IPAR

Public Assessment Report for a
Medicinal Product for Human Use

Scientific Discussion

Flucloxacillin 500 mg capsules
FLUCLOXACILLIN SODIUM
PA0298/016/002

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.

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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 250 mg Capsules, Flucloxacillin 500 mg Capsules and Flucloxacillin 125 mg/5 ml Oral Solution BP, from Athlone Laboratories Limited on 14th October 2011 for the treatment of infections due to sensitive Gram-positive organisms.

This application for a marketing authorisation was submitted in accordance with Article 10(1) of Directive 2001/83/EC and is referred to as a 'generic' application. Flucloxacillin 250 mg Capsules, Flucloxacillin 500 mg Capsules, and Flucloxacillin 125 mg/5 ml Oral Solution BP have the same qualitative and quantitative composition in terms of actives substances and the same pharmaceutical form as Floxapen 250 mg Capsules, Floxapen 500 mg Capsules, and Floxapen Syrup 125mg/5ml Powder for Oral Suspension respectively.

The products are subject to a prescription which may not be renewed.

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

Name of the product	Flucloxacillin 250 mg Capsules, Flucloxacillin 500 mg Capsules, Flucloxacillin 125 mg/5 ml Oral Solution BP
Name of the active substance (INN)	FLUCLOXACILLIN as FLUCLOXACILLIN SODIUM
Pharmacotherapeutic classification (ATC code)	J01CF05
Pharmaceutical forms and strengths	Hard capsules containing 250 mg or 500 mg; powder for oral solution containing 125 mg/5 ml
Marketing Authorisation Number(s) in Ireland (PA)	PA 298/16/1-3
Marketing Authorisation Holder	Athlone Laboratories Ltd

II. QUALITY ASPECTS

II.1. Introduction

This application is for Flucloxacillin 250 mg Capsules, Flucloxacillin 500 mg Capsules and Flucloxacillin 125 mg/5 ml Oral Solution BP.

II.2 Drug substance

The active substance is flucloxacillin sodium, 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

Flucloxacillin 250 mg Capsules

Each capsule contains flucloxacillin 250 mg as flucloxacillin sodium.

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.

Flucloxacillin 500 mg Capsules

Each capsule contains flucloxacillin 500 mg as flucloxacillin sodium.

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.

Flucloxacillin 125 mg/5 ml Oral Solution BP.

A pink powder for oral solution.

When reconstituted as directed each 5 ml contains flucloxacillin 125 mg as flucloxacillin sodium.

The powder for oral solution also contains sodium benzoate, disodium edentate, saccharin sodium, ammonium glycyrrhizate, anhydrous sodium citrate, pineapple flavour, menthol flavour, erythrosine (E127) and sucrose.

P.2 Pharmaceutical Development

The products are established pharmaceutical forms and their development is adequately described in accordance with the relevant European guidelines.

P.3 Manufacture of the Product

The products are manufactured in accordance with the principles of good manufacturing practice (GMP) at a suitably qualified manufacturing site.

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. monographs or are adequately controlled by the manufacturer's specifications.

P.5 Control of Finished Product

The Finished Product Specifications are based on the pharmacopoeial monographs for 'hard capsules' and for 'powders and granules for oral solutions and suspensions'. The tests and control limits are considered appropriate for these types 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 the hard capsules is described in section 6.5 of the SmPC.
Evidence has been provided that the packaging complies with EU legislative requirements for foodstuffs.

The powder for oral solution is supplied in high-density polyethylene bottles closed with tamper-evident or tamper-evident and child resistant caps. The bottles are packed in an outer carton also containing a CE-marked 5 ml polypropylene spoon.

P.7 Stability of the Finished Product

Flucloxacillin 250 mg and 500 mg Capsules

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.

Flucloxacillin 125 mg/5 ml Oral Solution BP

Stability data on the finished product in the proposed packaging have been provided in accordance with EU guidelines demonstrating the stability of the powder for oral solution for 12 months when stored at a temperature not exceeding 25° C. Following reconstitution, the oral solution should be used within 7 days and be stored in a refrigerator at 2° C to 8° C.

II.4 Discussion on Chemical, Pharmaceutical and Biological Aspects

The important quality characteristics of the products are well-defined and controlled. Satisfactory chemical and pharmaceutical documentation has been provided, assuring consistent quality of Flucloxacillin 250 mg Capsules, Flucloxacillin 500 mg Capsules and Flucloxacillin 125 mg/5 ml Oral Solution BP.

III. NON-CLINICAL ASPECTS

Not applicable.

IV. CLINICAL ASPECTS

IV.1 Introduction

Flucloxacillin is a well known active substance with established efficacy, safety and tolerability.
The content of the SPC approved during the national procedure is in accordance with that accepted for the reference product Floxapen marketed by Actavis and similarly in line with EU licensed flucloxacillin medicinal products, the MAH has committed to updating the product information following comments from RMS and CMS during the procedure.
For this generic application, the applicant has submitted a bioequivalence study in which the pharmacokinetic profile of the test product flucloxacillin 500mg is compared with the pharmacokinetic profile of the reference product Floxapen 500 mgs
A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out.
Based on the pharmacokinetic parameters of active substance the reference tablet and test 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 Applicant has provided a justification for a biowaiver for the lower strength of 250 mg and for flucloxacillin powder for oral solution in compliance with the CHMP note for guidance on bioequivalence.
Therefore a single bioequivalence study conducted at 500 mg is sufficient.
This is also incompliance with other Flucloxacillin authorisations in other member states.

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

IV.2 Pharmacokinetics

Absorption:
Flucloxacillin is stable in acid media and can therefore be administered either by the oral or parenteral route. The peak serum levels of flucloxacillin reached after one hour are as follows:

After 250 mg by the oral route (in fasting subjects): Approximately 8.8 mg/l.
After 500 mg by the oral route (in fasting subjects): Approximately 14.5mg/l.
After 500 mg by the IM route: Approximately 16.5 mg/l.

The total quantity absorbed by the oral route represents approximately 79% of the quantity administered.

Distribution:
Serum protein binding rate is 95%. Flucloxacillin diffuses well into most tissue.

Crossing the meningeal barrier: Flucloxacillin diffuses in only small proportion into the cerebrospinal fluid of subjects whose meninges are not inflamed.
Crossing into mother's milk: Flucloxacillin is excreted in small quantities in mother's milk.

Metabolism:
In normal subjects approximately 10% of the flucloxacillin administered is metabolised to penicilloic acid. The elimination half-life of flucloxacillin is in the order of 53 minutes.

Excretion:
Excretion occurs mainly through the kidney. Between 65.5% (oral route) and 76.1% (parenteral route) of the dose administered is recovered in unaltered active form in the urine within 8 hours. A small portion of the dose administered is excreted in the bile. The excretion of flucloxacillin is slowed in cases of renal failure.
Following oral administration flucloxacillin is almost completely absorbed achieving blood levels comparable to those achieved after intramuscular injection

IV.3 Pharmacodynamics

Pharmacotherapeutic classification: Beta-lactamase resistant penicillins
ATC code: J01C F05
Properties: Flucloxacillin is a narrow-spectrum antibiotic of the group of isoxazolyl penicillins; it is not inactivated by staphylococcal β-lactamases.

Activity: Flucloxacillin, by its action on the synthesis of the bacterial wall, exerts a bactericidal effect on streptococci except those of group D (*Enterococcus faecalis*) staphylococci. It is not active against methicillin-resistant staphylococci.

IV.4 Clinical Efficacy

There are no reasons to suggest that efficacy of this product is different to the recognised efficacy of the comparator product.

Efficacy of this essentially similar product will be the same as the already marketed product at equivalent doses.

The efficacy of the penicillins, including the isoxazolyl penicillins has been extensively evaluated and documented in the literature.
The indications described in the Summary of Product Characteristics are the recognised indications and justified based upon clinical study and experience.

Flucloxacillin is indicated for the treatment of infections due to sensitive Gram-positive organisms, including ß-lactamase -producing staphylococci and streptococci. Typical indications include skin and soft tissue infections, respiratory tract infections and other infections caused by sensitive organisms, such as, urinary tract infection, and enteritis.

IV.5 Clinical Safety

The safety profile of flucloxacillin is well known and the potential adverse events are reflected in section 4.8 of the SmPC.

There are no reasons to suggest that safety of this product is different to the recognised efficacy of the comparator product as bioequivalence has been demonstrated

The Marketing Authorisation Holder submitted a set of documents describing the Pharmacovigilance system, including information on the availability of an EU Qualified Person for Pharmacovigilance (EU QPPV) and the means for notification of adverse reaction reports in the EU or from a Third Country.

A Risk Management Plan was submitted, which adequately reflects the safety specification of Flucloxacillin and contains appropriate pharmacovigilance and risk minimisation measures.

The PSUR should be submitted in accordance with the list of European Union Reference Dates.

EU Birth Date is the 31 Mar 1970 and the DLP of the next report is 31 Mar 2015.

V. OVERALL CONCLUSIONS

BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Flucloxacillin 500 mg Capsules are a generic form of Floxapen 500 mg.

Floxapen 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 SPC is consistent with that of the reference product.
Adequate justification was provided for a biowaiver for the 250 mg strength and for flucloxacillin powder for oral solution in accordance with the CHMP note for guidance on bioequivalence.

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 demonstrated bioequivalence with the reference product as well as a satisfactory risk/benefit profile and therefore granted marketing authorisation.

VI. REVISION DATE

May 2014