IPAR

Public Assessment Report for a
Medicinal Product for Human Use

Scientific Discussion

Doxycycline 100 mg hard capsules
Doxycycline hyclate
PA1418/010/002

The Public Assessment Report reflects the scientific conclusion reached by the Health Products Regulatory Authority (HPRA) at the end of the evaluation process and provides a summary of the grounds for approval of a marketing authorisation for a specific medicinal product for human use. It is made available by the HPRA for information to the public, after deletion of commercially sensitive information. The legal basis for its creation and availability is contained in Article 21 of Directive 2001/83/EC, as amended. It is a concise document which highlights the main parts of the documentation submitted by the applicant and the scientific evaluation carried out by the HPRA leading to the approval of the medicinal product for marketing in Ireland.

CONTENTS

I. INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the HPRA has granted a marketing authorisation for Doxycycline 100mg hard capsules, from Athlone Pharmaceuticals Limited on 23rd August 2024.

Doxycycline has been found clinically effective in the treatment of a variety of infections caused by susceptible strains of Gram-positive and Gram-negative bacteria and certain other micro-organisms.

Respiratory Tract Infections:
Pneumonia and other lower respiratory tract infections due to susceptible strains of *Streptococcus pneumoniae, Haemophilus influenzae, Klebsiella pneumoniae, Moraxella catarrhalis* and other organisms. *Mycoplasma pneumonia*. Treatment of chronic bronchitis, sinusitis.

Urinary Tract Infections:
Infections caused by susceptible strains *of Klebsiella species, Enterobacter species, Escherichia coli, Streptococcus faecalis* and other organisms.

Sexually Transmitted Diseases:
Infections due to *Chlamydia trachomatis* including uncomplicated urethral, endocervical or rectal infections.
Non-gonococcal urethritis caused by *Ureaplasma urealyticum* (T-mycoplasma).
Doxycycline is also indicated in infections due to *Calymmatobacterium granulomatis.* Doxycycline is an alternative drug in the treatment of gonorrhoea and syphilis.

Since Doxycycline is a member of the tetracycline series of antibiotics, it may be expected to be useful in the treatment of infections, which respond to other tetracyclines such as:

Ophthalmic infections:
Doxycycline is indicated in the treatment of trachoma, although the infectious agent is not always eliminated, as judged by immunofluorescence. Inclusion conjunctivitis may be treated with oral Doxycycline alone or in combination with topical agents.

Rickettsial Infections:
Rocky Mountain spotted fever, typhus group, Q fever and Coxiella endocarditis.

Other Infections:
Psittacosis, brucellosis (in combination with streptomycin), cholera, bubonic plague, louse and tick-borne relapsing fever, including stage 1 and stage 2 Lyme disease, leptospirosis, tularaemia glanders, chloroquine-resistant falciparum malaria and acute intestinal amoebiasis (as an adjunct to amoebicides). Infections due to susceptible strains of *Bacteroides* species, *Listeria species* and *Bacillus anthracis*.
Doxycycline is an alternative drug in the treatment of leptospirosis, gas gangrene and tetanus.
Doxycycline is indicated for prophylaxis in the following conditions: Scrub typhus travellers' diarrhoea (enterotoxigenic *Escherichia coli*), leptospirosis, malaria and cholera.
Consideration should be given to official guidance on the appropriate use of antibacterial agents.

This application for a marketing authorisation was submitted under Article 10(1) of Directive 2001/83/EC as amended via national procedure.

The reference product is Vibramycin Capsules 100 mg (PA0822/193/001) from Pfizer Healthcare Ireland authorised in Ireland since 14/10/1977.

Doxycycline 50 mg and 100 mg hard capsules are generic versions of Vibramycin Capsules 50 mg and Vibramycin Capsules 100 mg.

The Summary of Product Characteristics for (SmPC) for this medicinal product is available on the HPRA's website at www.hpra.ie.

Name of the product	Doxycycline 100 mg hard capsules
Name(s) of the active substance(s)	Doxycycline hyclate

(INN)	
Pharmacotherapeutic classification (ATC Code)	J01AA02
Pharmaceutical form and strength(s)	Hard capsules, 100 mg
Marketing Authorisation Number(s) in Ireland (PA)	PA1418/010/002
Marketing Authorisation Holder	Athlone Pharmaceuticals Limited Connaught House 1 Burlington Road Dublin 4 D04 C5Y6 Ireland

II. QUALITY ASPECTS

II.1. Introduction
This application is for doxycycline 50 mg and 100 mg hard capsules.

II.2 Drug substance
The active substance is doxycycline (as doxycycline hyclate), an established active substance described in the European Pharmacopoeia, and is manufactured in accordance with the principles of Good Manufacturing Practice (GMP).

The active substance specification is considered adequate to control the quality and meets current pharmacopoeial requirements. Batch analytical data demonstrating compliance with this specification has been provided.

II.3 Medicinal product
P.1 Composition
Each hard capsule contains 50 mg or 100 mg of doxycycline (as hyclate).

The excipients in the medicinal product are listed in section 6.1 of the SmPC.
A visual description of the product is included in section 3 of the SmPC.

P.2 Pharmaceutical Development
The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines.

P.3 Manufacture of the Product
The product is manufactured in accordance with the principles of good manufacturing practice (GMP) at suitably qualified manufacturing sites.

The manufacturing process has been validated according to relevant European/ICH guidelines and the process is considered to be sufficiently validated.

P.4 Control of Other Substances
All ingredients comply with Ph. Eur. or are adequately controlled by the manufacturer's specifications.

P.5 Control of Finished Product
The Finished Product Specification is based on the pharmacopoeial monograph for hard capsules, and the tests and control limits are considered appropriate for this type of product.

The analytical methods used are described in sufficient detail and are supported by validation data.

Batch analytical data for a number of batches from the proposed production site have been provided and demonstrate the ability of the manufacturer to produce batches of finished product of consistent quality.

P.6 Packaging material
The approved packaging for this product is described in section 6.5 of the SmPC.

Evidence has been provided that the packaging complies with Ph. Eur./EU legislation for use with foodstuffs requirements.

P.7 Stability of the Finished Product
Stability data on the finished product in the proposed packaging have been provided in accordance with EU guidelines and support the shelf-life and storage conditions listed in sections 6.3 and 6.4 of the SmPC.

II.4 Discussion on Chemical, Pharmaceutical and Biological Aspects
The important quality characteristics of the product are well-defined and controlled. Satisfactory chemical and pharmaceutical documentation has been provided, assuring consistent quality of doxycycline 50 mg and 100 mg hard capsules.

III. NON-CLINICAL ASPECTS

III.1 Introduction
This active substance is a generic formulation of Vibramycin 50 mg and Vibramycin 100 mg capsules on the European market. No new preclinical data have been submitted.

III.2 Pharmacology
N/A

III.3 Pharmacokinetics
N/A

III.4 Toxicology
N/A

III.5 Ecotoxicity/environmental risk assessment
Since Doxycycline 50 mg and 100 mg hard Capsules are generic products, they will not lead to an increased exposure to the environment. Additional studies on environmental risk assessment are therefore not deemed necessary.

III.6 Discussion on the non-clinical aspects
Pharmacodynamic, pharmacokinetic and toxicological properties of doxycycline hyclate are well known. As doxycycline hyclate is a widely used, well-known active substance, the applicant has not provided additional nonclinical studies and further studies are not required. A nonclinical overview based on literature review was provided and is acceptable for this type of application. Non-clinical findings are adequately represented in the appropriate sections of the SmPC.

IV. CLINICAL ASPECTS

IV.1 Introduction
This is a generic application submitted under article 10(1) of Directive 2001/83/EC.
Doxycycline is a well-known active substance with established efficacy and tolerability.
The content of the SmPCs approved during the decentralised procedure is in accordance with that accepted for the reference product Vibramycin Capsules 100 mg (PA0822/193/001) from Pfizer Healthcare Ireland authorised in Ireland since 14/10/1977.

To support the application, the applicant has submitted the report of a bioequivalence study with the 100mg strength and a justification for waiver of a bioequivalence study with the 50mg strength in accordance with the EMA Guideline on the investigation of bioequivalence CPMP/EWP/QWP/1401/98 Rev. 1/Corr**.

The bioequivalence study was an open-label, balanced, randomised, single-dose, two-treatment, two-sequence, two-period, two-way crossover bioequivalence study of Doxycycline capsules 100mg of Kopran Ltd India and Vibracina 100mg capsulas duras of Invicta Farma, S.A., Grupo Pfizer, Spain, in adult, male, human subjects under fasted conditions. The Spanish reference product used in the bioequivalence study is part of the same global marketing authorisation as the reference product authorised in Ireland. Bioequivalence was demonstrated.

Adequate justification for waiver of a study with the 50 mg strength was provided in accordance with recommendations in the bioequivalence guideline i.e.
- Both strengths are manufactured by the same manufacturer and process,
- The qualitative composition of the two strengths are the same,

- Composition of strengths are quantitatively proportional,
- The dissolution profiles are comparable over the pH range 1 to 6.8 under appropriate conditions,
- The pharmacokinetics of the active substance are linear in the therapeutic range.

The results of the bioequivalence study performed with the Doxycycline hard capsules 100 mg therefore apply to the Doxycycline hard capsules 50 mg strength.

The HPRA has been assured that GCP standards were followed in an appropriate manner in the studies conducted.

IV.2 Pharmacokinetics
Tetracyclines are readily absorbed and are bound to plasma proteins in varying degrees. They are concentrated by the liver in the bile and excreted in the urine and faeces at high concentrations and in a biologically active form. Doxycycline is virtually completely absorbed after oral administration. Studies reported to date indicate that the absorption of doxycycline, unlike certain other tetracyclines, is not notably influenced by the ingestion of food or milk.
Following a 200 mg dose, normal adult volunteers averaged peak serum levels of 2.6 micrograms/ml of doxycycline at 2 hours decreasing to 1.45 micrograms/ml at 24 hours.
Studies have shown no significant difference in serum half-life of doxycycline (range 18 to 22 hours) in individuals with normal or severely impaired renal function.
Haemodialysis does not alter the serum half-life of doxycycline.

IV.3 Pharmacodynamics
Doxycycline is primarily bacteriostatic and is believed to exert its antimicrobial effect by the inhibition of protein synthesis.

Doxycycline is active against a wide range of Gram-positive and Gram-negative bacteria and certain other micro-organisms

IV.4 Clinical Efficacy
The efficacy of doxycycline in the proposed indications is established in clinical use. No new clinical efficacy studies are provided, and none are required.

IV.5 Clinical Safety
The overall safety profile of doxycycline is established and generally known. No new safety studies are provided, and none are required.

The safety information in the SmPC and Package Leaflet are in line with those of the reference medicinal product.

Risk Management Plan
The MAH has submitted a risk management plan, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Doxycycline 50mg, 100mg hard capsules.
Summary table of safety concerns in approved RMP:

Important identified risks	None
Important potential risks	None
Missing information	None

Pharmacovigilance plan
Routine pharmacovigilance is suggested and no additional pharmacovigilance activities are proposed by the applicant, which is endorsed.

Risk minimisation measures
Routine risk minimisation is suggested and no additional risk minimisation activities are proposed by the applicant, which is endorsed.

Periodic Safety Update Report (PSUR)
With regard to PSUR submission, the MAH should take the following into account:

- PSURs shall be submitted in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c (7) of Directive 2001/83/EC and published on the European medicines web-portal. Marketing authorisation holders shall continuously check the European medicines web-portal for the DLP and frequency of submission of the next PSUR.

- For medicinal products authorized under the legal basis of Article 10(1) or Article 10a of Directive 2001/83/EC, no routine PSURs need to be submitted, unless otherwise specified in the EURD list.
- For medicinal products that do not fall within the categories waived of the obligation to submit routine PSURs by the revised pharmacovigilance legislation, the MAH should follow the DLP according to the EURD list.

Common renewal date

Common renewal date will be 5 years after the finalisation of the procedure.

IV.6 Discussion on the clinical aspects

As this is a generic application under Article 10(1) of Directive 2001/83/EC, additional non-clinical and clinical studies to demonstrate efficacy and safety are not required.

The applicant submitted the results of a suitable bioequivalence study, which demonstrated the similarity of the test product Doxycycline hard capsules 100mg of Kopran Ltd India and Vibracina 100mg capsulas duras of Invicta Farma, S.A., Grupo Pfizer, Spain in accordance with the relevant guidance. The Spanish reference product used in the bioequivalence study is part of the same global marketing authorisation as the reference product authorised in Ireland. A justification for waiver of a study with the 50 mg strength has been provided.

V. OVERALL CONCLUSIONS

Doxycycline 50 mg and 100 mg hard capsules from Athlone Pharmaceuticals Limited are generic forms of Vibramycin Capsules 50 mg and Vibramycin Capsules 100 mg from Pfizer Healthcare Ireland.

Vibramycin Capsules 100 mg (PA0822/193/001) is a well-known medicinal product with a proven chemical-pharmaceutical quality and an established favourable efficacy and safety profile.

Bioequivalence has been shown to in compliance with the CHMP guidance documents. The SmPC is consistent with that of the reference product.

The MAH has provided written confirmation that systems and services are in place to ensure compliance with their pharmacovigilance obligations.

The HPRA, based on the data submitted considered that Doxycycline 50 mg and 100 mg hard capsules demonstrated bioequivalence with the reference product as well as a satisfactory risk/benefit profile and therefore granted a marketing authorisation.

VI. REVISION DATE

VII. UPDATES

This section reflects the significant changes following finalisation of the initial procedure.

SCOPE	PROCEDURE NUMBER	PRODUCT INFORMATION AFFECTED	DATE OF START OF PROCEDURE	DATE OF END OF PROCEDURE
New National	N/A	SmPC, Product Leaflet		