Public Assessment Report

Decentralised Procedure

Flucloxacillin 250 mg Capsules
Flucloxacillin 500 mg Capsules

(flucloxacillin)

Procedure No: UK/H/1101/001-002/DC

UK Licence No: PL 21880/0017-0018

Medreich plc
LAY SUMMARY

Flucloxacillin 250mg Capsules
Flucloxacillin 500mg Capsules
(flucloxacillin)

This is a summary of the Public Assessment Report (PAR) for Flucloxacillin 250 mg and 500 mg Capsules (PL 21880/0017-0018; UK/H/1101/001-002/DC). It explains how Flucloxacillin 250 mg and 500mg Capsules were assessed and their authorisation recommended, as well as their conditions of use. It is not intended to provide practical advice on how to use Flucloxacillin 250 mg and 500 mg Capsules.

For practical information about using Flucloxacillin 250 mg and 500 mg Capsules, patients should read the package leaflet or contact their doctor or pharmacist.

The products, Flucloxacillin 250 mg and 500 mg Capsules, may be referred to as ‘Flucloxacillin Capsules’ in this report.

What are Flucloxacillin Capsules and what are they used for?
Flucloxacillin Capsules are ‘generic’ medicines. This means that Flucloxacillin Capsules are similar to reference medicines already authorised in the UK called Floxapen Capsules 250 mg and 500 mg (Actavis Group PTC ehf), which were granted on 11 and 12 October 2007, respectively, through a Change of Ownership Procedure from the original licences, Floxapen Capsules 250 mg and 500 mg (PL 00038/5055R and 5056R, Beecham Group plc). Floxapen Capsules 250 mg and 500 mg (Beecham Group plc) were authorised on 17 July 1987.

Flucloxacillin Capsules belong to a group of antibiotics called ‘penicillins’ and are used to treat the following:
• chest infections
• throat or nose infections
• ear infections
• skin and soft tissue infections
• heart infections
• bone and joint infections
• meningitis
• digestive system infections
• blood infections
• kidney, bladder or urethra (the tube which carries urine from the bladder) infections.

Flucloxacillin Capsules may also be used to prevent infections during major surgery, particularly heart or orthopaedic surgery.

How do Flucloxacillin Capsules work?
Flucloxacillin Capsules contain the active substance flucloxacillin, which works by killing the bacteria that can cause infections.

How are Flucloxacillin Capsules used?
Flucloxacillin Capsules are available as hard capsules and are taken by mouth.
Flucloxacillin Capsules can only be obtained with a prescription. The capsules should be taken exactly as instructed by the prescribing doctor. The patient should check with the doctor or pharmacist if not sure.

The capsules should be taken when the stomach is empty, that is, an hour before food or two hours after food.

It is important that the capsules are taken at the right times. The capsules should be swallowed whole with water. The dose will depend on the patient and will be decided by the patient’s doctor.

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

**What benefits of Flucloxacillin Capsules have been shown in studies?**

As Flucloxacillin Capsules, are generic medicines, studies in patients have been limited to tests to determine that Flucloxacillin Capsules are bioequivalent to the reference medicines, Floxapen Capsules 250 mg and 500 mg (Actavis Group PTC ehf), respectively. Two medicines are bioequivalent when they produce the same levels of the active substance in the body.

**What are possible side effects of Flucloxacillin Capsules?**

Because Flucloxacillin Capsules are generic medicines and are bioequivalent to the reference medicines Floxapen Capsules 250 mg and 500 mg (Actavis Group PTC ehf), the possible side effects are taken as being the same as those of the reference medicines.

For the full list of restrictions, see the package leaflet available on the MHRA website.

**Why are Flucloxacillin Capsules approved?**

It was concluded that, in accordance with EU requirements, Flucloxacillin 250 mg and 500 mg Capsules, have been shown to have comparable quality and to be bioequivalent to Floxapen Capsules 250 mg and 500 mg (Actavis Group PTC ehf). Therefore, the MHRA decided that, as for Floxapen Capsules 250 mg and 500 mg, the benefits outweigh the risks and recommended that Flucloxacillin 250 mg and 500 mg Capsules be approved for use.

**What measures are being taken to ensure the safe and effective use of Flucloxacillin Capsules?**

Safety information has been included in the Summaries of Product Characteristics and the package leaflet for Flucloxacillin Capsules, including the appropriate precautions to be followed by healthcare professionals and patients.

**Other information about Flucloxacillin Capsules.**

The UK recommended the grant of Marketing Authorisations for Flucloxacillin Capsules on 22 February 2010. A Marketing Authorisation was granted in the UK on 24 March 2010.

The full PAR for Flucloxacillin Capsules follows this summary.

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

This summary was last updated in December 2014.
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## Module 1

### Information about the Initial Procedure

| Product Name | Flucloxacillin 250 mg Capsules  
|             | Flucloxacillin 500 mg Capsules |
| Type of Application | Generic, Article 10.1 |
| Active Substance | Flucloxacillin sodium |
| Form | Capsules |
| Strength | 250 mg and 500 mg |
| MA Holder | Medreich plc  
|           | 9 Royal Parade,  
|           | Kew Gardens,  
|           | London,  
|           | TW9 3QD |
| Reference Member State (RMS) | UK |
| Concerned Member State / s (CMS) | UK/H/1101/01/DC - none  
|                                  | UK/H/1101/02/DC - none |
| Procedure Number | UK/H/1101/01-02/DC |
| Timetable | End of Procedure: Day 120 – 22\textsuperscript{nd} February 2010 |
Module 2

Summary of Product Characteristics
In accordance with Directive 2010/84/EU, the Summaries of Product Characteristics (SmPCs) for products granted Marketing Authorisations at a national level are available on the MHRA website.
Module 3

Patient Information Leaflet

In accordance with Directive 2010/84/EU, the Patient Information Leaflets (PILs) for products granted Marketing Authorisations at a national level are available on the MHRA website.
Module 4
Labelling

Flucloxacillin 250mg capsules

Flucloxacillin 250mg Capsules
Flucloxacillin Sodium
KEEP ALL MEDICINES OUT OF REACH AND SIGHT OF CHILDREN.

Flucloxacillin 250mg Capsules
Flucloxacillin Sodium
Each capsule contains Flucloxacillin Sodium equivalent to 262.5 mg Flucloxacillin 250mg Oral capsule. See leaflet for further information.

Blistefoil
Flucloxacillin 500mg capsules

Each capsule contains Flucloxacillin Sodium 545 mg equivalent to Flucloxacillin 500mg. Oral capsule. See leaflet for further information.

Plastic blister pack of 28 capsules

Blisters marked with the following characters for easy identification:

[Characters shown on the image]
Module 5

Scientific discussion during the initial procedure

I  INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the MHRA granted Medreich plc Marketing Authorisations for the medicinal products Flucloxacillin 250 mg and 500 mg Capsules (PL 21880/0017-0018, UK/H/1101/01-02/DC) on 24th March 2010. The products are prescription-only medicines.

These are abridged applications for Flucloxacillin 250 mg and 500 mg Capsules, two strengths of flucloxacillin, submitted under Article 10.1 of 2001/83 EC, as amended. The applications refer to the UK reference products, Floxapen Capsules 250 mg and 500 mg (PL 30306/0015 and 0016 respectively), authorised to Actavis Group PTC ehf on 11th and 12th October 2007 respectively, through Change of Ownership from the original licences, PL 00038/5055R and 5056R respectively, authorised to Beecham Group plc on 17th July 1987. The reference products have been authorised in the UK for more than 10 years, so the period of data exclusivity has expired.

Flucloxacillin is indicated for the treatment of the following infections when caused by organisms that are known to be sensitive to Flucloxacillin (see section 5.1 of SmPC for details):

- Skin and soft tissue infections
- Pneumonia caused by Staphylococcus Aureus
- Empyema
- Lung abscess
- Sinusitis
- Otitis media and externa
- Osteomyelitis
- Endocarditis caused by Staphylococcus Aureus

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

Flucloxacillin is a narrow-spectrum antibiotic of the group of isoxazolyl penicillins. It is not inactivated by staphylococcal β-lactamases. It exerts a bacteriostatic effect by inactivation of transpeptidases (enzymes required to cross-link peptidoglycan polymer chains of the cell wall of Gram-positive bacteria). Flucloxacillin is insensitive to penicillinase as a result of steric hindrance caused by the isoxazolyl group on its acyl side chain.

Flucloxacillin is stable in acid media and can therefore be administered either by the oral or parenteral route. The oral bioavailability of flucloxacillin is approximately 79 %. Peak serum concentrations of 8.8 mg/L and 14.5 mg/L have been reported in fasting subjects one hour after oral doses of 250 mg and 500 mg flucloxacillin respectively. The administration of increasing doses of flucloxacillin results in a corresponding increase in the peak serum concentrations of the drug. The absorption of flucloxacillin is delayed by the presence of food. Mean peak serum concentrations in fed subjects have been found to be half those obtained in fasting subjects. It is therefore recommended that flucloxacillin be taken half an hour to one hour before meals.

95 % of circulating flucloxacillin is bound to serum proteins. The reported volume of distribution of flucloxacillin varies from 8 to 21 litres. It diffuses well into body tissues and fluids. In normal subjects approximately 10% of the flucloxacillin administered is metabolised to the inactive compound penicilloic acid. The elimination half-life of flucloxacillin is in the order of 53 minutes. 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 rate of excretion of flucloxacillin is reduced in patients with renal failure but dosage reductions or extensions of dosage intervals are not necessary except in cases of severe renal failure (creatinine clearance < 10 ml/minute).

No new preclinical or clinical efficacy studies were conducted for these applications, which is acceptable given that the applications are for generic versions of products that have been licensed for over 10 years.

The applications are supported by the single bioequivalence study presented by the applicant comparing the pharmacokinetic profile of the test product, Flucloxacillin 500mg Capsules, to that of the reference product, Floxapen Capsules 500 mg (GlaxoSmithKline, UK). The bioequivalence study was carried out in accordance with Good Clinical Practice (GCP). As the test products, Flucloxacillin 250mg and 500mg Capsules, were deemed to meet the criteria specified in the Note for Guidance on the investigation of bioavailability and bioequivalence (CPMP/EWP/QWP/1401/98), the results and conclusions of the bioequivalence study on the 500mg strength were extrapolated to the 250mg strength capsules.

The RMS has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for these product types at all sites responsible for the manufacture and assembly of these products. Evidence of compliance with GMP has been provided for the named manufacturing and assembly sites. For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

For manufacturing sites outside the community, the RMS has accepted copies of current GMP Certificates or satisfactory inspection summary reports, ‘close-out letters’ or ‘exchange of information’ issued by the inspection services of the competent authorities (or those countries with which the EEA has a Mutual Recognition Agreement for their own territories) as certification that acceptable standards of GMP are in place at those non-Community sites.

The RMS considers that the pharmacovigilance system as described by the MAH fulfils the requirements and provides adequate evidence that the MAH has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

The Marketing Authorisation Holder has provided adequate justification for not submitting an Environmental Risk Assessment (ERA). These were applications for generic products and there is no reason to conclude that marketing of these products will change the overall use pattern of the existing market. The Marketing Authorisation Holder has provided adequate justification for not submitting a Risk Management Plan (RMP). As the applications are for generic versions of already authorised reference products, for which safety concerns requiring additional risk minimisation have not been identified, a risk minimisation system is not considered necessary. The reference products have been in use for many years and the safety profile of the active is well established.
## II. ABOUT THE PRODUCT

<table>
<thead>
<tr>
<th>Description</th>
<th>Details</th>
</tr>
</thead>
</table>
| Name of the product in the Reference Member State        | Flucloxacillin 250 mg Capsules  
|                                                          | Flucloxacillin 500 mg Capsules                                         |
| Name(s) of the active substance(s) (INN)                 | Flucloxacillin sodium                                                   |
| Pharmacotherapeutic classification (ATC code)            | Beta-lactamase resistant penicillin (J01C F05)                         |
| Pharmaceutical form and strength(s)                     | Capsules  
|                                                          | 250 mg and 500 mg                                                      |
| Reference numbers for the Mutual Recognition Procedure   | UK/H/1101/01-02/DC                                                    |
| Reference Member State                                  | United Kingdom                                                         |
| Member States concerned                                 | UK/H/1101/01/DC - none  
|                                                          | UK/H/1101/02/DC - none                                                |
| Marketing Authorisation Number(s)                        | PL 21880/0017-0018                                                    |
| Name and address of the authorisation holder             | Medreich plc  
|                                                          | 9 Royal Parade,  
|                                                          | Kew Gardens,  
|                                                          | London,  
|                                                          | TW9 3QD                                                               |
III  SCIENTIFIC OVERVIEW AND DISCUSSION

III.1  QUALITY ASPECTS

ACTIVE SUBSTANCE

Flucloxacillin

Nomenclature:

INN:  Flucloxacillin sodium
Chemical name:  Sodium(2S,5R,6R)-6-[[3-(2-chloro-6-fluorophenyl)-5-methylisoxazol-4-yl]carbonyl] amino]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylate

Structure:

\[
\text{\begin{align*}
\text{Cl} & \quad \text{F} \\
\text{N} & \quad \text{O} \\
\text{CH}_3 & \quad \text{O} \\
\text{H} & \quad \text{H} \\
\text{H} & \quad \text{S} \\
\text{CO}_2\text{Na} & \quad \text{CH}_3 \\
& \quad \text{CH}_3 \\
\text{H}_2\text{O} & \\
\end{align*}}\]

Molecular formula:  \(\text{C}_{19}\text{H}_{16}\text{ClF}_3\text{NaO}_5\text{S} \cdot \text{H}_2\text{O}\)
Molecular weight:  493.9 g/mol
CAS No:  1847-24-1
Physical form:  White or almost white powder
Solubility:  A white or almost white, crystalline powder, hygroscopic, freely soluble in water and methanol, soluble in alcohol

The active substance, flucloxacillin sodium, is the subject of a European Pharmacopeia (Ph. Eur.) monograph.

All aspects of the manufacture and control of flucloxacillin sodium are supported by an EDQM Certificate of Suitability. This Certificate is accepted as confirmation of the suitability of flucloxacillin sodium for inclusion in these medicinal products.

The container closure system is described in the CEP as a polythene bag packed in to a sealed laminated bag. The CEP states a re-test period for the active substance of 4 years when stored in the stated container closure system.
MEDICINAL PRODUCT

Description and Composition

The medicinal products are presented as hard gelatin capsules with different sizes and markings (see individual SmPCs / patient information leaflet for full descriptions of capsules). Each capsule contains flucloxacillin sodium equivalent to 250mg or 500mg of flucloxacillin free base. The capsules are filled with white to almost-white granular powder.

Other ingredients consist of pharmaceutical excipients, namely colloidal anhydrous silica, magnesium stearate, gelatin, black iron oxide (E172), titanium dioxide (E171), iron oxide red (E172), and iron oxide yellow (E172). The white printing ink used for the markings on the capsules is comprised of titanium dioxide (E171), shellac, and Tween-80. Appropriate justification for the inclusion of each excipient has been provided.

Colloidal anhydrous silica and magnesium stearate comply with their current European / British Pharmacopoeia monographs. The remaining excipients comply with appropriate in-house specifications. Satisfactory Certificates of Analysis have been provided for all excipients.

Satisfactory TSE statements are provided by the suppliers of magnesium stearate, colloidal anhydrous silica and hard gelatin capsule shells. A Certificate of Suitability has been provided for gelatin stating that it meets the criteria described in the current version of the monograph ‘Products with risk of transmitting agents of animal spongiform encephalopathies’.

There were no novel excipients used and no overages.

Dissolution profiles

Comparative dissolution data were provided for both strengths of the proposed generic flucloxacillin capsules against appropriate reference capsule formulations. The dissolution profiles were found to be similar and were satisfactory.

Pharmaceutical development

Details of the pharmaceutical development of the medicinal products have been supplied and are satisfactory.

Manufacture

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

In-process controls are appropriate considering the nature of the products and the method of manufacture. Process validation studies were conducted on three commercial scale batches for both strengths and are satisfactory. All validation data were within specification.

Finished product specification

The finished product specifications include tests and criteria to apply for both release and end of shelf life testing and are satisfactory. They provide an assurance of the quality and consistency of the finished products. Acceptance limits have been justified with respect to conventional pharmaceutical requirements and, where appropriate, safety. Test methods have been described and have been adequately validated, as appropriate. Batch data have been provided for three commercial scale batches for both strengths and they comply with the release specifications. Certificates of Analysis have been provided for any reference standards used.

Container Closure System

The finished products are licensed for marketing in PVC (polyvinylchloride) / aluminium foil blister strips, which are placed with the Patient Information Leaflet (PIL) into cardboard outer cartons. The
capsules are packaged in pack sizes of 20 (500 mg strength only) and 28. The MA Holder has stated that not all pack sizes may be marketed for the 500 mg strength capsules.

Satisfactory specifications and Certificates of Analysis for all packaging components used have been provided. All primary product packaging complies with EU legislation, Directive 2002/72/EC (as amended), and is suitable for contact with foodstuffs.

**Stability**

Finished product stability studies have been conducted in accordance with current guidelines and results were within the proposed specification limits. Based on the results, a shelf-life of 24 months has been set, which is satisfactory. Storage conditions are ‘Do not store above 25°C. Store in the original pack’.

**Bioequivalence Study**

A bioequivalence study was presented comparing the test product, Flucloxacillin 500 mg Capsules, to the reference product, Floxapen Capsules 500 mg (GlaxoSmithKline, UK).

An evaluation of the bioequivalence study is found in the Clinical Aspects section.

**Quality Overall Summary**

A satisfactory quality overview is provided, and has been prepared by an appropriately qualified expert. The CV of the expert has been supplied.

**Product Information**

The approved SmPCs, leaflet, and labelling are satisfactory. Colour mock-ups of the labelling and PIL have been provided. The labelling fulfils the statutory requirements for Braille.

**Conclusion**

The drug products correspond to the current EU definition of a generic medicinal product because they comply with the criteria of having the same qualitative and quantitative composition in terms of the active substance and pharmaceutical form. On this basis, and considering the bioequivalence data provided, the applicant’s claim that Flucloxacillin 500mg Capsules is a generic medicinal product of Floxapen Capsules 500 mg (GlaxoSmithKline, UK) appears justified.

As the proposed products, Flucloxacillin 250 mg and 500 mg Capsules, meet the criteria specified in the Note for Guidance on the investigation of bioavailability and bioequivalence (CPMP/EWP/QWP/1401/98), the results and conclusions of the bioequivalence study on the 500 mg strength can be extrapolated to the 250 mg strength capsules.

All pharmaceutical issues have been resolved and the quality grounds for these applications are considered adequate. Marketing Authorisations were therefore granted.

**III.2 PRE-CLINICAL ASPECTS**

Specific non-clinical studies have not been performed, which is acceptable for these applications for generic versions of products that have been licensed for over 10 years. The non-clinical overview provides a satisfactory review of the pharmacodynamic, pharmacokinetic, and toxicological properties of flucloxacillin, a widely used and well-known active substance. The CV of the non-clinical expert has been supplied. For generic applications of this nature, the need for repetitive tests on animals and
humans is avoided. Reference is made to the reference medicinal products, Floxapen Capsules 250 mg and 500 mg.

III.3 CLINICAL ASPECTS

BACKGROUND
Flucloxacillin is a well-established antibiotic with bactericidal activity against Gram-positive bacteria. It has been in clinical use in the treatment of infections caused by susceptible Gram-positive organisms since 1970. It is orally active and is resistant to hydrolysis by penicillinase. It is therefore particularly useful in the treatment of infections caused by penicillinase-producing staphylococci.

INDICATIONS
Flucloxacillin capsules are indicated for the treatment of the following infections when caused by organisms that are known to be sensitive to Flucloxacillin (see section 5.1 of SmPC for further information):

- Skin and soft tissue infections
- Pneumonia caused by Staphylococcus Aureus
- Empyema
- Lung abscess
- Sinusitis
- Otitis media and externa
- Osteomyelitis
- Endocarditis caused by Staphylococcus Aureus

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

The indications are consistent with those for the reference products and are satisfactory.

POSOLOGY AND METHOD OF ADMINISTRATION
The posology is consistent with that for the reference products and is satisfactory.

TOXICOLOGY
No new data have been submitted and none are required for these types of application.

CLINICAL PHARMACOLOGY
The clinical pharmacology of flucloxacillin is well known. No novel pharmacodynamic data are supplied or required for these applications.

Drug interactions
Probenecid decreases the renal tubular secretion of flucloxacillin resulting in increased plasma concentrations of flucloxacillin. This is not thought to be associated with clinical adverse effects at normal doses.

It has been suggested that weak acids such as flucloxacillin can successfully compete with methotrexate for excretion via the kidney tubules. The resulting retention of methotrexate could lead to a potentiation of its effects and its toxicity. However, the results of a study of the use of oral flucloxacillin 500 mg four
times daily in 10 patients taking methotrexate showed no clinically significant effects on the pharmacokinetics of the methotrexate.

In volunteer studies, the co-administration of flucloxacillin and piperacillin led to a reduction in the rate of excretion of flucloxacillin and higher serum concentrations of the drug.

Like other antibiotics, flucloxacillin may affect the gut flora, leading to lower oestrogen reabsorption and reduced efficacy of combined oral contraceptives.

**Pharmacokinetics – bioequivalence study**

The application is supported by the bioequivalence study presented by the applicant comparing the pharmacokinetic profiles of Flucloxacillin 500 mg Capsules (test) and Floxapen Capsules 500 mg - GlaxoSmithKline, UK (reference). The study was of an appropriate design and was conducted to principles of Good Clinical Practice (GCP). Certificates of Analysis have been provided for both the test and reference product.

This was a randomised, two-treatment, two-way, two-period, single dose crossover bioavailability and bioequivalence study conducted in 26 healthy adult human subjects under fasting conditions. A single dose of the investigational products was administered orally to each subject in each period after a period of fasting of at least 10hrs. Fasting was continued for 4 hours post-dose after which a standard meal was provided. A satisfactory washout period of 7 days was maintained between the two dosing days in each group.

Blood samples were taken pre-dose (0.0) and at specified time points up to 24.0 hours after administration of test or reference product. The drug concentration levels in plasma were determined by a validated HPLC/UV method.

The primary pharmacokinetic parameters for this study were $C_{max}$, $AUC_{0-t}$, and $AUC_{0-\infty}$. Bioequivalence of the test product versus the reference product was concluded if the 90% CI fell within the acceptance range, 0.80-1.25 (80.00%-125.00%), for log-transformed $C_{max}$, $AUC_{0-t}$, and $AUC_{0-\infty}$.

**Results:**

One subject withdrew voluntarily from the study (in accordance with protocol). Twenty-five subjects completed the study and were used in the statistical analysis. There were no serious or significant adverse events reported in the study.

The summary of the results of the bioequivalence study are tabulated overleaf:

<table>
<thead>
<tr>
<th>Treatment</th>
<th>$C_{max}$ ng/ml</th>
<th>$AUC_{0-t}$ ng/ml/h</th>
<th>$AUC_{0-\infty}$ ng/ml/h</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test</td>
<td>16.7 ± 6.7</td>
<td>37.7 ± 13.3</td>
<td>39.5 ± 13.1</td>
</tr>
<tr>
<td>Reference</td>
<td>15.5 ± 6.2</td>
<td>36.3 ± 13.3</td>
<td>37.7 ± 13.4</td>
</tr>
<tr>
<td>Ratio (90% CI)</td>
<td>106% (93.9 – 120.3)</td>
<td>104% (95.7 – 113)</td>
<td>105% (96.6 – 113.8)</td>
</tr>
</tbody>
</table>

Pharmacokinetic results for flucloxacillin in a randomised, two-way, two-period, single dose crossover study. n=25 healthy subjects, dosed fasted; t=24 hours. Wash-out period: 7 days. Log-transformed values.
Conclusion on Bioequivalence

The results of the bioequivalence study show that the test and reference products are bioequivalent, under fasting conditions, as the confidence intervals for $C_{\text{max}}$, $\text{AUC}_{0-t}$, and $\text{AUC}_{0-\infty}$ fall within the acceptance criteria ranges of 80.00-125.00% in line with current CHMP guidelines.

Satisfactory justification is provided for a bio-waiver for Flucloxacillin 250 mg Capsules. As Flucloxacillin 250 mg and 500 mg Capsules meet the criteria specified in the Note for Guidance on the investigation of bioavailability and bioequivalence (CPMP/EWP/QWP/1401/98), the results and conclusions of the bioequivalence study on the 500 mg strength can be extrapolated to the 250 mg capsules.

Clinical efficacy

No new data have been submitted and none are required. The reference products are established and the applications depend upon the ability to demonstrate bioequivalence. Efficacy is reviewed in the clinical overview. The efficacy of flucloxacillin is well-established from its extensive use in clinical practice.

Clinical safety

No new data have been submitted and none are required for applications of this type. No new or unexpected safety concerns arose from these applications. Safety is reviewed in the clinical overview. The safety profile of flucloxacillin is well-known.

PRODUCT INFORMATION:

Summary of Product Characteristics (SmPC)

The approved SmPCs are consistent with those for the reference products, and are acceptable.

Patient Information Leaflet

The final PIL is in line with the approved SmPCs and is satisfactory.

Labelling

The labelling is satisfactory.

Expert report

A satisfactory clinical overview is provided, and has been prepared by an appropriately qualified expert. The CV of the clinical expert has been supplied.

CONCLUSIONS

All issues have been adequately addressed by the applicant. The bioequivalence study was of an appropriate design and demonstrates the bioequivalence of the test (Flucloxacillin 500 mg Capsules) and reference (Floxapen Capsules 500 mg, GlaxoSmithKline, UK) products within general acceptance limits. The results and conclusions of the bioequivalence study on the 500 mg strength were extrapolated to the 250 mg strength product. For generic applications of this nature, the need for repetitive tests on animals and humans is avoided. Reference is made to the reference medicinal product, Floxapen Capsules 250 mg and 500 mg.
Sufficient clinical information has been submitted to support these applications. When used as indicated, the products have a favourable benefit-to-risk ratio. The grant of Marketing Authorisations was therefore recommended on medical grounds.
IV OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

QUALITY
The important quality characteristics of Flucloxacillin 250 mg and 500 mg Capsules 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.

PRE-CLINICAL
No new pre-clinical data were submitted and none are required for applications of this type.

EFFICACY
Bioequivalence has been demonstrated between the applicant’s Flucloxacillin 500 mg Capsules, and the reference product, Floxapen Capsules 500 mg (GlaxoSmithKline, UK).

As the proposed products, Flucloxacillin 250 mg and 500 mg Capsules, meet the criteria specified in the Note for Guidance on the investigation of bioavailability and bioequivalence (CPMP/EWP/QWP/1401/98), the results and conclusions of the bioequivalence study on the 500 mg strength were extrapolated to the 250 mg strength capsules, and omission of further bioequivalence studies can be accepted.

No new or unexpected safety concerns arise from these applications.

PRODUCT LITERATURE
The approved SmPCs, PIL and labelling are satisfactory and consistent with those for the reference products.

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.

The approved labelling artwork complies with statutory requirements. In line with current legislation, the name of the product in Braille appears on the outer packaging and sufficient space has been included for a standard UK pharmacy dispensing label. The Marketing Authorisation Holder has stated that not all pack sizes may be marketed. They have committed to submitting mock-ups for all packaging for assessment before packs are commercially marketed.

RISK BENEFIT ASSESSMENT
The quality of the products is acceptable and no new pre-clinical or clinical safety concerns have been identified. The bioequivalence study and its conclusions support the claim that the applicant’s products and their respective reference products are interchangeable. Extensive clinical experience with flucloxacillin is considered to have demonstrated the therapeutic value of the active substance. The risk benefit is, therefore, considered to be positive.
Module 6

STEPS TAKEN AFTER INITIAL PROCEDURE - SUMMARY

There have been no variation applications submitted after approval of the initial procedure.

<table>
<thead>
<tr>
<th>Date submitted</th>
<th>Application type</th>
<th>Scope</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>16 October 2013</td>
<td>Type IB</td>
<td>To update sections 2, 4.1, 4.2, 4.3, 4.4, 4.5, 4.6, 4.8, 4.9, 5.1 and 5.2 of the Summaries of Product Characteristics (SmPCs) to bring in line with Flucloxacillin 250 mg and 500 mg Capsules (PL 06453/0015-0016); Athlone Laboratories Ltd). Consequentially, the leaflet has been updated.</td>
<td>Approved on 10 November 2014</td>
</tr>
</tbody>
</table>
ANNEX 1

Our Reference: PL 21880/0017, Application 47
PL 21880/0018, Application 48
Products: Flucloxacillin 250 mg and 500 mg Capsules
Marketing Authorisation Holder: Medreich plc.
Active Ingredient(s): Flucloxacillin
Type of Procedure: Mutual Recognition
Submission Type: Variation
Submission Category: Type IB
Submission Complexity: Standard
EU Procedure Number (if applicable): UK/H/1101/001-002/IB/13

Reason:
To update sections 2, 4.1, 4.2, 4.3, 4.4, 4.5, 4.6, 4.8, 4.9, 5.1 and 5.2 of the Summaries of Product Characteristics (SmPCs) to bring in line with Flucloxacillin 250 mg and 500 mg Capsules (PL 06453/0015-0016); Athlone Laboratories Ltd). Consequentially, the leaflet has been updated.

Supporting Evidence:
Revised SmPCs
Revised Patient Information Leaflet

Evaluation:

RECOMMENDATION
Based on the review of the information provided the RMS considers that the variations for Flucloxacillin 250 mg and 500 mg Capsules should be approved.

EXECUTIVE SUMMARY

Scope of the variation
The purpose of this type IB variation is to amend the Summary of Product Characteristics (SmPCs) and Package Leaflet, to bring them in line with those of Flucloxacillin 500mg Capsules (PL 06453/0016) and Flucloxacillin 250mg Capsules (PL 06453/0015).

SCIENTIFIC DISCUSSION

Quality aspects
N/A

Non clinical aspects
No new non-clinical data have been submitted in support of this variation.

Clinical aspects
No new clinical data have been submitted in support of this variation.

Product information
The amended SmPC sections and PIL have been provided and are acceptable.
In accordance with Directive 2010/84/EU the Summaries of Product Characteristics (SmPCs) and Patient Information Leaflets (PILs) for products granted Marketing Authorisations at a national level are available on the MHRA website.

OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT
The benefit-risk is not changed due to this variation and remains positive.

The amendments made to SmPC and PIL are in line with those already approved for Flucloxacillin 500mg Capsules (PL 06453/0016) and are, therefore, acceptable.

In accordance with Directive 2010/84/EU the Summaries of Product Characteristics (SmPCs) and Patient Information Leaflets (PILs) for products granted Marketing Authorisations at a national level are available on the MHRA website.

Decision:
Approved on 10 November 2014.