

FLUCLOXACILLIN 250MG CAPSULES
PL 17907/0052

FLUCLOXACILLIN 500MG CAPSULES
PL 17907/0053

UKPAR

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FLUCLOXACILLIN 250MG CAPSULES
PL 17907/0052

FLUCLOXACILLIN 500MG CAPSULES
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LAY SUMMARY

The MHRA granted Bristol Laboratories Limited Marketing Authorisations (licences) for the medicinal products Flucloxacillin 250mg Capsules and Flucloxacillin 500mg Capsules (PL 17907/0052-3) on 28th February 2008. These medicines are used to treat a wide range of infections caused by bacteria.

Flucloxacillin is an antibiotic for treating infections. It belongs to a group of antibiotics called “penicillins”. Flucloxacillin works by killing the bacteria that can cause infections.

No new or unexpected safety concerns arose from these applications and it was therefore judged that the benefits of taking Flucloxacillin Capsules outweigh the risks, hence Marketing Authorisations have been granted.

**FLUCLOXACILLIN 250MG CAPSULES
PL 17907/0052**

**FLUCLOXACILLIN 500MG CAPSULES
PL 17907/0053**

SCIENTIFIC DISCUSSION

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INTRODUCTION

Based on the review of the data on quality, safety and efficacy the MHRA granted marketing authorisations for the medicinal products Flucloxacillin 250mg Capsules and Flucloxacillin 500mg Capsules to Bristol Laboratories Limited (PL 17907/0052-3) on 28th February 2008. These products are prescription-only medicines.

These applications were submitted as abridged applications according to Article 10.1 of Directive 2001/83/EC, as amended, claiming to be generic medicinal products of the reference products Floxapen 250mg and 500mg capsules which are marketed in the UK by Beecham Group (trading as GlaxoSmithKline UK) under PL0038/5055R-56R.

Flucloxacillin Capsules are indicated for the treatment of infections due to flucloxacillin sensitive grampositive organisms, including β -lactamase-producing staphylococci and streptococci. It 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. Flucloxacillin, by its action on the synthesis of the bacterial wall, exerts a bactericidal effect on streptococci, except those of group D (*Streptococcus faecalis*), staphylococci, including the β -lactamase-producing strains, Clostridia and Neisseria. It is not active against methicillin-resistant staphylococci.

PHARMACEUTICAL ASSESSMENT

DRUG SUBSTANCE

INN: Flucloxacillin sodium

Molecular Weight: 439.9

White or almost white crystalline powder, hygroscopic; freely soluble in water and methanol, soluble in alcohol.

A valid Certificate of Suitability has been provided.

An appropriate specification based on the European Pharmacopoeia has been provided.

Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications.

Flucloxacillin sodium is stored in appropriate packaging. The specifications and analytical test reports provided are satisfactory.

Batch analysis data are provided and comply with the proposed specification.

Satisfactory certificates of analysis have been provided for working standards used by the active substance manufacturer and finished product manufacturer during validation studies.

Appropriate stability data have been generated.

DRUG PRODUCT

Other Ingredients

Other ingredients consist of pharmaceutical excipients namely, magnesium stearate, titanium dioxide E171, Indigo carmine E132, Methylparaben, Propyl paraben and gelatine.

All excipients comply with European Pharmacopoeia monographs with the exception of titanium dioxide E171, Methylparaben, Propyl paraben which comply with USP.

Satisfactory certificates of analysis have been provided for all ingredients showing compliance with their respective monograph.

A statement has been provided by the supplier, to confirm that magnesium stearate is of vegetable origin.

Gelatin is derived from an animal source. Ph. Eur Certificates of Suitability for TSE have been provided by the suppliers of this material

Pharmaceutical development

The objective of the pharmaceutical development programme was to produce products with flucloxacillin sodium that can be considered as generic equivalents to the originator products Floxapen 250 and 500mg Capsules.

The rationale for the type of pharmaceutical form developed and formulation variables evaluated during development have been stated and are satisfactory.

Manufacturing Process

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

In-process controls are satisfactory based on process validation data and controls on the finished product. Process validation has been carried out on batches of each strength. The results are satisfactory.

Finished Product Specification

The finished product specifications proposed for all strengths are acceptable. Test methods have been described and have been adequately validated, as appropriate. Batch data have been provided and comply with the release specification. Certificates of analysis have been provided for any working standards used.

Container-Closure System

The product is packed in either PVC/PVdC blister packs sealed with aluminium foil. Specifications and Certificates of Analysis for all packaging types used have been provided. These are satisfactory. All primary product packaging complies with EU legislation regarding contact with food.

Stability of the product

Stability studies were performed on pilot-scale batches of all strengths of finished product and all packaging types, in accordance with current guidelines. All results from stability studies on pilot batches were within specified limits. These data support a shelf-life of 18 months, with storage condition 'Store in the original package' and 'Do not store above 25°C'

Bioequivalence/bioavailability

Satisfactory Certificates of Analysis have been provided for the test and reference batches used in the bioequivalence study.

SPC, PIL, Labels

The SPC, PIL and Labels are pharmaceutically acceptable.

The PIL is in compliance with current guidelines. The marketing authorisation holder has provided a commitment to update the marketing authorisation with a package leaflet in compliance with Article 59 of Council Directive 2001/83/EC and that the leaflet shall reflect the results of consultation with target patient groups, no later than 1st July 2008.

CONCLUSION

It is recommended that Marketing Authorisations are granted for these applications.

The proposed products are considered to be a generic medicinal product to the reference product with respect to qualitative and quantitative content of the active substance, pharmaceutical form and bioequivalence.

PRECLINICAL ASSESSMENT

No new preclinical data have been supplied with these applications and none are required for an application of this type.

CLINICAL ASSESSMENT

1. INTRODUCTION AND BACKGROUND

These are two abridged, national, standard, non-committee applications in the old format, based on essential similarity to Floxapen capsules (250 and 500mg) from Beecham Group Plc, (PL 00038/5055R and 56R). The brand leader was first authorised in the UK in Jul 1987 and renewed subsequently in Nov 92. The current MA holder for the brand leader are SmithKline and Beecham Pharmaceuticals T/A GlaxoSmithKline. In accordance with the EC article relating to essential similarity, the applicant has provided bioequivalence studies in support of the application.

2. INDICATIONS

The indications proposed are consistent with those for the originator products and are, therefore, satisfactory.

3. DOSE & DOSE SCHEDULE

Oral doses should be administered half to one hour before meals.

Depends on the age, weight and renal function of the patient, as well as the severity of the infection.

Usual adult dosage (including elderly patients)

250 mg four times a day.

The above systemic dosage may be doubled where necessary.

Osteomyelitis, endocarditis - up to 8g daily, in divided doses six to eight hourly.

Surgical prophylaxis – 1 to 2 g IV at induction of anaesthesia followed by 500 mg six hourly IV, IM or orally for up to 72 hours.

Usual children's dosage

2-10 years: half adult dose

Under 2 years: quarter adult dose.

Where oral doses of less than 250 mg are required flucloxacillin syrup should be administered.

Abnormal renal function

In common with other penicillins, flucloxacillin usage in patients with renal impairment does not usually require dosage reduction. However, in the presence of severe renal failure (creatinine clearance < 10 ml/min) a reduction in dose or an extension of dose interval should be considered. Flucloxacillin is not significantly removed by dialysis and hence no supplementary dosages need to be administered either during or at the end of the dialysis period.

The dose and dose schedule proposed are consistent with those for the originator products and are, therefore, satisfactory.

4. CLINICAL PHARMACOLOGY

The pharmacology of Flucloxacillin has been well established. This is well supported by the clinical knowledge and the relevant sections of the SmPC. The applicant has not submitted any new data except for the bioequivalence studies that are discussed below in this report. The expert report is well written with adequate support for the indications claimed.

Bioequivalence:

The applicant has submitted a single bioequivalence study (500mg Strength) in support of this application based on essential similarity. This was a randomised, open label, -two treatment, two-period, and crossover single dose study, in healthy, subjects. A total of 26 were screened and enrolled in the study, 24 completed and analysed. The two standby subjects were not analysed as per protocol. Samples were collected pre-dose and timed intervals post dose and the washout period was 3 days.

Results

Parameter	Test: Flucloxacillin 500mg	Reference: Floxapen 500 caps	90% CI and point estimate
t _{max} (h)	0.823 ± 1.726	0.875 ± 0.2331	
t _{1/2} (h)	1.462 ± 0.2317	1.427 ± 0.2388	
C _{max}	40.78 ± 9.98	37.18 ± 10.87	110.72 _(98.92 to 123.92)
AUC _{0-t}	81.30 ± 19.53	76.32 ± 20.65	106.90 _(99.63 to 114.7)
AUC _∞	83.42 ± 20.58	78.35 ± 21.29	106.73 _(99.63 to 11.34)

Discussion: The study was carried out with the higher dose of 500mg where it is likely to show any differences between the products (as per BA and BE NfG; CPMP/EWP/QWP/1401/98). The sample size appears adequate and the design is appropriate for a medicinal product with linear kinetic profile. The washout period is only 3days. However, considering the elimination half-life of flucloxacillin of 53 minutes and that 65% of the administered dose is recovered unchanged in the urine within 8 hours, this washout period appears adequate. From the quality assessment it appears that the assay methodology is appropriate and adequate, as is the LoQ of the assay. The AUC_{0-t} is > 80% of the AUC_∞ (99% for test and 97% reference product means). The 90% CI for all relevant parameters are within the accepted limits for bioequivalence as per CPMP guidelines.

The statistical methodologies adopted appear to be appropriate and satisfactory.

Assessor's Comments: The applicant provides only a single biostudy. It is considered that two products are bioequivalent at 500 mg dose. The expert in his report justifies the single bioequivalence study by applying the biowaiver criteria. The capsules (both strengths) are manufactured by the same manufacturer, the relative composition of the capsules remains the same (excipient to active ratio) and similar dissolution profiles. Therefore, 250mg strength capsules could be considered bioequivalent using the biowaiver criteria.

5. EFFICACY

The applicant has not submitted any new data in support of these applications based on essential similarity and none are required. The expert report provides sufficient analysis of the review and available published data to support the indications claimed. This is therefore acceptable.

6. SAFETY

The applicant has not submitted any new safety data and none are required. The Bio study did not raise any new concerns and there have been no regulatory actions for Flucloxacillin since first approval. This is therefore acceptable.

7. EXPERT REPORTS

A clinical expert report is provided, written by an appropriately qualified pharmaceutical consultant. It includes a suitable review of the bioequivalence study.

8. SUMMARY OF PRODUCT CHARACTERISTICS (SPC)

The SPCs are consistent with the approved SPCs for the originator products and are satisfactory.

9. PATIENT INFORMATION LEAFLET (PIL)

The PIL has been provided and is consistent the SPC.

10. LABELLING

Labelling has been provided and these are satisfactory.

11. APPLICATION FORM (MAA)

The MAA form is satisfactory.

12. DISCUSSION

Bioequivalence has been satisfactorily demonstrated for the 500mg product in accordance with CPMP criteria. As these products meet all the criteria as 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 can be extrapolated to the other strength tablets.

The SPC, PIL and Labelling are consistent with those approved in the UK for the originator product Floxapen 250mg and 500mg Capsules and are satisfactory.

13. MEDICAL CONCLUSION

Marketing authorisations may be granted for these products.

OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT

QUALITY

The important quality characteristics of Flucloxacillin 250 and 500mg 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.

PRECLINICAL

No new preclinical data were submitted and none are required for applications of this type.

EFFICACY

Bioequivalence has been demonstrated between the applicant's Flucloxacillin 500mg and 500mg Floxapen capsules. As these products meet all the criteria as 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 can be extrapolated to the other strength tablets.

No new or unexpected safety concerns arise from these applications.

The SPC, PIL and labelling are satisfactory and consistent with that for Floxapen Capsules.

RISK BENEFIT ASSESSMENT

The quality of the product is acceptable and no new preclinical or clinical safety concerns have been identified. The bioequivalence study supports the claim that the applicant's products and the innovator products are interchangeable. Extensive clinical experience with Flucloxacillin is considered to have demonstrated the therapeutic value of the compound. The risk benefit is, therefore, considered to be positive.

FLUCLOXACILLIN 250MG CAPSULES
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FLUCLOXACILLIN 500MG CAPSULES
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STEPS TAKEN FOR ASSESMENT

1	The MHRA received the marketing authorisation applications on 23 rd June 2003
2	Following standard checks and communication with the applicant the MHRA considered the applications valid on 21 st August 2003
3	Following assessment of the applications the MHRA requested further information relating to the quality dossiers on 12 th March 2004, 20 th July 2004, 30 th June 2005, 3 rd April 2006, 2 nd January 2007, 10 th April 2007, 10 th October 2007 and on the clinical dossier 4 th August 2004, 15 th February 2005
4	The applicant responded to the MHRA's requests, providing further information on the quality dossiers on 29 th April 2004, 11 th April 2005, 28 th October 2006, 10 th April 2007, 7 th August 2007, 6 th November 2007 and on the clinical dossier 17 th September 2004, 11 th April 2005
5	The applications were determined on 28 th February 2008

**FLUCLOXACILLIN 250MG CAPSULES
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**FLUCLOXACILLIN 500MG CAPSULES
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STEPS TAKEN AFTER AUTHORISATION - SUMMARY

Date submitted	Application type	Scope	Outcome

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Flucloxacillin 250 mg Capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 250mg flucloxacillin as flucloxacillin sodium.

For full list of excipients, see Section 6.1.

3 PHARMACEUTICAL FORM

Hard gelatin capsules

Blue cap/blue body capsule printed with "F 250" and containing a white, free flowing powder.

4 CLINICAL PARTICULARS

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.

4.1 Therapeutic indications

Flucloxacillin Capsules are indicated for the treatment of infections due to flucloxacillin sensitive grampositive organisms, including β -lactamase-producing staphylococci and streptococci. Typical indications include:

Skin and soft tissue infections:		
<i>Boils</i>	Cellulitis	Infected burns
<i>Abscesses</i>	Infected skin conditions, e.g. ulcer, eczema, and acne	Protection for skin grafts
<i>Carbuncles</i>	Impetigo	
<i>Furunculosis</i>	Infected wounds	
<i>Respiratory tract infections:</i>		
<i>Pneumonia</i>	Lung abscess	Empyema
<i>Sinusitis</i>	Pharyngitis	Otitis media and externa
<i>Tonsillitis</i>	Quinsy	
<i>Other infections caused by flucloxacillin-sensitive organisms:</i>		
<i>Osteomyelitis</i>	Urinary tract infection	Enteritis
<i>Meningitis</i>	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. Consideration should be given to official guidance on appropriate use of antibacterial agents.

4.2 Posology and method of administration

Oral doses should be administered half to one hour before meals.

Depends on the age, weight and renal function of the patient, as well as the severity of the infection.

Usual adult dosage (including elderly patients)

250 mg four times a day.

The above systemic dosage may be doubled where necessary.

Osteomyelitis, endocarditis - up to 8 g daily, in divided doses six to eight hourly.

Surgical prophylaxis – 1 to 2 g IV at induction of anaesthesia followed by 500 mg six hourly IV, IM or orally for up to 72 hours.

Usual children's dosage

2-10 years: half adult dose

Under 2 years: quarter adult dose.

Where oral doses of less than 250 mg are required flucloxacillin syrup should be administered.

Abnormal renal function

In common with other penicillins, flucloxacillin usage in patients with renal impairment does not usually require dosage reduction. However, in the presence of severe renal failure (creatinine clearance < 10 ml/min) a reduction in dose or an extension of dose interval should be considered. Flucloxacillin is not significantly removed by dialysis and hence no supplementary dosages need to be administered either during or at the end of the dialysis period.

4.3 Contraindications

Flucloxacillin should not be given to patients with a history of hypersensitivity to flucloxacillin, other β -lactam antibiotics (e.g. penicillins, cephalosporins) or any of the excipients in the capsule.

Flucloxacillin is contraindicated in patients with a previous history of flucloxacillin-associated jaundice/hepatic dysfunction.

4.4 Special warnings and precautions for use

Before initiating therapy with flucloxacillin, careful enquiry should be made concerning previous hypersensitivity reactions to β -lactams.

Serious and occasionally fatal hypersensitivity reactions (anaphylaxis) have been reported in patients receiving β -lactam antibiotics. Although anaphylaxis is more frequent following parenteral therapy, it has occurred in patients on oral therapy. These reactions are more likely to occur in individuals with a history of β -lactam hypersensitivity.

Flucloxacillin should be used with caution in patients with evidence of hepatic dysfunction (see section 4.8).

During prolonged treatments (e.g. osteomyelitis, endocarditis), regular monitoring of hepatic and renal functions is recommended.

Prolonged use may occasionally result in overgrowth of non-susceptible organisms.

Sodium Content: Flucloxacillin capsules contain approximately 51 mg sodium per g of flucloxacillin. This should be included in the daily allowance of patients on sodium restricted diets.

4.5 Interaction with other medicinal products and other forms of interaction

Probenecid decreases the renal tubular secretion of flucloxacillin. Concurrent administration of probenecid delays the renal excretion of flucloxacillin.

4.6 Pregnancy and lactation

Pregnancy: Animal studies with flucloxacillin have shown no teratogenic effects. The product has been in clinical use since 1970 and the limited number of reported cases of use in human pregnancy have shown no evidence of untoward effects. The decision to administer any drug during pregnancy should be taken with the utmost care. Therefore flucloxacillin should only be used in pregnancy when the potential benefits outweigh the potential risks associated with treatment.

Lactation: trace quantities of flucloxacillin can be detected in breast milk. The possibility of hypersensitivity reactions must be considered in breast-feeding infants. Therefore flucloxacillin should only be administered to a breast-feeding mother when the potential benefits outweigh the potential risks associated with the treatment.

4.7 Effects on ability to drive and use machines

Adverse effects on the ability to drive or operate machinery have not been observed.

4.8 Undesirable effects

The following convention has been utilised for the classification of undesirable effects:- Very common (>1/10), common (>1/100, <1/10), uncommon (>1/1000, <1/100), rare (>1/10,000, <1/1,000), very rare (<1/10,000).

Unless otherwise stated, the frequency of the adverse events has been derived from more than 30 years of post-marketing reports.

Blood and lymphatic system disorders

Very rare: Neutropenia (including agranulocytosis) and thrombocytopenia. These are reversible when treatment is discontinued.

Immune system disorders

Very rare: Anaphylactic shock (exceptional with oral administration) (see Section 4.4 Special warnings and special precautions for use), angioneurotic oedema.

If any hypersensitivity reaction occurs, the treatment should be discontinued. (See also Skin and subcutaneous tissue disorders).

Gastrointestinal disorders

***Common:** Minor gastrointestinal disturbances.

Very rare: Pseudomembranous colitis.

If pseudomembranous colitis develops, flucloxacillin treatment should be discontinued and appropriate therapy, e.g. oral vancomycin should be initiated.

Hepato-biliary disorders

Very rare: Hepatitis and cholestatic jaundice. (See Section 4.4 Special Warnings and Special Precautions for Use). Changes in liver function test results (reversible when treatment is discontinued).

These reactions are related neither to the dose nor to the route of administration. The onset of these effects may be delayed for up to two months post-treatment; in several cases the course of the reactions has been protracted and lasted for some months. In very rare cases, a fatal outcome has been reported, almost always in patients with serious underlying disease.

Skin and subcutaneous tissue disorders

***Uncommon:** Rash, urticaria and purpura.

Very rare: Erythema multiforme, Stevens-Johnson syndrome and toxic epidermal necrolysis. (See also Immune system disorders).

Musculoskeletal and connective tissue disorders

Very rare: Arthralgia and myalgia sometimes develop more than 48 hours after the start of the treatment.

Renal and urinary disorders

Very rare: Interstitial nephritis.

This is reversible when treatment is discontinued.

General disorders and administration site conditions

Very rare: Fever sometimes develops more than 48 hours after the start of the treatment.

*The incidence of these AEs was derived from clinical studies involving a total of approximately 929 adult and paediatric patients taking flucloxacillin.

4.9 Overdose

Gastrointestinal effects such as nausea, vomiting and diarrhoea may be evident and should be treated symptomatically.

Flucloxacillin is not removed from the circulation by haemodialysis.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

ATC code: J01CF05

Group: Anti-infectives for systemic use

Properties: flucloxacillin is a narrow-spectrum antibiotic of the group of isoxazolyl penicillins; it is not inactivated by staphylococcal β -lactamases.

Activity: flucloxacillin, by its action on the synthesis of the bacterial wall, exerts a bactericidal effect on streptococci, except those of group D (*Streptococcus faecalis*), staphylococci, including the β -lactamase-producing strains, Clostridia and Neisseria. It is not active against methicillin-resistant staphylococci.

Breakpoints: Breakpoints established by the British Society of Antimicrobial Chemotherapy (BSAC) is provided in the table below.

The prevalence of acquired resistance may vary geographically and with time for selected species and local information on resistance is desirable, particularly when treating severe infections. As necessary, expert advice should be sought when the local prevalence of resistance is such that the utility of the agent in at least some types of infections is questionable.

Species	Breakpoint Concentration (mg/L)	
	Susceptible \leq	Resistant \leq
<i>Staphylococci, streptococci, M. catarrhalis, H influenzae</i>	4	8
<i>Enterobacteriaceae, Pseudomonas spp.</i>	-	-

Notes:

^{a.} For *H influenzae* and *M. catarrhalis*, test for β -lactamase, since MICs may be close to the breakpoint, which has been shifted down in relevant cases to allow for this as far as possible.

^{b.} For *S Pneumoniae*: breakpoint of 0.06 mg/L for susceptible, 0.12 mg/L for intermediate, ≥ 2 mg/L for resistant. Organisms requiring an MIC ≤ 1 mg/L are considered susceptible to β -lactam antibiotics, except in infections of the CNS.

5.2 Pharmacokinetic properties

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

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

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

Distribution: flucloxacillin diffuses well into most tissue. Specifically, active concentrations of flucloxacillin have been recovered in bones: 11.6 mg/l (compact bone) and 15.6 mg/l (spongy bone), with a mean serum level of 8.9 mg/l.

Crossing the meningeal barrier: flucloxacillin diffuses in only small proportion into the cerebrospinal fluid of subjects whose meninges are not inflamed.

Crossing into mothers' milk: flucloxacillin is excreted in small quantities in mothers' milk.

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

Excretion: excretion occurs mainly through the kidney. About 65.5% (oral route) and 76.1% (parenteral route) of the dose administered is recovered in unaltered active form in the urine within 8 hours. A small portion of the dose administered is excreted in the bile. The excretion of flucloxacillin is slowed in cases of renal failure.

Protein binding: the serum protein-binding rate is 95%.

5.3 Preclinical safety data

No additional data of relevance.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Magnesium stearate

Capsule Shell

Titanium dioxide E171

Indigo carmine E132

Gelatin

Methyl hydroxybenzoate

Propyl hydroxybenzoate

Shellac

6.2 Incompatibilities

Not applicable

6.3 Shelf life

18 months

6.4 Special precautions for storage

Do not store above 25°C. Store in the original package.

6.5 Nature and contents of container

PVC/PVDC/Aluminium foil blisters, packs of 28 and 56 capsules.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements

7 MARKETING AUTHORISATION HOLDER

Bristol Laboratories Ltd,

Unit 3, Canalside

Northbridge Road

Berkhamsted

Herts

HP4 1EG

8 MARKETING AUTHORISATION NUMBER(S)
PL 17907/0052

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
28/02/2008

10 DATE OF REVISION OF THE TEXT
28/02/2008

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Flucloxacillin 500mg Capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 500mg flucloxacillin as flucloxacillin sodium.

For full list of excipients, see Section 6.1.

3 PHARMACEUTICAL FORM

Hard gelatin capsules

Blue cap/blue body capsule printed with "F 500" and containing a white, free flowing powder.

4 CLINICAL PARTICULARS

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.

4.1 Therapeutic indications

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<i>Boils</i>	Cellulitis	Infected burns
<i>Abscesses</i>	Infected skin conditions, e.g. ulcer, eczema, and acne	Protection for skin grafts
<i>Carbuncles</i>	Impetigo	
<i>Furunculosis</i>	Infected wounds	
<i>Respiratory tract infections:</i>		
<i>Pneumonia</i>	Lung abscess	Empyema
<i>Sinusitis</i>	Pharyngitis	Otitis media and externa
<i>Tonsillitis</i>	Quinsy	
<i>Other infections caused by flucloxacillin-sensitive organisms:</i>		
<i>Osteomyelitis</i>	Urinary tract infection	Enteritis
<i>Meningitis</i>	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. Consideration should be given to official guidance on appropriate use of antibacterial agents.

4.2 Posology and method of administration

Oral doses should be administered half to one hour before meals.

Depends on the age, weight and renal function of the patient, as well as the severity of the infection.

Usual adult dosage (including elderly patients)

250 mg four times a day.

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Osteomyelitis, endocarditis - up to 8 g daily, in divided doses six to eight hourly.

Surgical prophylaxis – 1 to 2 g IV at induction of anaesthesia followed by 500 mg six hourly IV, IM or orally for up to 72 hours.

Usual children's dosage

2-10 years: half adult dose

Under 2 years: quarter adult dose.

Where oral doses of less than 250 mg are required flucloxacillin syrup should be administered

Abnormal renal function

In common with other penicillins, flucloxacillin usage in patients with renal impairment does not usually require dosage reduction. However, in the presence of severe renal failure (creatinine clearance < 10 ml/min) a reduction in dose or an extension of dose interval should be considered. Flucloxacillin is not significantly removed by dialysis and hence no supplementary dosages need to be administered either during or at the end of the dialysis period.

4.3 Contraindications

Flucloxacillin should not be given to patients with a history of hypersensitivity to flucloxacillin, other β -lactam antibiotics (e.g. penicillins, cephalosporins) or any of the excipients in the capsule.

Flucloxacillin is contraindicated in patients with a previous history of flucloxacillin-associated jaundice/hepatic dysfunction.

4.4 Special warnings and precautions for use

Before initiating therapy with flucloxacillin, careful enquiry should be made concerning previous hypersensitivity reactions to β -lactams.

Serious and occasionally fatal hypersensitivity reactions (anaphylaxis) have been reported in patients receiving β -lactam antibiotics. Although anaphylaxis is more frequent following parenteral therapy, it has occurred in patients on oral therapy. These reactions are more likely to occur in individuals with a history of β -lactam hypersensitivity.

Flucloxacillin should be used with caution in patients with evidence of hepatic dysfunction (see section 4.8).

During prolonged treatments (e.g. osteomyelitis, endocarditis), regular monitoring of hepatic and renal functions is recommended.

Prolonged use may occasionally result in overgrowth of non-susceptible organisms.

Sodium Content: flucloxacillin capsules contain approximately 51 mg sodium per g of flucloxacillin. This should be included in the daily allowance of patients on sodium restricted diets.

4.5 Interaction with other medicinal products and other forms of interaction

Probenecid decreases the renal tubular secretion of flucloxacillin. Concurrent administration of probenecid delays the renal excretion of flucloxacillin.

4.6 Pregnancy and lactation

Pregnancy: animal studies with flucloxacillin have shown no teratogenic effects. The product has been in clinical use since 1970 and the limited number of reported cases of use in human pregnancy have shown no evidence of untoward effects. The decision to administer any drug during pregnancy should be taken with the utmost care. Therefore flucloxacillin should only be used in pregnancy when the potential benefits outweigh the potential risks associated with treatment.

Lactation: trace quantities of flucloxacillin can be detected in breast milk. The possibility of hypersensitivity reactions must be considered in breast-feeding infants. Therefore flucloxacillin should only be administered to a breast-feeding mother when the potential benefits outweigh the potential risks associated with the treatment.

4.7 Effects on ability to drive and use machines

Adverse effects on the ability to drive or operate machinery have not been observed.

4.8 Undesirable effects

The following convention has been utilised for the classification of undesirable effects:- Very common ($>1/10$), common ($>1/100$, $<1/10$), uncommon ($>1/1000$, $<1/100$), rare ($>1/10,000$, $<1/1000$), very rare ($<1/10,000$).

Unless otherwise stated, the frequency of the adverse events has been derived from more than 30 years of post-marketing reports.

Blood and lymphatic system disorders

Very rare: Neutropenia (including agranulocytosis) and thrombocytopenia.
These are reversible when treatment is discontinued.

Immune system disorders

Very rare: Anaphylactic shock (exceptional with oral administration) (see Item 4.4 Warnings), angioneurotic oedema.

If any hypersensitivity reaction occurs, the treatment should be discontinued. (See also Skin and subcutaneous tissue disorders).

Gastrointestinal disorders

*Common: Minor gastrointestinal disturbances.

Very rare: Pseudomembranous colitis.

If pseudomembranous colitis develops, flucloxacillin treatment should be discontinued and appropriate therapy, e.g. oral vancomycin should be initiated.

Hepato-biliary disorders

Very rare: Hepatitis and cholestatic jaundice. (See Section 4.4 Special Warnings and Special Precautions for Use). Changes in liver function test results (reversible when treatment is discontinued).

These reactions are related neither to the dose nor to the route of administration. The onset of these effects may be delayed for up to two months post-treatment; in several cases the course of the reactions has been protracted and lasted for some months. In very rare cases, a fatal outcome has been reported, almost always in patients with serious underlying disease.

Skin and subcutaneous tissue disorders

*Uncommon: Rash, urticaria and purpura.

Very rare: Erythema multiforme, Stevens-Johnson syndrome and toxic epidermal necrolysis.

(See also Immune system disorders).

Musculoskeletal and connective tissue disorders

Very rare: Arthralgia and myalgia sometimes develop more than 48 hours after the start of the treatment.

Renal and urinary disorders

Very rare: Interstitial nephritis.

This is reversible when treatment is discontinued.

General disorders and administration site conditions

Very rare: Fever sometimes develops more than 48 hours after the start of the treatment.

*The incidence of these AEs was derived from clinical studies involving a total of approximately 929 adult and paediatric patients taking flucloxacillin.

4.9 Overdose

Gastrointestinal effects such as nausea, vomiting and diarrhoea may be evident and should be treated symptomatically.

Flucloxacillin is not removed from the circulation by haemodialysis.

5 PHARMACOLOGICAL PROPERTIES**5.1 Pharmacodynamic properties**

ATC code: J01CF05

Group: Anti-infectives for systemic use

Properties: flucloxacillin is a narrow-spectrum antibiotic of the group of isoxazolyl penicillins; it is not inactivated by staphylococcal β -lactamases.

Activity: flucloxacillin, by its action on the synthesis of the bacterial wall, exerts a bactericidal effect on streptococci, except those of group D (*Streptococcus faecalis*), staphylococci,

including the β -lactamase-producing strains, Clostridia and Neisseria. It is not active against methicillin-resistant staphylococci.

Breakpoints: Breakpoints established by the British Society of Antimicrobial Chemotherapy (BSAC) is provided in the table below.

The prevalence of acquired resistance may vary geographically and with time for selected species and local information on resistance is desirable, particularly when treating severe infections. As necessary, expert advice should be sought when the local prevalence of resistance is such that the utility of the agent in at least some types of infections is questionable.

Species	Breakpoint Concentration (mg/L)	
	Susceptible \leq	Resistant \leq
<i>Staphylococci, streptococci, M. catarrhalis, H influenzae</i>	4	8
<i>Enterobacteriaceae, Pseudomonas spp.</i>	-	-

Notes:

^a For *H influenzae* and *M. catarrhalis*, test for β -lactamase, since MICs may be close to the breakpoint, which has been shifted down in relevant cases to allow for this as far as possible.

^b For *S Pneumoniae*: breakpoint of 0.06 mg/L for susceptible, 0.12 mg/L for intermediate, ≥ 2 mg/L for resistant. Organisms requiring an MIC ≤ 1 mg/L are considered susceptible to β -lactam antibiotics, except in infections of the CNS.

5.2 Pharmacokinetic properties

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

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

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

Distribution: flucloxacillin diffuses well into most tissue. Specifically, active concentrations of flucloxacillin have been recovered in bones: 11.6 mg/l (compact bone) and 15.6 mg/l (spongy bone), with a mean serum level of 8.9 mg/l.

Crossing the meningeal barrier: flucloxacillin diffuses in only small proportion into the cerebrospinal fluid of subjects whose meninges are not inflamed.

Crossing into mothers' milk: flucloxacillin is excreted in small quantities in mothers' milk.

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

Excretion: excretion occurs mainly through the kidney. About 65.5% (oral route) and 76.1% (parenteral route) of the dose administered is recovered in unaltered active form in the urine within 8 hours. A small portion of the dose administered is excreted in the bile. The excretion of flucloxacillin is slowed in cases of renal failure.

Protein binding: the serum protein-binding rate is 95%.

5.3 Preclinical safety data

No additional data of relevance.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Magnesium stearate

Capsule Shell

Titanium dioxide E171

Indigo carmine E132

Gelatin

Methyl hydroxybenzoate

Propyl hydroxybenzoate
Shellac

6.2 Incompatibilities

Not applicable

6.3 Shelf life

18 months

6.4 Special precautions for storage

Do not store above 25°C. Store in the original package.

6.5 Nature and contents of container

PVC/PVDC/Aluminium foil blisters, packs of 28 and 56 capsules.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements

7 MARKETING AUTHORISATION HOLDER

Bristol Laboratories Ltd,

Unit 3, Canalside

Northbridge Road

Berkhamsted

Herts

HP4 1EG

8 MARKETING AUTHORISATION NUMBER(S)

PL 17907/0053

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10 DATE OF REVISION OF THE TEXT

28/02/2008

PATIENT INFORMATION LEAFLET

FLUCLOXACILLIN 250mg CAPSULES
FLUCLOXACILLIN 500mg CAPSULES
 Flucloxacillin sodium

PATIENT INFORMATION LEAFLET

What you should know about Flucloxacillin Capsules

Keep this leaflet, as you may need to read it again. This medicine has been prescribed for you personally and you should not pass it on to others, even if they have the same symptoms.

Please read all of this leaflet carefully before you start taking this medicine.

What your Capsules contain

Flucloxacillin 250 mg Capsules are blue capsules printed with "F 250".

Flucloxacillin 500 mg Capsules are blue capsules printed with "F 500".

Each capsule contains:

The active ingredient – flucloxacillin 250mg or 500mg (as flucloxacillin sodium).

Other ingredients - magnesium stearate, gelatin, indigo carmine (E132), titanium dioxide (E171), shellac, methyl hydroxybenzoate and propyl hydroxybenzoate.

Flucloxacillin Capsules are available in packs containing 28 and 56 capsules. (Your pharmacist will then provide you with the required number of capsules as prescribed by your doctor. Not all pack sizes may be marketed).

Each 250mg capsule contains approximately 13mg of sodium and each 500mg capsule contains approximately 25mg of sodium. This should be taken into consideration by patients on a controlled sodium diet.

Product Licence holder and manufacturer

Bristol Laboratories Limited, Unit 3, Canalside, Northbridge Road, Berkhamsted, Herts, HP4 1EG

What Flucloxacillin is used for

Flucloxacillin is an antibiotic for treating infections. It belongs to a group of antibiotics called "penicillins". Flucloxacillin works by killing the bacteria that can cause infections.

Flucloxacillin is used to treat a wide range of infections caused by bacteria which may include the following:

- Skin and soft tissue infections (including boils, abscesses, carbuncles, ulcers, infected eczema and acne, wounds and burns)
- Chest, ear, nose and throat infections (including pneumonia, lung abscess, tonsils (tonsillitis), sinuses (sinusitis), pharynx (pharyngitis), ears (otitis media and otitis externa),
- Other infections including those of the heart (endocarditis), bones and joints (osteomyelitis), membranes of the brain (meningitis), guts (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 during major surgical procedures, particularly in heart or orthopaedic surgery.

If you are not sure why Flucloxacillin Capsules have been prescribed for you, ask your doctor.

Before taking Flucloxacillin Capsules

Do not take Flucloxacillin Capsules if

- You are allergic to flucloxacillin, any of the other ingredients in the capsule, or any other antibiotics (especially penicillin)
- You have a previous history of jaundice (yellowing of the skin) or liver problems related to flucloxacillin

Take special care if

- You have had a skin rash, swelling of the face or neck, or any serious complaint when taking any antibiotic
- You have liver problems
- You are pregnant or think you might be pregnant, or you are breast-feeding
- You are on a low-sodium diet

Before taking your medicine

- Are you being treated for kidney problems or gout?

If any of the above apply to you, you must speak to your doctor or pharmacist **BEFORE** starting this medicine.

How to take Flucloxacillin Capsules

Take flucloxacillin exactly as directed by your doctor and follow the instructions given on the dispensing label. If you do not understand these directions ask your pharmacist, nurse or doctor to explain them to you.

Take each dose of Flucloxacillin with a full glass of water half to one hour before meals.

Adults: Usually one 250 mg capsule four times a day. Your doctor may prescribe a different dose for severe infections or after surgery.

For infections of the joints (osteomyelitis) or heart (endocarditis) the usual dose is up to 8 g daily in divided doses six to eight hourly.

Children: The usual dose for children aged 2-10 years is half the adult dose. The dose for children under 2 years old is quarter the adult dose. If a dose of less than 250 mg is required your doctor will prescribe flucloxacillin in a dosage form that is suitable for your needs.

Take all of the Flucloxacillin Capsules that have been prescribed for you, even if you begin to feel better. Your symptoms may start to improve before the condition is completely treated. If you stop taking Flucloxacillin Capsules too soon, your symptoms may return.

What to do if you miss a dose:

Take the missed dose as soon as you remember, however, if it is almost time for your next dose, skip the missed dose and then take your next dose when it is due. Do not take a double dose to make up for the missed dose.

What to do if you take too many capsules:

If you or someone else has taken too many capsules, contact your doctor or the nearest hospital emergency department immediately. Please take any remaining capsules or this leaflet with you.

Possible side effects

As with all medicines, some people may experience side effects with Flucloxacillin.

The more common side effects of Flucloxacillin that could happen to between 1 in 10 people and 1 in 100 people taking it include:

- minor gastrointestinal disturbances e.g. stomach upset or diarrhea.

Uncommon side effects that could happen to between 1 in 100 and 1 in 1,000 people taking Flucloxacillin include:

- allergic skin reactions e.g. 'hives' or 'nettle' rash. If you start to itch or get a rash, stop taking Flucloxacillin and tell your doctor at once.

Rare side effects could happen to less than 1 in 1,000 and 1 in 10,000 people. There are no rare side effects documented for Flucloxacillin.

Very rare side effects that could happen to less than 1 in 10,000 people taking Flucloxacillin include:

- hypersensitivity or severe allergic reaction including swollen face or breathing problems. An unexpected skin reaction, e.g. a rash and/or a sore mouth or eyes. Tell your doctor straight away if you notice any of these symptoms and STOP taking Flucloxacillin.
- reduction (reversible) in blood cell counts.
- inflammation of the kidney, bowel and/or liver.
- joint or muscle pain. This may develop after 2 days or more from the start of treatment with Flucloxacillin.
- fever. This may develop after two days or more from the start of treatment with Flucloxacillin.

Tell your doctor that you are taking Flucloxacillin if you are having urine tests or blood tests because Flucloxacillin may affect the results.

See your doctor straight away if you experience any of the following very rare side effects:

- severe diarrhea with bleeding.
- notice your urine becoming darker or your faeces (otherwise known as poo) becoming paler.
- notice your skin or the white of your eyes turning yellow.
- notice any unexplained bleeding, bruising or skin discolouration.

Some of these reactions can be delayed for up to two months after finishing the treatment.

If you get any other problems while taking this medicine tell your doctor or pharmacist.

Where to keep Flucloxacillin Capsules

Keep out of the reach and sight of children.

Do not store above 25°C. Store in the original package.

Unless your doctor tells you to, do not keep any Flucloxacillin Capsules that you no longer need. Return any unused capsules back to your pharmacist. Do not take Flucloxacillin Capsules after the expiry date as shown on the carton or label.

Further information

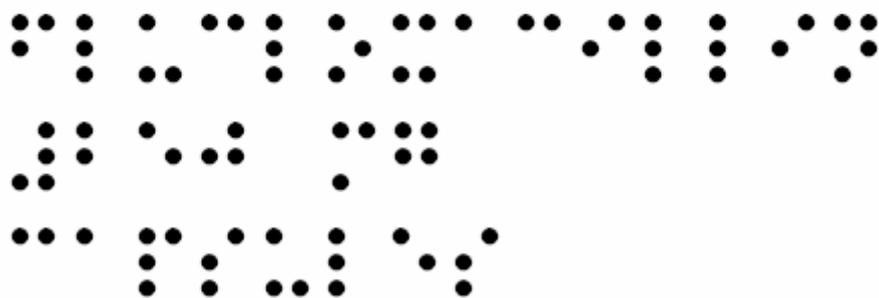
This leaflet does not contain all the information about your medicine. If you have any questions or are not sure about anything, ask your doctor or pharmacist who has the information you need and will advise you.

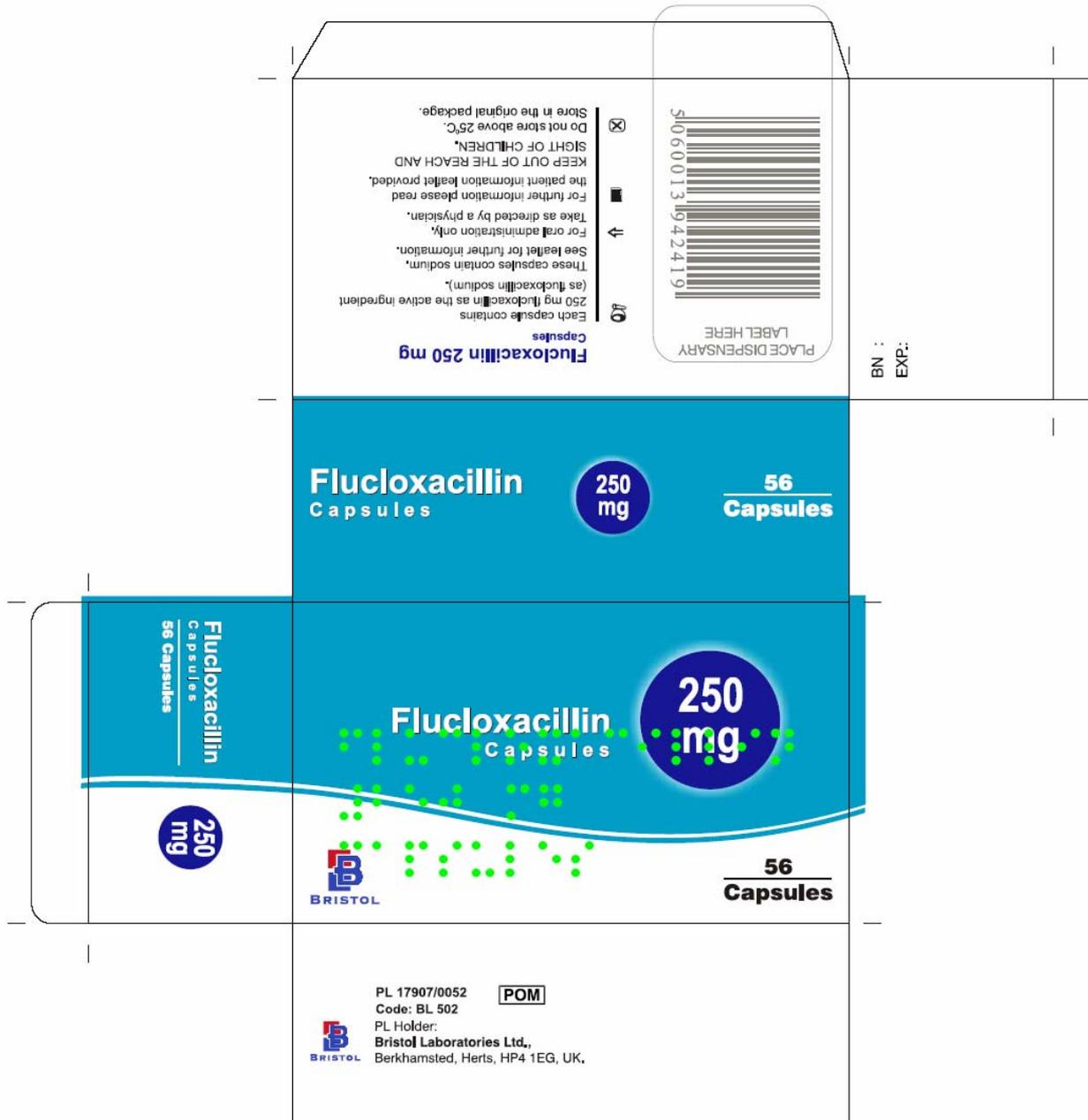
This leaflet was prepared in September 2006.

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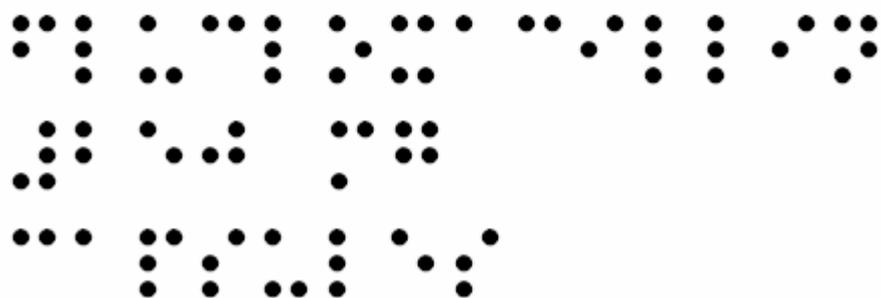


Flucloxacillin 250 mg capsules





Flucloxacillin 250 mg capsules



Flucloxacillin 250mg Capsules
PL Holder
Bristol Laboratories Ltd.
Code: BL 502

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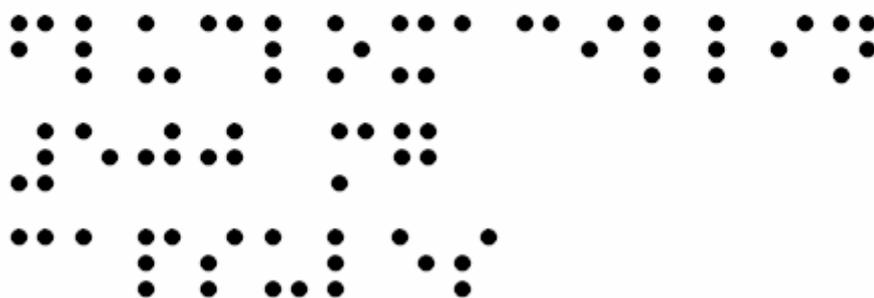
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Bristol Laboratories Ltd.
Code: BL 502

B.No. Exp.

B.No. Exp.



Flucloxacillin 500 mg capsules





Flucloxacillin 500 mg capsules

