Public Assessment Report

UKPAR

Flucloxacillin 250 mg powder for solution for injection/infusion
Flucloxacillin 500 mg powder for solution for injection/infusion
Flucloxacillin 1 g powder for solution for injection/infusion
(flucloxacillin sodium)

UK Licence No: PL 41947/0031-33

ELC Group s.r.o.
This is a summary of the Public Assessment Report (PAR) for Flucloxacillin 250 mg powder for solution for injection/infusion (PL 41947/0031), Flucloxacillin 500 mg powder for solution for injection/infusion (PL 41947/0032) and Flucloxacillin 1 g powder for solution for injection/infusion (PL 41947/0033). It explains how the applications for Flucloxacillin 250mg, 500mg and 1g powder for solution for injection/infusion 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 250mg, 500mg and 1g powder for solution for injection/infusion.

For practical information about using Flucloxacillin 250mg, 500mg and 1g powder for solution for injection/infusion, patients should read the package leaflet or contact their doctor or pharmacist.

For ease of reading, these products will be referred to as Flucloxacillin for the remainder of this summary.

What are Flucloxacillin powders for solution and what are they used for?
Flucloxacillin powders for solution are ‘generic medicines’. This means that Flucloxacillin powders are similar to ‘reference medicines’ already authorised in the European Union (EU) called Floxapen Vials for Injection 250 mg, 500 mg and 1 g.

Flucloxacillin powders for solution are used to treat a wide range of infections caused by bacteria which may include those affecting the chest (pneumonia, empyema and lung abscess), tonsils (tonsillitis, quinsy), pharynx (pharyngitis), sinuses (sinusitis), ears (otitis media and otitis externa), skin and soft tissue (boils, abscesses, carbuncles, impetigo, cellulitis, furunculosis, ulcers, eczema and acne), wounds, burns, heart (endocarditis), bones and joints (osteomyelitis), membranes of the brain (meningitis), gut (enteritis), blood (septicaemia) and the kidney, bladder or the urethra (the tube which carries urine from the bladder). Flucloxacillin can also be used to prevent infections following skin grafts or during major surgical procedures, particularly in chest or orthopaedic surgery.

How do Flucloxacillin powders for solution work?
These medicines contain the active ingredient flucloxacillin sodium. Flucloxacillin is an antibiotic for treating infections. It belongs to a group of antibiotics called “penicillins”. Flucloxacillin works by killing the bacteria that cause infection.

How are Flucloxacillin powders for solution used?
These medicines can only be obtained with a prescription.

The medicine will usually be given by injection into the muscle (intramuscular) or injection into a vein (intravenous). It can also be given by injection into a joint (intra-articular) or injection into the lining of the lung (intrapleural), or by breathing in the medicine from a mask (nebuliser).

Flucloxacillin powders for solution should not be administered into the eye.

A doctor will decide which strength is needed depending upon the severity and type of infection the patient has, as well as the age, body weight and kidney function.

The usual recommended dose for treating infection in adults and children over 12 years is a total daily
dosage of 1g to 6g administered in 3 to 6 divided doses, by i.v. or i.m injection. No intramuscular single bolus injection should exceed 2g. The maximum dose of 12g per day should not be exceeded.

In cases of severe infections up to 8g per day can be administered in three to four infusions (over 20 to 30 min).

In premature infants, neonates, sucklings and infants other pharmaceutical forms/strengths may be more appropriate for administration.

For infections of the bones and joints (osteomyelitis), or the heart (endocarditis) – up to 8g daily can be given, in divided doses six to eight hourly.

Flucloxacillin may be administered by other routes, together with systemic therapy (proportionally lower doses should be given in children).

- intrapleural (into the lining of the lung) - 250 mg once daily
- by nebulizer - 125 mg to 250 mg four times a day
- intra-articular (into a joint) - 250 mg to 500 mg once daily

In children and adolescents under 12 years of age the recommended dose is 25 to 50mg/kg/24 hours administered in three to four equally divided doses by i.m. or i.v. injection.

In cases of severe infections up to 100mg/kg/24 hours can be administered in three to four divided doses.

No single bolus injection or infusion should exceed 33mg/kg.

In children and adolescents aged 10 to 14 years the recommended daily dose is 1.5g to 2g and in children aged 6 to 10 years it is 0.75g to 1.5g, divided into three to four equal doses.

What benefits of Flucloxacillin powders for solution have been shown in studies?
The company provided data from the published literature on flucloxacillin sodium. No additional studies were needed as Flucloxacillin powders for solution are generic medicines that are given as an injection and contain the same active substance, in the same concentration, as the reference medicines, Floxapen Vials for Injection 250 mg, 500 mg and 1 g.

What are the possible side effects of Flucloxacillin powders for solution?
As Flucloxacillin powders for solution are generic medicines, their possible side effects are taken as being the same as those of the reference medicines, Floxapen Vials for Injection 250 mg, 500 mg and 1 g.

For the full list of all side effects reported with Flucloxacillin powders for solution, see section 4 of the package leaflet.

For the full list of restrictions, see the package leaflet.

Why were Flucloxacillin powders for solution approved?
It was concluded that, in accordance with EU requirements, Flucloxacillin powders for solution have been shown to have comparable quality and to be comparable to Floxapen Vials for Injection 250 mg, 500 mg and 1 g. Therefore, the MHRA decided that, as for Floxapen Vials for Injection 250 mg, 500 mg and 1 g, the benefits outweigh the identified risks and recommended that Flucloxacillin powders for solution can be approved for use.
What measures are being taken to ensure the safe and effective use of Flucloxacillin powders for solution?
A risk management plan (RMP) has been developed to ensure that Flucloxacillin powders for solution are used as safely as possible. Based on this plan, safety information has been included in the Summary of Product Characteristics (SmPC) and the package leaflet for Flucloxacillin powders for solution 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 powders for solution
Marketing Authorisations were granted in the UK on 25 January 2018.

The full PAR for Flucloxacillin powders for solution follows this summary. For more information about treatment with Flucloxacillin powders for solution read the package leaflet, or contact your doctor or pharmacist.

This summary was last updated in February 2018.
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 ELC Group s.r.o. Marketing Authorisations for the medicinal products Flucloxacillin 250mg, 500mg and 1g powder for solution for injection/infusion (PL 41947/0031-33) on 25 January 2018.

These products are prescription-only medicines (legal classification POM).

These were applications made according to Article 10(1) of Directive 2001/83/EC, as amended. The reference products are Floxapen Vials for Injection 250 mg, 500 mg and 1 g (PL 30306/0019-21), which were granted Marketing Authorisations to Actavis Group PTC ehf, in the UK, on 12 October 2007. This followed a Change of Ownership from PL 00038/5051R-53R (Beecham Group Plc), which were granted Marketing Authorisations on 15 May 1987.

Flucloxacillin 250mg, 500mg and 1g powder for solution for injection/infusion are indicated for the treatment of infections due to sensitive Gram-positive organisms, including β-lactamase-producing staphylococci and streptococci. Typical indications include:

- Skin and soft tissue infections: boils, cellulitis, infected burns, abscesses, infected skin conditions, protection for skin, grafts, impetigo, carbuncles (e.g. ulcer, eczema, and acne), infected wounds, furunculosis.
- Respiratory tract infections: pneumonia, lung abscess, empyema, sinusitis, pharyngitis, otitis media and externa, tonsillitis, quinsy.
- Other infections caused by flucloxacillin-sensitive organisms: osteomyelitis, urinary tract infection, enteritis, meningitis, endocarditis, septicaemia.

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

Parenteral usage is indicated where oral dosage is inappropriate.

These products contain the active substance flucloxacillin sodium, which is a semisynthetic penicillin (beta-lactam antibiotic; isoxazolylpenicillin) with a narrow-spectrum of activity, primarily against Gram-positive organisms, including β-lactamase-producing strains. It works by inhibiting one or more enzymes (often referred to as penicillin-binding proteins, PBPs) in the biosynthetic pathway of bacterial peptidoglycan, which is an integral structural component of the bacterial cell wall. Inhibition of peptidoglycan synthesis leads to weakening of the cell wall, which is usually followed by cell lysis and death.

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

Flucloxacillin 250mg, 500mg and 1g powder for solution for injection/infusion are aqueous solutions at the time of administration and in line with the Notes for Guidance on the Investigation of Bioavailability and Bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **), bioequivalence studies were not required.

The MHRA has been assured that acceptable standards of Good Manufacturing Practice are in place for this product type at all sites responsible for the manufacture, assembly and batch release of the products.
A summary of the pharmacovigilance system and a detailed Risk Management Plan (RMP) have been provided with these applications and these are satisfactory.

II QUALITY ASPECTS
II.1 Introduction
Each vial of flucloxacillin 250mg powder for solution for injection/infusion contains 250mg of flucloxacillin as flucloxacillin sodium.

Each vial of flucloxacillin 500mg powder for solution for injection/infusion contains 500mg of flucloxacillin as flucloxacillin sodium.

Each vial of flucloxacillin 1g powder for solution for injection/infusion contains 1g of flucloxacillin as flucloxacillin sodium.

These medicinal products contain no pharmaceutical excipients.

The finished products are packaged in Type II clear glass vials, closed with bromobutyl rubber stoppers and flip-off caps, in a pack size of 10 vials.

Satisfactory specifications and Certificates of Analysis have been provided for all packaging components. All primary packaging complies with the current European regulations concerning materials in contact with food.

II.2 Drug substance
rINN: Flucloxacillin
Ph. Eur name: 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

Structure:

\[ \text{Molecular formula: } \text{C}_{19}\text{H}_{16}\text{ClF}_{2}\text{N}_{3}\text{NaO}_{5}\text{S}, \text{H}_{2}\text{O} \]
\[ \text{Molecular weight: } 493.9 \]
\[ \text{Appearance: } \text{White or almost white, hygroscopic, crystalline powder} \]
\[ \text{Solubility: } \text{Freely soluble in water and in methanol, soluble in ethanol (96%)} \]

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 (CEP).

II.3 Medicinal Product
Pharmaceutical Development
The objective of the development programme was to formulate stable products that could be considered generic medicinal products of the currently licensed products, Floxapen Vials for Injection 250 mg, 500 mg and 1 g (Actavis Group PTC ehf).
A satisfactory account of the pharmaceutical development has been provided.

Comparative impurity profiles have been provided for the applicant’s products versus reference products.

These products contain no excipients and do not contain or consist of genetically modified organisms (GMO).

**Manufacturing Process**
Satisfactory batch formulae have been provided for the manufacture of the products, along with an appropriate description of the manufacturing process. Suitable in-process controls are in place to ensure the quality of the finished product. Process validation has been carried out on two production scale batches for the 250 mg and 1000 mg strengths and three production scale batches of the 500 mg strength of finished product. The results are satisfactory.

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

**Stability of the product**
Stability studies were performed, in accordance with current guidelines, on batches of finished product in the packaging proposed for marketing.

The results from these studies support a shelf-life of 2 years for the unopened vial, with no special storage conditions.

For the reconstituted solution, chemical and physical in-use stability has been demonstrated for 2 hours at 20-25°C and 24 hours at 2 to 8°C.

From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 to 8°C, unless reconstitution has taken place in controlled and validated aseptic conditions.

Reconstitution of the injection and preparation of the infusion solutions must be carried out under the appropriate aseptic conditions if these extended storage periods are required.

**II.4 Discussion on chemical, pharmaceutical and biological aspects**
It is recommended that Marketing Authorisations are granted for Flucloxacillin 250mg, 500mg and 1g powder for solution for injection/infusion.
III NON-CLINICAL ASPECTS

III.1 Introduction
The pharmacodynamic, pharmacokinetic and toxicological properties of flucloxacillin sodium are well known. No new non-clinical data have been submitted for this application and none are required.

The applicant has provided an overview based on published literature. The non-clinical overview has been written by an appropriately qualified person and is satisfactory, providing an appropriate review of the product’s pharmacology and toxicology.

III.2 Pharmacology
No new pharmacology data are required for these applications and none have been submitted.

III.3 Pharmacokinetics
No new pharmacokinetic data are required for these applications and none have been submitted.

III.4 Toxicology
No new toxicology data are required for these applications and none have been submitted.

III.5 Ecotoxicity/Environmental risk Assessment (ERA)
As these products are intended for generic substitution of products that are already marketed, no increase in environmental exposure to flucloxacillin sodium is anticipated. Thus the absence of an ERA is accepted.

III.6 Discussion of the non-clinical aspects
It is recommended that Marketing Authorisations are granted for Flucloxacillin 250mg, 500mg and 1g powder for solution for injection/infusion.

IV. CLINICAL ASPECTS

IV.1 Introduction
No new efficacy or safety studies have been performed and none are required for this type of application. A comprehensive review of the published literature has been provided by the applicant, citing the well-established clinical pharmacology, efficacy and safety of flucloxacillin sodium. The applicant’s clinical overview has been written by an appropriately qualified person and is considered acceptable.

IV.2 Pharmacokinetics
A bioequivalence study was not submitted as the products meet the criteria regarding parenteral solutions specified in the Notes for Guidance on the Investigation of Bioavailability and Bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/Corr **). The test products are aqueous solutions at the time of administration and contain an active substance in the same concentration as the reference product.

IV.3 Pharmacodynamics
No new pharmacodynamic data were submitted and none are required for applications of this type.

IV.4 Clinical efficacy
No new data on efficacy have been submitted and none are required for applications of this type.

IV.5 Clinical Safety
No new data on safety have been submitted and none are required for applications of this type.

IV.6 Risk Management Plan (RMP) and Pharmacovigilance System
The Pharmacovigilance System, as described by the applicant, fulfils the requirements and provides adequate evidence that the applicant 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 MAH has submitted a RMP, 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 250mg, 500mg and 1g powder for solution for injection/infusion.

A summary of safety concerns and planned risk minimisation activities, as approved in the RMP, are listed below:

<table>
<thead>
<tr>
<th>Safety Concern</th>
<th>Proposed Risk Minimisation Measures</th>
<th>Additional Risk Minimisation Measures</th>
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</thead>
<tbody>
<tr>
<td><strong>Important Identified Risks</strong></td>
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<tr>
<td>Hypersensitivity to β-lactam antibiotics</td>
<td>Guidance in SmPC Section:</td>
<td>Not applicable</td>
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<tr>
<td>(e.g. penicillins, cephalosporins) and</td>
<td>4.3 Contraindications</td>
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<tr>
<td>anaphylaxis</td>
<td>4.4 Special warnings and precautions</td>
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<td>for use</td>
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<td>4.6 Fertility, pregnancy and</td>
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<td>lactation</td>
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<td></td>
<td>4.8 Undesirable effects</td>
<td></td>
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<tr>
<td>Hepatitis and cholestatic jaundice</td>
<td>Guidance in SmPC Section:</td>
<td>Not applicable</td>
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<td></td>
<td>4.2 Posology and method of</td>
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<td>administration</td>
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<td>4.3 Contraindications</td>
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<td>4.8 Undesirable effects</td>
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<td></td>
<td>5.1 Pharmacodynamic properties</td>
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<tr>
<td></td>
<td>5.2 Pharmacokinetic properties</td>
<td></td>
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<tr>
<td>Hyperbilirubinaemia in newborns</td>
<td>Guidance in SmPC Section:</td>
<td>Not applicable</td>
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<td></td>
<td>4.4 Special warnings and precautions</td>
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<td>for use</td>
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<td></td>
<td>5.2 Pharmacokinetic properties</td>
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<tr>
<td>High serum level of flucloxacillin in</td>
<td>Guidance in SmPC Section:</td>
<td>Not applicable</td>
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<tr>
<td>newborn</td>
<td>4.4 Special warnings and precautions</td>
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<td></td>
<td>5.2 Pharmacokinetic properties</td>
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<tr>
<td>Safety Concern</td>
<td>Proposed Risk Minimisation Measures</td>
<td>Additional Risk Minimisation Measures</td>
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<tr>
<td>Overgrowth of non-susceptible organisms on prolonged use</td>
<td>Guidance in SmPC Section: 4.4 Special warnings and precautions for use</td>
<td>Not applicable</td>
</tr>
<tr>
<td>Nephrotoxicity and/or neurotoxicity in patients with impaired renal function</td>
<td>Guidance in SmPC Section: 4.2 Posology and method of administration 4.4 Special warnings and precautions for use 4.5 Interactions with other medicinal products and other forms of interaction 4.8 Undesirable effects 5.2 Pharmacokinetic properties</td>
<td>Not applicable</td>
</tr>
<tr>
<td>Neutropenia (including agranulocytosis)</td>
<td>Guidance in SmPC Section: 4.8 Undesirable effects</td>
<td>Not applicable</td>
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<tr>
<td>Severe skin reaction (Erythema multiforme, Stevens-Johnson Syndrome and Toxic Epidermal)</td>
<td>Guidance in SmPC Section: 4.3 Contra indications 4.4 Special warnings and precautions for use 4.6 Fertility, pregnancy and lactation 4.8 Undesirable effects</td>
<td>Not applicable</td>
</tr>
<tr>
<td>Incompatibilities</td>
<td>Guidance in SmPC Section: 6.2 Incompatibilities</td>
<td>Not applicable</td>
</tr>
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</table>

**Important Potential Risks**

<table>
<thead>
<tr>
<th>Use in patients on sodium restriction</th>
<th>Guidance in SmPC Section: 2. Qualitative and Quantitative composition 4.4 Special warnings and precautions for use</th>
<th>Not applicable</th>
</tr>
</thead>
<tbody>
<tr>
<td>Interaction with other medicinal products (probenecid and bacteriostatic drugs)</td>
<td>Guidance in SmPC Section: 4.5 Interaction with other medicinal products and other forms of interaction</td>
<td>Not applicable</td>
</tr>
<tr>
<td>Interaction when administered concomitantly with paracetamol</td>
<td>Guidance in SmPC Section:</td>
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<tr>
<td>Safety Concern</td>
<td>Proposed Risk Minimisation Measures</td>
<td>Additional Risk Minimisation Measures</td>
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<td></td>
<td>4.4 Special warnings and precautions for use</td>
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<td></td>
<td>4.5 Interaction with other medicinal products and other forms of interaction</td>
<td></td>
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<td></td>
<td>4.8 Undesirable effects</td>
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</tbody>
</table>

**Missing information**

| Use in pregnancy and lactation | Guidance in SmPC Section 4.6 Fertility, pregnancy and lactation | Not applicable                     |

**IV.7 Discussion of the clinical aspects**

It is recommended that Marketing Authorisations are granted for Flucloxacillin 250mg, 500mg and 1g powder for solution for injection/infusion.

**V. USER CONSULTATION**

The package leaflet has been evaluated in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC, as amended. The results indicate that the package leaflet is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that patients/users are able to act upon the information that it contains.

**VI OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT**

The quality of the product is acceptable, and no new non-clinical or clinical safety concerns have been identified. The data supplied support the claim that the applicant’s products and the reference products are interchangeable. Extensive clinical experience with flucloxacillin sodium is considered to have demonstrated the therapeutic value of the compound. The benefit-risk assessment is therefore considered to be positive.

**Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labels**

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

The approved labelling for Flucloxacillin 250mg, 500mg and 1g powder for solution for injection/infusion is presented below:
Flucloxacillin 250mg, 500mg and 1g powder for solution for injection/infusion

For single use only.
For IV injection, I.V. infusion. Read the package leaflet before use. Keep out of the sight and reach of children.
This medicinal product does not require any special storage conditions. Please refer to the package leaflet for information about in-use shelf life.

10 x 20 ml

CONTAINS PENCILLIN

Flucloxacillin 1 g
powder for solution for injection/infusion

Flucloxacillin 1 g
powder for solution for injection/infusion

Flucloxacillin 1 g
powder for solution for injection/infusion
Annex 1  Table of content of the PAR update for MRP and DCP

Steps taken after the initial procedure with an influence on the Public Assessment Report

<table>
<thead>
<tr>
<th>Scope</th>
<th>Procedure number</th>
<th>Product Information affected</th>
<th>Date of start of the procedure</th>
<th>Date of end of procedure</th>
<th>Approval/ non approval</th>
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