Public Assessment Report

National Procedure

Flucloxacillin 2g, powder for solution for injection or infusion

(Flucloxacillin sodium)

UK Licence No: PL 31745/0032

Ibigen Srl
LAY SUMMARY

Flucloxacillin 2g, powder for solution for injection or infusion

(Flucloxacillin sodium)

This is a summary of the Public Assessment Report (PAR) for Flucloxacillin 2g, powder for solution for injection or infusion (PL 31745/0032). The product may be called ‘Flucloxacillin’ or ‘Flucloxacillin 2g injection’ in this report. It explains how the application for Flucloxacillin 2g injection was assessed and its authorisation recommended, as well as the conditions of use. It is not intended to provide practical advice on how to use Flucloxacillin 2g injection.

For practical information about using Flucloxacillin 2g injection, patients should read the package leaflet or contact their doctor or pharmacist.

What is Flucloxacillin 2g injection and what is it used for?

Flucloxacillin 2g injection is a ‘hybrid generic medicine’. This means that Flucloxacillin 2g injection is similar to a ‘reference medicine’ already authorised in the UK called Floxapen Vials for Injection 1g (PL 30306/0021; Actavis Group PTC ehf). However unlike the reference product which contains 1g of flucloxacillin (as flucloxacillin sodium), Flucloxacillin 2g injection contains 2g of flucloxacillin (as flucloxacillin sodium).

The company has provided additional own data to demonstrate the safety and efficacy of Flucloxacillin 2g injection regarding this difference from the reference medicine.

Flucloxacillin 2g injection is used to treat:
- heart infections
- bone and joint infections.

Flucloxacillin 2g injection can also be used to prevent infections during major surgery, particularly heart or orthopaedic surgery.

How does Flucloxacillin 2g injection work?

Flucloxacillin 2g injection contains the active substance, flucloxacillin (as flucloxacillin sodium) which is one of a group of medicines called ‘penicillins’. These medicines are also known as ‘antibiotics’ and they work by killing the bacteria that cause infections.

How is Flucloxacillin 2g injection used?

Flucloxacillin 2g injection is available as a powder for solution for infusion or injection. It is prepared in the form of a liquid and administered by injection into a vein by a health professional (a doctor or nurse). The patient’s doctor will determine how much the patient needs and how often the injection should be given.

Please read section 3 of the package leaflet for detailed information on dosing recommendations, the route of administration and the duration of treatment.

Flucloxacillin 2g injection is a prescription only medicine

What benefits of Flucloxacillin 2g injection have been shown in studies?

No additional clinical studies were needed as Flucloxacillin 2g injection is a generic hybrid medicine that after reconstitution is an aqueous solution that is given by injection or infusion and contains the
same active substance as the reference medicine, Floxapen Vials for Injection 1g (PL 30306/0021; Actavis Group PTC ehf).

**What are the possible side effects of Flucloxacillin 2g injection?**
Like all medicines, Flucloxacillin 2g injection used can cause side effects, although not everybody gets them.

Since Flucloxacillin 2g injection is a generic hybrid medicine, the benefits and possible side effects are taken as being the same as the reference medicine.

Stomach upset is a common side effect (may affect up to 1 in 10 people) with Flucloxacillin 2g injection.

For the full list of all side effects reported with Flucloxacillin 2g injection, see section 4 of the package leaflet.

For the full list of restrictions, see the package leaflet for Flucloxacillin 2g injection.

**Why is Flucloxacillin 2g injection approved?**
It was concluded that, in accordance with EU requirements, Flucloxacillin 2g injection has been shown to be comparable to Floxapen Vials for Injection 1g (PL 30306/0021; Actavis Group PTC ehf). Therefore, the view was that, as for Floxapen Vials for Injection 1g (PL 30306/0021; Actavis Group PTC ehf), the benefits outweigh the identified risks.

**What measures are being taken to ensure the safe and effective use of Flucloxacillin 2g injection?**
A Risk Management Plan has been developed to ensure that Flucloxacillin 2g injection is used as safely as possible. Based on this plan, safety information has been included in the Summary of Product Characteristics and the package leaflet for flucloxacillin, including the appropriate precautions to be followed by healthcare professionals and patients.

**Other information about Flucloxacillin 2g injection**
A Marketing Authorisation was granted in the UK to Ibigen Srl on 05 January 2017.

The full PAR approved for Flucloxacillin 2g injection follows this summary.

For more information about treatment with Flucloxacillin 2g injection, read the package leaflet, or contact your doctor or pharmacist.

This summary was last updated in February 2017.
SCIENTIFIC DISCUSSION

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I. INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the Medicines and Healthcare products Regulatory Agency (MHRA) granted Ibigen Srl a Marketing Authorisation for the medicinal product Flucloxacillin 2g, powder for solution for injection or infusion (PL 31745/0032) on 05 January 2017.

The product may be referred to as ‘Flucloxacillin 2g injection’ or ‘Flucloxacillin’ in the remainder of this report. Flucloxacillin 2g injection’ is a prescription only medicine (POM). Flucloxacillin is indicated for the treatment of the following infections, when due to sensitive Gram-positive organisms:
• osteomyelitis
• endocarditis

Flucloxacillin is also indicated for use as a prophylactic agent during major surgical procedures when appropriate; for example cardiothoracic and orthopaedic surgery.

The application was submitted under Article 10(3) of Directive 2001/83/EC, as amended, as a hybrid application and cross-refers to Floxapen Vials for Injection 1g (PL 30306/0021; Actavis Group PTC ehf), which was granted on 12 October 2007 following a Change of Authorisation (COA) procedure of Floxapen Vials for Injection 1g (PL 00038/5053R; Beecham Group Plc). Floxapen Vials for Injection 1g was authorised in the UK on 15 May 1987.

The active ingredient, flucloxacillin, is a narrow-spectrum antibiotic of the group of isoxazolyl penicillins; it is not inactivated by staphylococcal β-lactamases. Flucloxacillin inhibits the synthesis of the bacterial cell wall and exerts a bactericidal effect on streptococci, except those of group D (Enterococcus faecalis) staphylococci. It is not active against methicillin-resistant staphylococci.

Flucloxacillin is stable in acid media and can therefore be administered either by the oral or parenteral route. The total quantity absorbed by the oral route represents approximately 79% of the quantity administered. Flucloxacillin diffuses well into most tissue.

No new non-clinical studies were performed, which is acceptable given that the application was based on being a generic medicinal product of originator product that has been in clinical use for over 10 years.

No new clinical data have been submitted and none are required for an application of this type. A bioequivalence study was not necessary to support this application for a parenteral product and the applicant submitted none. According to CPMP guidelines, bioequivalence studies are not generally required for parenteral aqueous solutions (CPMP/EWP/QWP/1401/98 Rev. 1/Corr**, Guideline on the Investigation of Bioequivalence).

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

No new or unexpected safety concerns arose during review of information provided by the Marketing Authorisation Holder and it was, therefore, judged that the benefits of Flucloxacillin powder for solution for injection outweigh the risks and a Marketing Authorisation was granted.
II. QUALITY ASPECTS
II.1 Introduction
The submitted documentation concerning the proposed product is of sufficient quality and meets the current EU regulatory requirements.

The quality overall summary has been written by an appropriately qualified person and is a suitable summary of the pharmaceutical aspects of the dossier.

The product is a white powder for solution for injection or infusion.

Each vial of Flucloxacillin powder for solution for injection contains 2g flucloxacillin as flucloxacillin sodium.

The product contains no excipients.

Flucloxacillin 2g injection is packed in clear Type I glass vials, each with a bromobutyl rubber closure. The product is available in cartons in pack sizes of 1, 5, 10, 20 or 50 vials. Not all pack sizes may be marketed.

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 parenteral products.

II.2 DRUG SUBSTANCE
Flucloxacillin sodium
INN: Sodium (2S,5R,6R)-6-[[3-(2-chloro-6-fluorophenyl)-5-methyl-1,2-oxazol-4-yl]carbonyl]amino]-3,3-dimethyl-7-oxo-1-azabicyclo[3.2.0]heptane-2-carboxylate monohydrate.

Molecular formula: Structure:

\[
\text{Mr: 493.9}
\]

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
The objective of the development programme was to produce a safe, efficacious, stable powder for solution for injection or infusion that was equivalent to the reference product Floxapen Vials for Injection, 1g (Actavis Group PTC ehf). Suitable pharmaceutical development data have been provided for this application.
Comparative impurity profiles have been provided for this product and the reference product Floxapen Vials for injection 1g (Actavis Group PTC ehf). The impurity profiles were satisfactory.

**Manufacturing Process**
A satisfactory batch formula has been provided for the manufacture of the product, along with an appropriate account of the manufacturing process. The manufacturing process has been validated with pilot-scale batches that have shown satisfactory results. The Marketing Authorisation Holder has committed to performing process validation studies on full-scale production batches.

**Control of Finished Product**
The finished product specification is acceptable. Test methods have been described that have been validated adequately. Batch data have been provided that comply with the release specification. Certificates of Analysis have been provided for all working standards used.

**Stability of the Product**
Finished product stability studies were performed in accordance with current guidelines on batches of finished product in the packaging proposed for marketing. Based on the results, a shelf-life of 3 years for the product in the unopened vial with the special storage conditions “Store below 25°C.” has been accepted.

The reconstituted/diluted product should be used immediately.

Suitable post approval stability commitments have been provided to continue stability testing on batches of finished product.

**Bioequivalence/Bioavailability**
A bioequivalence study was not necessary to support this application for a parenteral product, since Flucloxacillin 2g injection, after reconstitution, is an aqueous parenteral solution containing the same active substance in the same concentration as the currently authorised product, Floxapen Vials for injection 1g.

**II.4 Discussion on chemical, pharmaceutical and biological aspects**
It is recommended that a Marketing Authorisation is granted for Flucloxacillin 2g injection.

**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.

The applicant’s non-clinical overview has been written by an appropriately qualified person and is satisfactory, providing an appropriate review of the relevant non-clinical pharmacology, pharmacokinetics and toxicology.

**III.2 Pharmacology**
No new data have been submitted and none are required for an application of this type. Refer to Section III.1 Introduction, above.

**III.3 Pharmacokinetics**
No new data have been submitted and none are required for an application of this type. Refer to Section III.1 Introduction, above.
III.4 Toxicology
No new data have been submitted and none are required for an application of this type. Refer to Section III.1 Introduction, above.

III.5 Ecotoxicity/Environmental Risk Assessment (ERA)
Suitable justification has been provided for non-submission of an Environmental Risk Assessment. As the application is for a hybrid generic version of an already authorised product, it is not expected that environmental exposure will increase following approval of the Marketing Authorisation for the proposed product.

III.6 Discussion of the non-clinical aspects
No new non-clinical studies were conducted, which is acceptable given that the application was based on being a generic medicinal product of a reference product that have been licensed for over 10 years.

It is recommended that a Marketing Authorisation, from a non-clinical point of view.

IV. CLINICAL ASPECTS
IV.1 Introduction
The clinical pharmacology of flucloxacillin is well-known. No new clinical pharmacology data have been submitted and none are required for this type of application. A bioequivalence study was not necessary to support this application for a parenteral product and the applicant submitted none. According to CPMP guidelines, bioequivalence studies are not generally required for parenteral aqueous solutions (CPMP/EWP/QWP/1401/98 Rev. 1/Corr**, Guideline on the Investigation of Bioequivalence).

All the relevant clinical information provided is literature based. The clinical overview has been written by an appropriately qualified person and is a suitable summary of the clinical aspects of the dossier.

IV.2 Pharmacokinetics
The pharmacokinetic properties of flucloxacillin are well known and are adequately described in the applicant’s clinical overview. No new pharmacokinetic data were submitted and none are required for an application of this type.

IV.3 Pharmacodynamics
The clinical pharmacodynamic properties of flucloxacillin are well-known. No new pharmacodynamic data were submitted and none are required for this type of application.

IV.4 Clinical Efficacy
The clinical efficacy of flucloxacillin is well-known. No new efficacy data are presented or are required for this type of application.

IV.5 Clinical Safety
The safety profile of flucloxacillin is well known. No new safety data have been submitted with this application and none are required. No new or unexpected safety concerns arose from this application.

IV.6 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 powder for solution for injection.

A summary of safety concerns is listed in the table below.
Table 1: Summary of safety concerns

| Important identified risks | Neutropenia (including agranulocytosis and thrombocytopenia. Haemolytic anaemia. |
|                           | Anaphylactic shock, angioneurotic oedema. |
|                           | Neurological disorders with convulsions. |
|                           | Pseudomembranous colitis. |
|                           | Hepatitis and cholestatic jaundice. Changes in liver function laboratory test results. |
|                           | Erythema multiforme, Stevens-Johnson syndrome, and toxic epidermal necrolysis |
|                           | Arthralgia and myalgia |
|                           | Interstitial nephritis |
|                           | Methotrexate toxicity with concomitant use |

| Important potential risks | Hyperbilirubinemia in newborns |
|                          | Use in patient on sodium restriction |

| Important missing information | Pregnancy |

Routine pharmacovigilance and risk minimisation measures are proposed. 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**

A 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 language used for the purpose of user testing the pack leaflet was English.

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.

**IV. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION**

**QUALITY**

The important quality characteristics of Flucloxacillin 2g injection are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

**NON-CLINICAL**

No new non-clinical data were submitted and none are required for an application of this type.

**EFFICACY**

No new clinical data were submitted and none were required for an application of this type. No bioequivalence studies were submitted or required for this application for a parenteral product.
SAFETY
The safety profile of flucloxacillin is well-known. No new or unexpected safety issues or concerns arose from this application.

PRODUCT LITERATURE
The SmPC, PIL and labelling are satisfactory and in line with current guidance.

BENEFIT/RISK ASSESSMENT
The quality of the product is acceptable, and no new non-clinical safety concerns have been identified. Extensive clinical experience with flucloxacillin in the proposed indications is considered to have demonstrated the therapeutic value of the compound. The proposed product is considered comparable to the marketed reference product.

The overall benefit/risk balance is, therefore, considered to be positive.

RECOMMENDATION
The grant of a Marketing Authorisation is recommended.
In accordance with Directive 2010/84/EU, the current version of the SmPC and package leaflet is available on the MHRA website. The current labelling is presented below:
Flucloxacillin 2g, powder for solution for injection or infusion

(Flucloxacillin sodium)

PL 31745/0032

STEPS TAKEN AFTER AUTHORISATION - SUMMARY

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