Public Assessment Report

Decentralised Procedure

Flucloxacillin 500 mg powder for solution for injection or infusion

Flucloxacillin 1000 mg powder for solution for injection or infusion

(flucloxacillin sodium)

Product Licence Number: PL 17509/0086-0087

European Procedure Number: UK/H/6745/001-002/DC

Intrapharm Laboratories Ltd.
LAY SUMMARY

Flucloxacillin 500 mg powder for solution for injection or infusion
Flucloxacillin 1000 mg powder for solution for injection or infusion

(flucloxacillin sodium)

This is a summary of the Public Assessment Report (PAR) for Flucloxacillin 500 mg powder for solution for injection or infusion (PL 17509/0086; UK/H/6745/001/DC) and Flucloxacillin 1000 mg powder for solution for injection or infusion (PL 17509/0087; UK/H/6745/002/DC). It explains how the applications for Flucloxacillin 500 mg powder for solution for injection or infusion and Flucloxacillin 1000 mg powder for solution for injection or infusion were assessed and their authorisation recommended, as well as the conditions of use. It is not intended to provide practical advice on how to use Flucloxacillin 500 mg powder for solution for injection or infusion and Flucloxacillin 1000 Flucloxacillin 500 mg powder for solution for injection or infusion.

These products will be referred to as ‘Flucloxacillin injection’ or ‘Flucloxacillin 500 mg and 1000 mg injection’ in this lay summary, for ease of reading.

For practical information about using Flucloxacillin injection, patients should read the package leaflet or contact their doctor or pharmacist.

What is Flucloxacillin injection and what is it used for?
These applications are for generic medicines. This means that these medicines are the same as, and considered interchangeable with, reference medicines already authorised in the European Union (EU) called Floxapen Vials for Injection 500 mg (Accord Healthcare Limited) Floxapen Vials for Injection 1000mg (Accord Healthcare Limited).

Flucloxacillin injection is used for the treatment of a range of bacterial infections including bone infections (osteomyelitis) and infections within the lining of the heart (endocarditis). Flucloxacillin can also be used to prevent infections that can occur during major surgical operations, such as heart (cardiothoracic surgery) or bone, joint and muscle operations (orthopaedic surgery).

How does Flucloxacillin injection work?
Flucloxacillin injection contains the active substance, flucloxacillin (as flucloxacillin sodium), which is an antibiotic used to treat infections by killing the bacteria that cause them. Flucloxacillin belongs to a group of antibiotics called penicillins.

How is Flucloxacillin injection used?
The pharmaceutical form of these medicines is a powder for solution for infusion or injection. These medicines are prepared in the form of a liquid and administered by injection into a muscle (intramuscular) or vein (intravenous) by a health professional (a doctor or nurse). Flucloxacillin can also be given by injection into a joint (intra-articular) or injection into the lining the lung (intrapleural), or by breathing in the medicine from a mask (nebuliser). Flucloxacillin injection should not be administered into the eye.

The patient’s doctor will decide on the dose and duration of treatment. This will depend on the severity and type of infection the patient has.

For further information on how Flucloxacillin injection are used, refer to the package leaflet and Summaries of Product Characteristics available on the Medicines and Healthcare products Regulatory Agency (MHRA) website.

These medicines can only be obtained with a prescription. The patient should always take these medicines exactly as their doctor has told them. The patient should check with their doctor or
pharmacist if they are not sure.

**What benefits of Flucloxacillin injection have been shown in studies?**
Flucloxacillin 500 mg and 1000 mg injection are generic medicines that fulfil criteria, meaning that no additional studies are required. Flucloxacillin 500 mg and 1000 mg injection have been considered generic medicines of the reference medicines based on a comparison of their physical and chemical characteristics. Further information is provided in the main body of the PAR.

**What are the possible side effects of Flucloxacillin injection?**
Because Flucloxacillin 500 mg and 1000 mg injection are generic medicines, their benefits and possible side effects are considered to be the same as for the reference medicines.

For the full list of all side effects reported with these medicines, see Section 4 of the package leaflet or the Summaries of Product Characteristics (SmPCs) available on the MHRA website.

**Why is Flucloxacillin injection approved?**
It was concluded that, in accordance with EU requirements, Flucloxacillin 500 mg and 1000 mg injection have been shown to be comparable to the reference medicines.

Therefore, the MHRA decided that, as for the reference medicines, the benefits are greater than the risks and recommended that it can be approved for use.

**What measures are being taken to ensure the safe and effective use of Flucloxacillin injection?**
A Risk Management Plan (RMP) has been developed to ensure that Flucloxacillin injection is used as safely as possible. Based on this plan, safety information has been included in the Summaries of Product Characteristics and the package leaflet, including the appropriate precautions to be followed by healthcare professionals and patients.

Known side effects are continuously monitored. Furthermore, new safety signals reported by patients/healthcare professionals will be monitored and reviewed continuously.

**Other information about Flucloxacillin injection**
Marketing Authorisations for Flucloxacillin injection were granted in the UK on 01 March 2019.

The full PAR approved for Flucloxacillin injection follows this summary.

For more information about treatment with Flucloxacillin injection, read the package leaflet, or contact your doctor or pharmacist.

This summary was last updated in May 2019.
TABLE OF CONTENTS

Contents
I  Introduction ........................................................................................................................................... 5
II  Quality aspects ......................................................................................................................................... 5
III Non-clinical aspects ................................................................................................................................. 7
IV  Clinical aspects .......................................................................................................................................... 7
V  User consultation ......................................................................................................................................... 8
VI Overall conclusion, benefit/risk assessment and recommendation ...................................................... 8
Table of content of the PAR update ........................................................................................................... 111
Scientific discussion

I. INTRODUCTION
Based on the review of the data on quality, safety and efficacy, the Medicines and Healthcare products Regulatory Agency (MHRA) considered that the applications for Flucloxacillin 500 mg powder for solution for injection or infusion (PL 17509/0086; UK/H/6745/001/DC) and Flucloxacillin 1000 mg powder for solution for injection or infusion (PL 17509/0087; UK/H/6745/002/DC) could be approved.

The products are Prescription Only Medicines (POM) and are indicated for the treatment of the following infections in adults and children caused by flucloxacillin-sensitive gram-positive organisms:
• osteomyelitis
• endocarditis

Treatment of patients with bacteraemia that occurs in association with, or is suspected to be associated with, any of the infections listed above.

Flucloxacillin may also be used in the peri-operative prophylaxis for surgical procedures when appropriate, for example cardiothoracic or orthopaedic surgery.

Consideration should be given to official guidance on the appropriate use of antibacterial agents.

The active substance, flucloxacillin, is an isoxazolyl penicillin of the β-lactam group of antibiotics which exerts a bactericidal effect upon many Gram-positive organisms including β-lactamase-producing staphylococci and streptococci.

The Reference Member State (RMS) for these procedures was the UK and the Concerned Member State (CMS) was Ireland.

These applications were submitted under Article 10(1) of Directive 2001/83/EC, as amended, as generic applications. The reference medicinal products are Floxapen Vials for Injection 500 mg (PL 20075/0592; Accord Healthcare Limited) and Floxapen Vials for Injection 1000 mg (Accord Healthcare Limited), which were granted product licences in the UK on 13 April 2017 following a series of Change of Authorisation (COA) procedures of Floxapen Vials for Injection 500 mg (PL 00038/5052R; Beecham Group Plc) and Floxapen Vials for Injection 1g (PL 00038/5053R; Beecham Group Plc), which were authorised in the UK on 15 May 1987.

No new non-clinical studies were conducted, which is acceptable given that the application are based on being generic medicinal products of reference products that have been licensed for over 10 years.

A biowaiver was submitted with these applications, which was accepted. No bioequivalence study was required and no new clinical studies were provided with these application(s).

The MHRA has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for these products at all sites responsible for the manufacture, assembly and batch release of these products.

The RMS and CMS considered that the applications could be approved at the end of procedure (Day 208) on 25 January 2019. After a subsequent national phase, licences were granted in the UK on 01 March 2019.

II. QUALITY ASPECTS
II.1 Introduction
Each medicinal product is a white or almost white powder for solution for injection or infusion.

Each vial of Flucloxacillin 500 mg or 1000 mg powder for solution for injection or infusion contains 500 mg or 1000 mg flucloxacillin (as flucloxacillin sodium). The products contains no excipients.
The finished products are packaged in colourless glass vials, each sealed with a bromobutyl rubber stopper and aluminium cap with plastic lid. The products are available in a pack size of 10 vials per carton.

Satisfactory specifications and Certificates of Analysis for the primary packaging material have been provided. All primary packaging is controlled to European Pharmacopoeia standards that comply with guidance concerning materials in contact with food.

II.2 DRUG SUBSTANCE
Flucloxacillin sodium
INN: Flucloxacillin sodium
Chemical name: Sodium (2S,5R,6R)-6-[[3-(2-chloro-6-fluorophenyl)-5-methyl-1,2-oxazol-4-yl]carbonyl]amino]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylate monohydrate.
Molecular formula: \( \text{C}_{19}\text{H}_{16}\text{ClFN}_{3}\text{NaO}_{5}\text{S}, \text{H}_{2}\text{O} \)
Chemical structure:

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\[ 
\text{Cl} \quad \text{N} \quad \text{F} \quad \text{O} \\
\text{N} \quad \text{H} \quad \text{S} \\
\text{CH}_3 \quad \text{CH}_3
\]
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Mr: 493.9
Appearance: White or almost white, hygroscopic, crystalline powder
Solubility: Freely soluble in water and in methanol, soluble in ethanol (96 per cent).

Flucloxacillin sodium is the subject of a European Pharmacopoeia monograph.

All aspects of the manufacture and control of the active substance, flucloxacillin sodium, are covered by a European Directorate for the Quality of Medicines and Healthcare (EDQM) Certificate of Suitability.

II.3 MEDICINAL PRODUCT
Pharmaceutical Development
A satisfactory account of the pharmaceutical development has been provided.

No excipients of animal or human origin are used in the final products.

Manufacture of the products
A description and flow-chart of the manufacturing method has been provided.

Satisfactory batch formulae have been provided for the manufacture of the products, along with an appropriate account of the manufacturing process. The manufacturing process has been validated and has shown satisfactory results.

Finished Product Specifications
The finished product specifications are satisfactory. The test methods have been described and adequately validated. Batch data have been provided that comply with the release specifications. Certificates of Analysis have been provided for any working standards used.

Stability
Finished product stability studies have been conducted in accordance with current guidelines, using batches of the finished product stored in the packaging proposed for marketing. Based on the results, a shelf-life of 3 years for the unopened product, with the storage conditions 'Do not store above 25°C.', is acceptable.

Reconstituted solutions for intramuscular or direct intravenous should normally be administered within 30 minutes of preparation.
Suitable post approval stability commitments have been provided to continue stability testing on batches of finished products.

II.4 Discussion on chemical, pharmaceutical and biological aspects
The grant of a Marketing Authorisations is recommended.

III. NON-CLINICAL ASPECTS
III.1 Introduction
As the pharmacodynamic, pharmacokinetic and toxicological properties of flucloxacillin are well-known, no new non-clinical data have been submitted and none are required. An overview based on the literature review is, thus, appropriate.

III.2 Pharmacology
No new pharmacology data were provided and none were required for these applications.

III.3 Pharmacokinetics
No new pharmacokinetic data were provided and none were required for these applications.

III.4 Toxicology
No new toxicity data were provided and none were required for these applications.

III.5 Ecotoxicity/Environmental Risk Assessment (ERA)
Suitable justification has been provided for non-submission of an Environmental Risk Assessment. As the applications are for generic versions of already authorised products, an increase in environmental exposure is not anticipated following approval of the Marketing Authorisations for the proposed products.

III.6 Discussion of the non-clinical aspects
The grant of Marketing Authorisations is recommended.

IV. CLINICAL ASPECTS
IV.1 Introduction
The clinical pharmacology, efficacy and safety of flucloxacillin are well-known. According to the regulatory requirements, the applicant has provided a suitable biowaiver and a bioequivalence study is not required for this product. An overview based on a literature review is, thus, satisfactory.

IV.2 Pharmacokinetics
No new pharmacokinetic data have been submitted for these applications and none were required.

IV.3 Pharmacodynamics
No new pharmacodynamic data have been submitted for these applications and none were required.

IV.4 Clinical Efficacy
No new efficacy data were submitted with these applications and none were required.

IV.5 Clinical Safety
No new safety data were submitted with these applications and none were required. The safety profile for these products is considered to be the same as Floxapen Vials for Injection 500 mg (Accord Healthcare Limited) and Floxapen Vials for Injection 1000 mg (Accord Healthcare Limited).

IV.6 Risk Management Plan
The Applicant has submitted a RMP, in accordance with the requirements of Directive 2001/83/EC, as amended. The Applicant proposes only routine pharmacovigilance and routine risk minimisation measures for all safety concerns. This is acceptable.

IV.7 Discussion of the clinical aspects
It is recommended that a Marketing Authorisation is granted, from a clinical point of view.
V. USER CONSULTATION
The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The results show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION
The quality of the products is acceptable, and no new non-clinical or clinical safety concerns have been identified. Extensive clinical experience with flucloxacillin is considered to have demonstrated the therapeutic value of the compound. The benefit/risk is, therefore, considered to be positive.

The Summaries of Product Characteristics (SmPCs), Patient Information Leaflet (PIL) and labelling are satisfactory, in line with current guidelines and consistent with the reference products.

In accordance with Directive 2012/84/EU, the current approved UK versions of the SmPCs and PILs for these products are available on the MHRA website.

Representative copies of the labels at the time of UK licensing are provided below.
Flucloxacillin 500 mg and 1000 mg, powder for solution for injection or infusion

Each vial contains 500mg flucloxacillin as flucloxacillin sodium. Contains no excipients.

For intramuscular or intravenous use
Reconstitute before use and use immediately. Once reconstituted any unused portion of solution should be discarded. For full directions for use, read the package leaflet. Keep out of the sight and reach of children. Do not store above 25°C. Use as directed by your doctor.

Marketing authorisation holder:
Intrapharm Laboratories Ltd.
The Courtyard Barns
Choke Lane, Maidenhead, Berkshire SL6 6PT, UK
M.A. No.: PL 17509/0086
PA 0997/011/001
Flucloxacillin 1000 mg powder for solution for injection or infusion

Each vial contains 1000 mg flucloxacillin as flucloxacillin sodium. It contains no excipients. It contains Penicillin.

For intramuscular or intravenous use, reconstitute before use and use immediately. Once reconstituted any unused portion of solution should be discarded. For full directions for use, read the package leaflet. Keep out of the sight and reach of children. Do not store above 25°C. Use as directed by your doctor.

Marketing authorisation holder: Inrapharm Laboratories Ltd., The Courtyard Barns, Cheyne Lane, Maidenhead, Berkshire SL6 6PT, UK

M.A. No.: PL 17309/0087
Par 0997/011/002

10 vials

Flucloxacillin 1000 mg
Powder for solution for injection or infusion
Flucloxacillin sodium
TABLE OF CONTENT OF THE PAR UPDATE

Steps taken after the initial procedure with an influence on the Public Assessment Report (non-safety variations of clinical significance).

Please note that only non-safety variations of clinical significance are recorded below and in the annexes to this PAR. The assessment of safety variations where significant changes are made are recorded on the MHRA website or European Medicines Agency (EMA) website. Minor changes to the product licence are recorded in the current SmPC and/or PIL available on the MHRA website.

<table>
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<th>Application type</th>
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<th>Product information affected</th>
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<th>Date of end of procedure</th>
<th>Outcome</th>
<th>Assessment report attached Y/N</th>
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