LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Flucloxacillin Orion
(flucloxacillin sodium)

SE/H/981/03/DC

This module reflects the scientific discussion for the approval of Flucloxacillin Orion. The procedure was finalised on 2016-05-23. 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.mpa.se E-mail: registrator@mpa.se

I. INTRODUCTION

The application for Flucloxacillin Orion, 1 g, film-coated tablet, is a generic application made according to Article 10(1) of Directive 2001/83/EC. The active substance flucloxacillin is the same as in Flucloxacillin Orion 500 mg and 750 mg film-coated tablet, marketed by Orion Corporation since 2011.
The applicant, Orion Corporation applies through the Decentralised Procedure with Sweden acting as reference member state (RMS) and DK, FI and NO as concerned member states (CMS).

The reference medicinal product chosen for the purposes of establishing the expiry of the data protection period is Heracillin, 500 mg, film-coated tablet authorised in Sweden since 1975, with Meda AB as marketing authorisation holder.
The reference product used in the bioequivalence study is Heracillin, 750 mg, film-coated tablet from Sweden with Meda AB as marketing authorisation holder.
Since the reference product is not authorised in CMS, the concept of European Reference Product (ERP) is used in CMS referring to the reference product in the RMS (Heracillin).

For approved indications, see the Summary of Product Characteristics.

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

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

III.1 Discussion on the non-clinical aspects

Since this product has been shown to be essentially similar and refer to a product approved based on a full application with regard to preclinical data, no further such data have been submitted or are considered necessary.

IV. CLINICAL ASPECTS

IV.1 Pharmacokinetics

Flucloxacillin has an oral bioavailability of 50-70 %. Following an oral dose of flucloxacillin in fasting subjects, maximal plasma concentrations occur at approximately 1 hour. Concomitant food intake results in a significant delay in absorption and decreases the plasma levels by up to 50 %, and therefore fluconazole should be administered between meals.

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 of flucloxacillin occurs mainly through the kidneys via tubular secretion and glomerular filtration. The serum elimination half-life is approximately 80-90 minutes. Within 6 hours, approximately 50-55 % of a peroral dose is excreted in the urine.

One bioequivalence study has been submitted for the already approved 750 mg strength. From a pharmacokinetic point of view, it is sufficient to establish bioequivalence with only one strength as the pharmacokinetics of flucloxacillin is linear within the therapeutic dose range. For drugs with linear pharmacokinetics the bioequivalence study should in general be conducted at the highest strength. If the drug is highly soluble, it is also possible to use a lower strength. Data on solubility show that the highest administered single dose is not possible to dissolve in 250 ml of buffer with low pH, but that the solubility is sufficient at higher pH values. Thus, the substance cannot be classified as highly soluble according to the definition in the Bioequivalence guideline and the highest strength should normally be studied. However, the difference in strength between 750 and 1000 mg is small, and it is not considered likely that an additional study with the strength 1000 mg would contribute significantly. Thus, biowaiver of the strength 1000 mg is acceptable from a pharmacokinetic perspective.

The bioequivalence study was assessed and approved during the original application for Flucloxacillin Orion 500 and 750 mg film-coated tablets. No new assessment of the study has been performed since this is a line extension procedure, but the study is summarised below.

Bioequivalence was evaluated in one single-dose, two-way crossover study conducted in 36 healthy volunteers, comparing Flucloxacillin, 750 mg, tablets with Heracillin, 750 mg, tablets under fasting conditions. Blood samples were collected pre-dose and up to 12 hours post-dose. The study design is considered acceptable. Plasma concentrations of flucloxacillin were determined with an adequately validated LC/MS/MS method. 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%.

In conclusion, Flucloxacillin Orion 1 g film-coated tablets are considered bioequivalent with Heracillin 1 g film-coated tablets.

IV.2 Discussion on the clinical aspects

Since this product has been shown to be essentially similar and refer to a product approved based on a full application with regard to clinical efficacy/safety data, no further such data have been submitted or are considered necessary.

IV.3 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 Orion.

Safety specification
Summary table of safety concerns as approved in RMP

Summary of safety concerns	
Important identified risks	• Hypersensitivity/anaphylactic reactions • Hepatotoxicity • Pseudomembranous colitis
Important potential risk	None identified
Missing information	• None identified

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.

Summary of Safety Concerns and Planned Risk Minimisation Activities as proposed/ approved in RMP

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Important identified risk: • Hypersensitivity/anaphylactic reactions	Information given in SmPC sections 4.3, 4.4, 4.8 and 4.9. Other routine risk minimisation measures: • Prescription only medicine • Close monitoring through routine pharmacovigilance	None proposed.
Important identified risk: • Hepatotoxicity	Information given in SmPC sections 4.4 and 4.8. Other routine risk minimisation measures: • Prescription only medicine • Close monitoring through routine pharmacovigilance	None proposed.
Important identified risk: • Pseudomembranous colitis	Information given in SmPC sections 4.4 and 4.8. Other routine risk minimisation measures: • Prescription only medicine • Close monitoring through routine pharmacovigilance	None proposed.

Summary of the RMP
The RMP is approved.

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 RMS;
- 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 (PIL) has been performed on the basis of a bridging report making reference to Flucloxacillin 500 mg and 750 mg, film-coated tablets, assessed and accepted in SE/H/981/01-02. The bridging report submitted by the applicant has been found acceptable.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The benefit/risk ratio is considered positive and Flucloxacillin Orion, 1 g, film-coated tablet, is recommended for approval.

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

N/A

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

N/A

VII. APPROVAL

The Decentralised procedure for Flucloxacillin Orion, 1 g, film-coated tablet, was positively finalised on 2016-05-23.

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Public Assessment Report – Update

Procedure number*	Scope	Product Information affected	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.mpa.se E-mail: registrator@mpa.se