacopoeial name: (4S,4aR,5S,5aR,6R,12aS)-4-(Dimethylamino)-3,5,10,12,12a-pentahydroxy-6-methyl-1,11-dioxo-1,4,4a,5,5a,6,11,12a-octahydrotetracene-2-carboxamide monohydrate.

Chemical names: [4S-(4α,4aα,5a,5aα,6a,12aα)]-4-(Dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,5,10,12,12a-pentahydroxy-6-methyl-1,11-dioxo-2-naphthacenecarboxamide monohydrate.

2-Naphthacenecarboxamide, 4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,5,10,12,12a-pentahydroxy-6-methyl-1,11-dioxo-, monohydrate, [4S-(4α,4aα,5α,5aα,6α, l2aα)].

4-dimethylamino-1,4,4a,5,5a,6,11,12a-octahydro-3,5,10,12,12a-pentahydroxy-6α-methyl-1,11-dioxonaphthacene-2-carboxamide, monohydrate.

Empirical formula: $C_{22}H_{24}N_2O_8 \cdot H_2O$

Relative molecular mass: 462.46

Doxycycline monohydrate is a semi-synthetic tetracycline antibiotic, first synthesised in the 1960s. However, in this product, 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).

All aspects of the manufacture and control of the drug substance are covered by a European Directorate for the Quality of Medicines (EDQM) certificate of suitability.

II.3 DRUG PRODUCT

Pharmaceutical development

The objective 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.

Satisfactory details of the pharmaceutical development of the medicinal product have been supplied. Suitable data have been provided to show that the dissolution properties of the product are satisfactory. 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.

With the exception of gelatin, none of the excipients are of animal or human origin. The supplier of gelatin has provided an EDQM certificate of suitability, to show compliance with current regulations concerning the minimisation of risk of transmission of BSE/TSE. None of the excipients are sourced from genetically modified organisms.

Manufacture of the product
A description and flow-chart of the manufacturing method have been provided.

Satisfactory batch formulae have been provided for the manufacture of the product, along with an appropriate account of the manufacturing process and controls. The manufacturing process has been validated and has shown satisfactory results.

Finished Product Specification
The finished product specification is satisfactory. Test methods have been described and adequately validated. Batch data have been provided that comply with the release specification. Certificates of Analysis have been provided for any working standards used.

Stability
Finished product stability studies have been conducted in accordance with current guidelines, using batches of the finished products stored in the packaging proposed for marketing. Based on the results, a shelf-life of 2 years and storage conditions of "Store in the original package in order to protect from light" for this product are satisfactory.

II.4 Discussion on chemical, pharmaceutical and biological aspects
The grant of a marketing authorisation is recommended for this application.

III 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.

The grant of a marketing authorisation is recommended for this application.

IV CLINICAL ASPECTS
IV.1 Introduction
Data from several clinical studies have been provided with this application.

IV. 2 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 immediate-release (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.

IV.3 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.

IV.4 Clinical efficacy

Below is a table of the clinical efficacy studies submitted with this application:

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

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.

IV.5 Clinical safety

Safety information contained in the dossier includes data from two Phase III studies and four pharmacokinetic 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.

IV.6 Risk Management Plan (RMP)

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

IV.7 Discussion on the clinical aspects

The grant of a marketing authorisation is recommended for this application.

V USER CONSULTATION

A user consultation with target patient groups on the PIL has been performed and the results submitted in accordance with Article 59 of Council Directive 2001/83/EC, as amended. The results indicate that the package leaflet is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that it contains.

VI OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The quality of the product is acceptable, and no new non-clinical or clinical safety concerns have been identified. The applications include an adequate review of published non-clinical and clinical data concerning the efficacy and safety of doxycycline, as well as additional clinical data submitted.

The benefit/risk of this product is positive. There are no outstanding issues that would have a negative impact on the benefit/risk balance.

The Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and labelling are satisfactory and in line with current guidelines. In accordance with Directive 2012/84/EU, the current approved UK versions of the SmPCs and PIL for these products are available on the MHRA website.

The currently approved labels are provided below:


EFRACEA
40 mg modified-release hard capsules
doxycycline
Each capsule contains 40 mg doxycycline (as monohydrate).
Also contains sucrose and Allura red AC aluminium lake (E129).
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 sight and reach 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
EFRACEA
40 mg modified-release hard capsules
doxycycline
56 modified-release hard capsules
GALDERMA
40 mg modified-release hard capsules
doxycycline
GALDERMA
EFRACEA

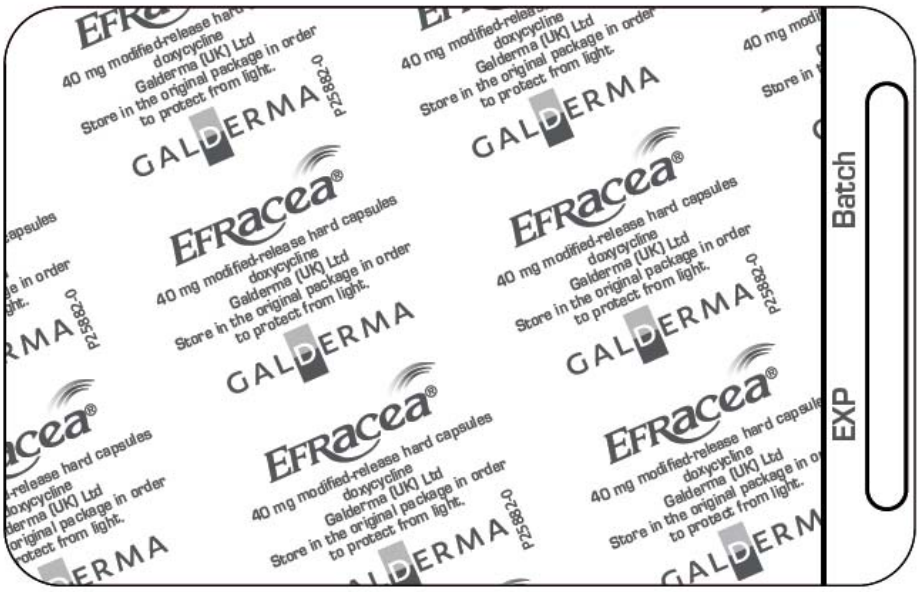
EFRACEA
40 mg modified-release hard capsules
doxycycline
Galderma (UK) Ltd
Store in the original package in order to protect from light.
GALDERMA
Batch
EXP

Table of content of the PAR update for MRP and DCP

Steps taken after the initial procedure with an influence on the Public Assessment Report (Type II variations, PSURs, commitments)

Date submitted	Application type	Scope	Outcome
11/05/2009	Type II variation	To update sections 2 (Qualitative and quantitative composition), 4.4 (Special warnings and precautions for use) and 6.1 (List of excipients) of the SmPC, label and leaflet regarding excipients according to the current guidelines.	Granted – 04/09/2009
11/05/2009	Type 1B variation	To change the name of the medicinal product in Ireland only to EFRACEA.	Granted – 24/07/2009
11/05/2009	Type 1B variation	To add a pack size of 28 capsules to the product licence; section 6.5 (Nature and content of container) of the SmPC, label and leaflet are updated.	Granted - 24/07/2009
24/06/2009	Type II variation	To update module 1.6-Environmental Risk Assessment in accordance with the current version of the Guideline on the environmental risk assessment of medicinal products for human use (EMEA/CHMP/SWP/4447/00).	Granted - 16/03/2010
24/06/2009	Type II variation	To update module 1.8-Information relating to Pharmacovigilance including sections 1.8.1-Pharmacovigilance system and 1.8.2-Risk-management System.	Granted - 18/03/2010
07/10/2009	MRP	Outgoing Mutual Recognition procedure UK/H/0892/001/E/001. CMS; BE, CZ, DK, EL, ES, FR, HU, NO, PL, PT, SK.	Granted - 12/11/2010
01/04/2011	Type II variation	To update sections 4.2, 4.3, 4.4, 4.6 and 6.1 of the SmPC, following a committment made during a Repeat Use procedure (UK/H/0892/001/E/001). Consequentially, the PIL has been updated.	Granted - 06/07/2011
01/04/2011	Type II variation	To update section 4.8 (Undesirable effects) of the SmPC, to include the following adverse events: benign	Granted - 04/07/2011

		intracranial hypertension and headache to be in line with the Core Data Sheet dated 23 September 2010. Consequentially, the PIL has been updated.	
27/02/2012	Type 1B variation	To add an additional pack size of 14 capsules to the licence; section 6.5 (Nature and content of container) of the SmPC, label and leaflet are updated.	Granted - 08/05/2012
17/02/2012	Type II variation	To add a new module 1.8.1 Detailed Description of the Pharmacovigilance System [DDPS] version 6.0, dated 2nd January 2012 including the introduction of a new EU QPPV.	Granted - 01/08/2012
23/11/2013	Type 1B variation	To change the name of the medicinal product from "ORAYCEA" to "EFRACEA" in Belgium and Luxembourg only. Consequently, the PIL has been updated.	Granted - 29/01/2014
25/11/2013	Type 1B variation	To update sections 1, 2, 4.1 - 4.8, 4.9, 5.1 - 5.3, 6.1 and 6.5 of the SmPC, the leaflet and the label as per the last version of the QRD template.	Granted - 04/04/2014
09/12/2013	Type 1B variation	To update sections 4.8 (undesirable effects) of the SmPC in line with the PRAC recommendation to add photo-onycholysis as an adverse event reaction. As a consequence, the PIL has also been updated.	Granted - 28/02/2014
16/02/2016	Type IA	To update the product information (SmPC and PIL) in-line with the findings of a worksharing agreement NL/H/XXXX/WS/063 (CMDh/326/2015, Rev 0)	Granted 04/03/2016
28/11/2016	Type II	To update sections 4.2 (Posology and method of administration) and 4.4 (Special warnings and precautions for use) of the SmPC and consequentially the leaflet regarding the effects of the concomitant administration of food with the drug and also the effect of a high pH on the bioavailability of doxycycline.	Granted – 28/09/2017

Annex I

Reference:	PL 10590/0056-0058
Product:	Efracea 40 mg modified-release hard capsules
Marketing Authorisation Holder:	Galderma (UK) Limited
Active Ingredients:	Doxycycline monohydrate
Reason:	To update sections 4.2 (Posology and method of administration) and 4.4 (Special warnings and precautions for use) of the SmPC and consequentially the leaflet regarding the effects of the concomitant administration of food with the drug, and also the effect of a high pH on the bioavailability of doxycycline.

Background

Efracea is an antibacterial agent belonging to the tetracycline group. It is for systemic use and is approved for the indication to reduce papulopustular lesions in adult patients with facial rosacea.

It is used in a low dose of 40mg. The plasma concentration of doxycycline following administration of Efracea is well below the level required to inhibit microorganisms commonly associated with bacterial diseases.

This variation has been submitted to update the SmPC and PIL, to align the information provided in these documents to that provided in other markets. A clinical overview to support these changes has been provided. No new data was provided with the overview addendum, since this assessment is based solely on previously submitted information.

Supporting Evidence

1. Effect of the concomitant administration of food with Efracea capsules

The effect of food on the pharmacokinetics of a single dose of Doxycycline 40 mg capsules was assessed in Study COL-101-SDPK-105 (Study 105), a randomized, two-way crossover study in 30 male and female subjects. This study was included in the Marketing Authorization Application dossier for Efracea under procedure UK/H/0892/001/DC (Applicant: FGK Representative Service GmbH) and procedure UK/H/0892/001/E01 (Applicant: Galderma (UK) Limited).

Based on the results of this study, it had been concluded that the concomitant administration of Doxycycline 40 mg capsules with a high-fat meal resulted in a decrease in the rate and extent of absorption (C_{max} and AUC) by about 45% and 22%, respectively, compared to dosing under fasting conditions. In addition, there was a delay of about 1 hour for the mean T_{max} in the fed state compared to the fasted state.

This information is currently reflected in the SmPC under Section 5.2:
"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%."

The effect on absorption of doxycycline of its coadministration with dairy products is mentioned in the SmPC, Section 4.5:
"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.…"

When reviewing the Core Company Data Sheet for Efracea early 2016, Galderma identified differences between the European SmPC and the US Product Information and the Canadian Product Monograph with regards to the way the effect of coadministration of Efracea with food was reflected in the respective methods of administration sections.

The EU SmPC states:
"The capsule should be taken in the morning with adequate amounts of water in order to reduce the risk of oesophageal irritation and ulceration."

Whereas, the Canadian Product Monograph states:
"One APPRILON capsule (40 mg, modified-release) should be taken once daily in the morning, on an empty stomach, preferably at least one hour prior to or two hours after the meal. Administration of adequate amounts of fluid along with the capsule is recommended to wash down the APPRILON capsule to reduce the risk of oesophageal irritation and ulceration."

And the US Product Information states:
"One ORACEA Capsule (40 mg) should be taken once daily in the morning on an empty stomach, preferably at least one hour prior to or two hours after meals. Administration of adequate amounts of fluid along with the capsules is recommended to wash down the capsule to reduce the risk of oesophageal irritation and ulceration."

Therefore, based on available (and previously submitted) data, and in order to emphasize that the coadministration of food (and in particular, but not limited to, dairy products or calcium-containing fruit juices) could reduce the absorption of doxycycline, the applicant proposes to amend the method of administration in Section 4.2. Posology and method of administration of the SmPC as follows (addition to the current text appears underlined):
"The daily dose is 40 mg (1 capsule). The capsule should be taken in the morning, <u>on an empty stomach, preferably at least one hour prior to or two hours after the meal,</u> with adequate amounts of water in order to reduce the risk of esophageal irritation and ulceration (see section Special warnings and precautions for use)."

The Patient Information Leaflet will be amended accordingly.

Assessor's comments

The study demonstrated a reduction in the C_{max} and AUC in the fed state. Therefore, the proposed change is considered acceptable.

2. Effect of a high pH on the bioavailability of doxycycline

A published study by Grahnen et al (1994) evaluated the effect of increased gastric pH (obtained by pre-treatment with omeprazole) on the bioavailability of doxycycline monohydrate and doxycycline carrageenate in 24 healthy subjects of both sexes using an open, randomized, four-treatment, four-period crossover, 2x2 factorial design. Each subject received a single dose of 100 mg of each doxycycline formulation with and without omeprazole pretreatment (40 mg/day for 7 days). After omeprazole, the monohydrate showed a significant decrease in bioavailability (38% for AUC and 45% for C_{max}) compared to the carrageenate formulation. Many subjects did not reach a therapeutic plasma level of doxycycline during the combination of omeprazole and doxycycline monohydrate, and most adverse events (mainly gastrointestinal) were reported after this combination. This study was presented and discussed in the initial application.

Based on this study, it was concluded that it is likely that the bioavailability of doxycycline is reduced in patients with gastrectomy or gastric bypass surgery, or who are otherwise deemed achlorhydric. This statement was included in the Summary of Product Characteristics in section "Contraindications".

It is also indicated in section "Interaction with other medicinal products and other forms of interaction" that "Medicinal products which increase gastric pH may reduce the absorption of doxycycline".

Galderma considers that, in addition to the previous warning, a more general one should be included with regards to the effect of a high pH on the bioavailability of doxycycline whatever the reason for the high pH. Therefore, it is proposed to add in section "Special warnings and precautions for use" the following sentence:
"The bioavailability of doxycycline is reported to be reduced at high pH."

Assessor's comments

The study demonstrated a reduction in the C_{max} and AUC when the pH is high. Therefore, the proposed change is considered acceptable.

Decision - Granted
Date - 28 September 2017