LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Flucloxacillin EQL Pharma
(flucloxacillin)

This module reflects the scientific discussion for the approval of Flucloxacillin EQL Pharma. The procedure was finalised on 2024-08-02. For information on changes after this date please refer to the module 'Update'.

Postadress/Postal address: P.O. Box 26, SE-751 03 Uppsala, SWEDEN
Besöksadress/Visiting address: Dag Hammarskjölds väg 42, Uppsala
Telefon/Phone: +46 (0)18 17 46 00 Fax: +46 (0)18 54 85 66
Internet: www.lakemedelsverket.se E-mail: registrator@lakemedelsverket.se

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, a marketing authorisation has been granted for Flucloxacillin EQL Pharma, 500 mg, 750 mg, 1 g, Film-coated tablet.

The active substance is flucloxacillin sodium monohydrate, flucloxacillin. A comprehensive description of the indication and posology is given in the SmPC.

For recommendations to the marketing authorisation not falling under Article 21a/22a/22 of Directive 2001/83/EC and conditions to the marketing authorisation pursuant to Article 21a/22a/ 22 of Directive 2001/83/EC to the marketing authorisation, please see section VI.

The application for Flucloxacillin EQL Pharma, 1 g, 500 mg, 750 mg, Coated tablet, is a generic application submitted according to Article 10(1) of Directive 2001/83/EC. The applicant applies for a marketing authorisation in Sweden through a National Procedure.

The reference medicinal product chosen for the purposes of establishing the expiry of the data protection period is Heracillin, 500 mg, coated tablet, authorised in SE since 1975, with Meda AB as marketing authorisation holder.

The reference product used in the bioequivalence study is Heracillin, 1 g, coated tablet, from SE with Meda AB as marketing authorisation holder.

Potential similarity with orphan medicinal products
According to the application form and a check of the Community Register of orphan medicinal products the following medicinal product(s) has/have been designated as orphan medicinal products, but not yet been granted a marketing authorisation in the EU: EU/3/12/968, EU/3/05/319 and EU/3/14/1294.

The applicant should monitor these products during the entire procedure to check if a marketing authorisation has been granted. In case a marketing authorisation is granted, the applicant should submit a report on similarity (Module 1.7.1) and, if applicable, submit the data to support derogation from orphan market exclusivity (Module 1.7.2).

II. QUALITY ASPECTS

II.1 Drug Substance

The structure of the drug substance has been adequately proven and its physico-chemical properties are sufficiently described.

The manufacture of the drug substance has been adequately described and satisfactory specifications have been provided for starting materials, reagents and solvents.

The drug substance specification includes relevant tests and the limits for impurities and degradation products have been justified. The analytical methods applied are suitably described and validated.

Stability studies confirm the retest period.

II.2 Medicinal Product

The medicinal product is formulated using excipients listed in section 6.1 in the Summary of Product Characteristics.

The manufacturing process has been sufficiently described and critical steps identified.

The tests and limits in the specification are considered appropriate to control the quality of the finished product in relation to its intended purpose.

Stability studies have been performed and data presented support the shelf life and special precautions for storage claimed in the Summary of Product Characteristics, sections 6.3 and 6.4.

III. NON-CLINICAL ASPECTS

Pharmacology/Pharmacokinetics/Toxicology
Pharmacodynamic, pharmacokinetic and toxicological properties of flucloxacillin are well known. As flucloxacillin is a widely used, well-known active substance, no further studies are required and the applicant provides none. Overview based on literature review is, thus, appropriate.

Environmental Risk Assessment (ERA)
Since Flucloxacillin EQL Pharma is a generic product, it will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

There are no objections to approval of Flucloxacillin EQL Pharma from a non-clinical point of view.

IV. CLINICAL ASPECTS

Pharmacokinetics
To support the marketing authorisation application the applicant has conducted one bioequivalence study comparing Flucloxacillin 1g film-coated tablets with the reference product Heracillin 1g film-coated tablets.

Pharmacokinetic properties of the active substance
Absorption: Flucloxacillin is well absorbed following oral administration and has an oral bioavailability of approximately 50-70%. Following an oral dose of flucloxacillin in fasting subjects, maximal plasma concentrations occur at approximately 1 hour.

Food effect: Concomitant food intake decreases the absorption, and therefore flucloxacillin should be administered between meals.

Linearity: A study by Nauta & Matie (1975) investigating urinary excretion following oral administration of 0.5 and 2 g showed dose proportional amount excreted in urine thus indicating dose proportional absorption of flucloxacillin, provided that there is no non-linearity in renal clearance. Since linear pharmacokinetics following iv administration of flucloxacillin has been demonstrated (Landersdorfer et al. 2007), non-linear renal clearance can be ruled out. Thus, available data support that the pharmacokinetics of flucloxacillin is linear in the therapeutic dose range.

Elimination: The half-life is approximately 80-90 minutes.

Study 20-008
Methods
This was a single-dose, four-period fully replicate crossover study conducted in 52 healthy volunteers, comparing Flucloxacillin, 1 g, film-coated tablet with Heracillin, 1 g, film-coated tablet under fasting conditions. Blood samples for concentration analysis were collected pre-dose and up to 24 hours post-dose. Plasma concentrations of flucloxacillin were determined with an LC-ESI-MS/MS method. Analysis of variance (ANOVA) was performed on the log-transformed data for AUC_{0-t} and C_{max}. The

study was conducted between 11 April 2022 and 11 May 2022.

Results
The results from the pharmacokinetic and statistical analysis are presented in Table 1 below.
Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, tmax median, range) for flucloxacillin, n=50.

Treatment	AUC_{0-24} µg*h/ml	C_{max} µg/ml	t_{max} h
Test	**92 ± 32**	**33 ± 14**	**1.0 (0.5-4.0)**
Reference	**97 ± 35**	**36 ± 17**	**1.0 (0.5-4.0)**
***Ratio (90% CI)**	**94.38 (88.38 - 100.78)**	**92.33 (83.86 - 101.66)**	**-**
AUC_{0-24} area under the plasma concentration-time curve from time zero to 24 hours C_{max} maximum plasma concentration t_{max} time for maximum plasma concentration			

**calculated based on ln-transformed data*

For AUC_{0-t} and C_{max} the 90% confidence interval for the ratio of the test and reference products fell within the conventional acceptance range of 80.00-125.00%.

A biowaiver was sought for the additional strengths of 500 mg and 750 mg.

Discussion and overall conclusion
The bioequivalence study and its statistical evaluation were in accordance with accepted standards for bioequivalence testing, as stated in the Guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1/Corr). The bioanalytical methods were adequately validated.

Based on the submitted bioequivalence study, Flucloxacillin EQL Pharma 1 g tablets are considered bioequivalent with Heracillin 1g tablets.

Absence of studies with the additional strengths of 750mg and 500 mg is acceptable, as all conditions for biowaiver for additional strengths, as described in the Guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1/Corr) are fulfilled and since the pharmacokinetics of flucloxacillin is linear in the therapeutic dose range.

Pharmacodynamics/Clinical efficacy/Clinical safety
No new studies on pharmacodynamics, clinical efficacy or clinical safety have been submitted. Provided that bioequivalence with the originator product is demonstrated, additional data is not necessary.

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 Flucloxacillin EQL Pharma.

Part II Safety specification
The MAH has submitted the version 0.2 RMP dated 2023-10-17 and proposed the following summary safety concerns:

Summary of safety concerns	
Important identified risks	• Hypersensitivity reactions including anaphylactic reactions • Neurotoxicity especially in patients with renal failure • Hepatotoxicity • Pseudomembranous colitis • Metabolic acidosis • Severe skin reactions
Important potential risks	• None
Missing information	• Use in pregnancy and lactation

Assessor´s comment: The proposed RMP for Flucloxacillin EQL Pharma is in line with the most recent version (dated 2020-22-30) of the originator's RMP (Heracillin) and is acceptable.

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

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

Part VI Summary of the RMP
The summary of the RMP is endorsed.

Conclusion of RMP assessment
The submitted Risk Management Plan, version 0.2 signed 2023-10-17 is considered acceptable.

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:
- At the request of the Swedish MPA;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time, but via different procedures.

V. USER CONSULTATION

A user consultation with target patient groups on the package information leaflet (PL) has been performed on the basis of a bridging report making reference to Heracillin, 1 g, film-coated tablet, 5.4.4-2016-53029, regarding content and Folsyra EQL Pharma, 1 mg, tablet, 5.4.1-2019-79155 regarding layout. The bridging report submitted by the applicant has been found acceptable.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The quality of the generic product, Flucloxacillin EQL Pharma is found adequate. There are no objections to approval of Flucloxacillin EQL Pharma, from a non-clinical and clinical point of view. Bioequivalence between the test and reference product has been adequately demonstrated. The product information is acceptable. The benefit/risk is considered positive, and the application is therefore recommended for approval.

List of recommendations not falling under Article 21a/22a/22 of Directive 2001/83/EC in case of a positive benefit risk assessment

N/A

List of conditions pursuant to Article 21a/22a or 22 of Directive 2001/83/EC

N/A

VII. APPROVAL

Flucloxacillin EQL Pharma, 500 mg, 750 mg, 1 g, Film-coated tablet was approved in the national procedure on 2024-08-02.

LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report – Update

Procedure number*	Scope	Product Information affected (Yes/No)	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse

*Only procedure qualifier, chronological number and grouping qualifier (when applicable)

Postadress/Postal address: P.O. Box 26, SE-751 03 Uppsala, SWEDEN
Besöksadress/Visiting address: Dag Hammarskjölds väg 42, Uppsala
Telefon/Phone: +46 (0)18 17 46 00 Fax: +46 (0)18 54 85 66
Internet: www.lakemedelsverket.se E-mail: registrator@lakemedelsverket.se