IPAR

Public Assessment Report for a
Medicinal Product for Human Use

Scientific Discussion

Flucloxacillin 500 mg Film-coated Tablets
FLUCLOXACILLIN SODIUM
PA22871/026/001

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.

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I. INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the HPRA has granted a marketing authorisation for Flucloxacillin 500mg & 1000 Film-coated Tablets, from Azure Pharmaceuticals Ltd on 24th March 2023 for the treatment of:
Infections due to sensitive Gram-positive organisms, including β-lactamase-producing staphylococci and streptococci such as:
- *Skin and soft tissue infections*
- *Respiratory tract infections*
- *Other infections caused by flucloxacillin-sensitive micro-organisms*

This application concerns an Article 10(1) generic version of flucloxacillin sodium, under the trade name Flucloxacillin 500 mg film coated tablets and Flucloxacillin 1000 mg film coated tablets.

This is a Decentralised Procedure, with IE as the Reference Member State (RMS) and Malta as the Concerned Member State (CMS).

This product is subject to prescription.

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	Flucloxacillin 500 mg Film-coated Tablets
Name(s) of the active substance(s) (INN)	Flucloxacillin Sodium
Pharmacotherapeutic classification (ATC code)	J01CF05
Pharmaceutical form and strength(s)	500 mg Film-coated Tablets
Marketing Authorisation Number(s) in Ireland (PA)	PA 22871/026/001
Marketing Authorisation Holder	Azure Pharmaceuticals Ltd
MRP/DCP No.	IE/H/1184/001/DC
Reference Member State	IE
Concerned Member State	MT

II. QUALITY ASPECTS

This application is for Flucloxacillin 500mg & 1000 Film-coated Tablets

II.2 Drug substance

The active substance is Flucloxacillin Sodium an established active substance described in the <European/British> 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

The medicinal product contains either 500 mg or 1000 mg of flucloxacillin.

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 (Excipients/*Ancillary 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 coated tablets, 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(s) 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 flucloxacillin 500mg and 1000 mg film coated tablets.

III. NON-CLINICAL ASPECTS

III.1 Introduction

This active substance, flucloxacillin, is a generic formulation of Heracillin 500 mg and Heracillin 1000 mg film-coated tablets (Meda AB) on the European market since 1975. No new preclinical data have been submitted.

The pharmacodynamic, pharmacokinetic and toxicological properties of flucloxacillin are well known. As flucloxacillin is a widely used, well-known active substances, and this is a generic application, the applicant has not provided additional nonclinical studies and further studies are not required. The overview provided based on literature review is thus appropriate.

III.2 Ecotoxicity/environmental risk assessment

The applicant has not provided a full environmental risk assessment (ERA) in accordance with the guideline (CHMP/SWP/4447/00). Instead justification for the absence of a full ERA is supplied. Since Flucloxacillin 500 mg and Flucloxacillin 1 g film-coated tablets are intended for generic substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

III.3 Discussion on the non-clinical aspects

The pharmacodynamic, pharmacokinetic and toxicological properties of flucloxacillin are well known. As flucloxacillin is a widely used, well-known active substances, and this is a generic application, the applicant has not provided additional nonclinical studies and further studies are not required. The non-clinical overview on the pre-clinical pharmacology, pharmacokinetics and toxicology provided is adequate. Non-clinical findings are adequately represented in the appropriate sections of the SmPC.

IV. CLINICAL ASPECTS

Flucloxacillin Sodium is a well known active substance with established efficacy and tolerability.

The content of the SmPC including the indication approved during this decentralised procedure is consistent with other flucloxacillin products.

For this generic application, the applicant has submitted one bioequivalence (BE) study, *An open-label, balanced, single-dose, randomised, two-treatment, two-sequence, crossover oral bioequivalence study was carried out in 32 healthy, adult, subjects under fasting conditions*, in which the pharmacokinetic profile of the test product Flucloxacillin 1000 mg film coated tablets is compared with the pharmacokinetic profile of the reference product Heracillin 1000 mg film-coated tablets (Meda Pharmaceutical Ltd, Sweden).

Based on the pharmacokinetic parameters of flucloxacillin sodium, the reference tablet Heracillin 1000 mg film coated tablets marketed by Meda Pharmaceutical Ltd., Sweden and test tablet Flucloxacillin 1000 mg film coated tablet are bioequivalent with extent to the rate and extent of absorption and fulfil the bioequivalence requirements outlined in the relevant CHMP Note for Guidance.

The biowaiver request for the 500mg strength is acceptable. The general biowaiver criteria outlined in the bioequivalence guideline are met therefore the results of the bioequivalence study performed with the 1000mg tablets can apply to the additional strength, Flucloxacillin 500 mg film coated tablets.

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

IV.2 Pharmacokinetics

As this is a generic application, only a bioequivalence study has been submitted. The known pharmacokinetics of flucloxacillin have been outlined by the applicant and are also described in the SmPC.

IV.3 Pharmacodynamics

The pharmacodynamics of Flucloxacillin sodium are established and have been adequately discussed by the applicant and the overview is based on published literature.
The applicant has not submitted any new pharmacodynamic data which is considered acceptable for this type of application.

IV.4 Clinical Efficacy

Apart from a single BE study the applicant has not provided additional clinical studies and further studies are not required.

IV.5 Clinical Safety

The overall safety profile of flucloxacillin sodium is established and generally known.

No new safety concerns were identified during the bioequivalence study submitted with this application.

No post-marketing data is available.

A Risk Management Plan, version 0.2, dated 29 June 2022 has been submitted, 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 flucloxacillin 500mg and 1000mg film coated tablets. It is concluded that routine pharmacovigilance and risk minimisation measures are sufficient.

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.

IV.6 Discussion on the clinical aspects

This application concerns an Article 10(1) generic version of flucloxacillin sodium. In line with the requirements for an Article 10(1) application, a bioequivalence study has been presented to demonstrate bioequivalence between the test and the designated reference product.

Flucloxacillin sodium is a well-known active substance with established efficacy and tolerability.

The clinical pharmacology, efficacy and safety of the active substance have been adequately discussed in the clinical overview.

The bioequivalence study design is in line with the requirements set out in Guideline on the investigation of Bioequivalence CPMP/EWP/QWP/1401/98 and is acceptable. The test product, Flucloxacillin 1000 mg tablets when compared with the reference product, Heracillin (Flucloxacillin sodium) 1000 mg tablets meets the bioequivalence criteria in terms of rate and extent of absorption after administration of single dose and fulfils the bioequivalence requirements.

The biowaiver for the 500 mg strength is considered acceptable.

V. OVERALL CONCLUSIONS

Flucloxacillin 500 mg and 1000 mg film coated tablets is a generic form of Heracillin 500 mg and 1000 mg film coated tablets. Heracillin 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 be in compliance with the CHMP guidance documents.

The product information is consistent with other authorised flucloxacillin products.

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

The HPRA, on the basis of the data submitted considered that Flucloxacillin 500 mg and 1000 mg film coated tablets demonstrated bioequivalence with the reference product as well as a satisfactory risk/benefit profile and therefore granted a marketing authorisation.

VI. REVISION DATE

17.01.2028