

SUMMARY OF PRODUCT CHARACTERISTICS

1 TRADE NAME OF THE MEDICINAL PRODUCT

Flucloxacillin 500mg Capsules and Flucloxin and Ladropen and Fluclomix

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 500 mg of flucloxacillin as flucloxacillin sodium Ph.Eur.

3 PHARMACEUTICAL FORM

Capsules

For excipients, see Section 6.1

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of infections due to sensitive Gram-positive organisms, including infections caused by β -lactamase-producing *Staphylococci*.

Typical indications include:

Skin and soft tissue infections:

Boils	Impetigo
Abscesses	Infected wounds
Carbuncles	Infected burns
Furunculosis	Protection for skin grafts
Cellulitis	

Infected skin conditions e.g. ulcers, eczema and acne.

Respiratory tract infections:

Pneumonia	Pharyngitis
Lung abscess	Tonsillitis
Empyema	Quinsy
Sinusitis	
Otitis media and externa	

Other infections caused by Flucloxacillin sensitive organisms:

Osteomyelitis
Enteritis
Endocarditis

Septicaemia
Meningitis
Urinary-tract infection

Flucloxacillin is also indicated for use as a prophylactic during major surgical procedures such as cardiothoracic and orthopaedic surgery. Parenteral usage is indicated where oral dosage is inappropriate.

Consideration should be given to official local guidance (e.g. national recommendations) on the appropriate use of antibacterial agents.

Susceptibility of the causative organism to the treatment should be tested (if possible), although therapy may be initiated before the results are available.

4.2 Posology and method of administration

Route of administration

Oral. To be administered ½ - 1 hour before meals.

Adults (including the elderly)

Oral: - 250mg four times daily.

In serious infections, the dosage may be doubled.

Children

2 - 10 years : half the adult dose.

Under 2 years: quarter the adult dose.

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

In cases of severe renal impairment (creatinine clearance < 10ml/min) a reduction in dosage may be necessary. 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.

Endocarditis or osteomyelitis

Up to 8g daily in divided doses six to eight hourly.

Surgical prophylaxis

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

s4.3 Contraindications

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

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

Flucloxacillin capsules contain approximately 52.3 mg sodium per g. This should be included in the daily allowance of patients on sodium restricted diets.

4.4 Special warnings and special precautions for use

The use of Flucloxacillin (like other penicillins) in patients with renal impairment does not usually require dosage reduction. In the presence of severe renal failure (creatinine clearance less than 10ml/min), however, a reduction in dose or an extension of dose interval should be considered because of the risk of neurotoxicity.

Flucloxacillin is not significantly removed by dialysis and so no supplementary dosages need to be administered either during or at the end of the dialysis period.

Hepatitis and cholestatic jaundice have been reported. These reactions are related neither to the dose nor to the route of administration. Flucloxacillin should be used with caution in patients with evidence of hepatic dysfunction, patients >50 years or patients with underlying disease all of whom are at increased risk of hepatic reactions. The onset of these hepatic 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 (see section 4.8).

As for other penicillins contact with the skin should be avoided as sensitisation may occur.

Patients with a known history of allergy are more likely to develop a hypersensitivity reaction.

Prolonged use of an anti-Infective agent may occasionally result in overgrowth of non-susceptible organisms.

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 parental 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.

Special caution is essential in the newborn because of the risk of hyperbilirubinaemia. Studies have shown that, at high dose following parenteral administration, flucloxacillin can displace bilirubin from plasma protein binding sites, and may therefore predispose to kernicterus in a jaundiced baby. In addition, special caution is essential in the newborn

because of the potential for high serum levels of flucloxacillin due to a reduced rate of renal excretion.

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

4.5 Interaction with other medicaments and other forms of interaction

Probenecid and sulfapyrazone slow down the excretion of flucloxacillin

Other drugs, such as piperacillin, which are excreted via renal tubular secretion, may interfere with flucloxacillin elimination.

In common with other antibiotics, flucloxacillin may affect the gut flora, leading to lower oestrogen reabsorption and reduced efficacy of the combined oral contraceptive.

Oral typhoid vaccine may be inactivated by flucloxacillin

Flucloxacillin reduces the excretion of methotrexate which can cause methotrexate toxicity

Flucloxacillin may reduce the response to sugammadex

4.6 Pregnancy and lactation

Animal studies with flucloxacillin have shown no teratogenic effects. Flucloxacillin preparations have been in use since 1970 and the limited number of reported cases of use in human pregnancy have shown no evidence of untoward effect. Flucloxacillin should only be used in pregnancy when the potential benefits outweigh the potential risks associated with treatment.

Flucloxacillin is secreted into mother's milk and may occasionally cause sensitisation of the infant. Therefore flucloxacillin should 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

None known.

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. Haemolytic anaemia.

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 laboratory 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. Hepatic events may be severe and in very rare circumstances a fatal outcome has been reported. Most reports of deaths have been in patients ≥ 50 years and 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

With high doses (mainly parenteral) neurotoxicity may develop

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 PARTICULARS

5.1 Pharmacodynamic properties

ATC Code: J01CF05

Group – Beta-lactamase resistant penicillins

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 (*Enterococcus faecalis*), and staphylococci. It is not active against methicillin-resistant staphylococci.

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 250mg by the oral route (in fasting subjects): Approximately 8.8 mg/l.
- After 500mg by the oral route (in fasting subjects): Approximately 14.5mg/l.
- After 500mg by the IM route: Approximately 16.5mg/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 proportions into the cerebrospinal fluid of subjects whose meninges are not inflamed.

Crossing into mother's 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. 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 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 relevant information additional to that already contained elsewhere in the SPC.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Magnesium Stearate
Sodium Starch Glycollate
Red Iron Oxide
Yellow Iron Oxide
Black Iron Oxide
Titanium Dioxide
Gelatin

6.2 Incompatibilities

None known.

6.3 Shelf life

36 months in Securitainers.
12 months in PVC/PE/PVDC and PVDC/PVC blister packs.

6.4 Special precautions for storage

Securitainers: Do not store above 25°C. Keep the container tightly closed. Store in the original container.

Blister Packs: Do not store above 25°C. Store in the original package. Keep container in the outer carton.

6.5 Nature and contents of container

Polypropylene securitainers with polyethylene air-proof cap, with jayfilla containing 15, 18, 20, 21, 28, 30, 100 or 250 capsules or an Opaque PVDC/PVC blister 250/40 with an Aluminium Lidding foil 20 micron containing 15, 18, 20, 21, 28, 30, 100 or 250 capsules or an Opaque PVC/PE/PVDC blister 250/25/90 with an Aluminium Lidding foil 20 micron containing 15, 18, 20, 21, 28, 30, 100 or 250 capsules.

6.6 Instructions for use/handling

None stated

7 MARKETING AUTHORIZATION HOLDER

ATHLONE LABORATORIES LIMITED,
BALLYMURRAY,
CO. ROSCOMMON,
IRELAND.

8 MARKETING AUTHORIZATION NUMBER

PL 6453/0016

9 DATE OF FIRST AUTHORIZATION/RENEWAL OF AUTHORIZATION

First authorisation: 3/12/1992
Renewal: 17/12/97

10 DATE OF PARTIAL REVISION OF TEXT

06/10/2011

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Flucloxacillin GAP 500mg Capsules BP

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

2.1 Qualitative composition

Flucloxacillin as Flucloxacillin sodium

2.2 Quantitative composition

Each capsule contains flucloxacillin 500 mg as flucloxacillin sodium.

Excipient:

Contains approximately 52.3mg sodium per gram of flucloxacillin.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Capsule, hard.

Size 0 elongated hard gelatin capsule having an opaque caramel body and opaque grey cap each printed 'FXN 500' in black ink

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 GAP Capsules are indicated for the treatment of infections due to sensitive Gram-positive organisms, including β -lactamase-producing staphylococci and streptococci. Flucloxacillin GAP Capsules are 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.

4.2 Posology and method of administration

The dosage 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)

Oral - 250mg four times daily. In serious infections, the dosage may be doubled.

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

10-18 years: same as adult dose

2-10 years: half adult dose.

Under 2 years: quarter adult dose.

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. In high dose regimens the maximum recommended dose is 1 g every 8 – 12 hours. 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.

Administration

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

4.3 Contraindications

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

Flucloxacillin is contra-indicated 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. Cross sensitivity between penicillins and cephalosporins is well documented.

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. If an allergic reaction occurs, flucloxacillin should be discontinued and the appropriate therapy instituted. Serious anaphylactoid reactions may require immediate emergency treatment with adrenaline. Oxygen, i.v. steroids, and airway management, including intubation, may also be required.

Flucloxacillin should be used with caution in patients with evidence of hepatic dysfunction, patients \geq 50 years and those with serious underlying disease. In these patients, hepatic events may be severe, and in very rare circumstances, deaths have been reported (see section 4.8 Undesirable effects).

Dosage should be adjusted in renal impairment (see Dosage and Administration).

Special caution is essential in the newborn because of the risk of hyperbilirubinemia. Studies have shown that, at high dose following parenteral administration, flucloxacillin can displace bilirubin from plasma protein binding sites, and may therefore predispose to kernicterus in a jaundiced baby. In addition, special caution is essential in the newborn because of the potential for high serum levels of flucloxacillin due to a reduced rate of renal excretion.

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

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

Flucloxacillin GAP capsules contain 52.3 mg sodium per g. 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 and sulfapyrazone decreases the renal tubular secretion of flucloxacillin. Concurrent administration of probenecid delays the renal excretion of flucloxacillin.

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

Other drugs, such as piperacillin, which are excreted via renal tubular secretion, may interfere with flucloxacillin elimination.

Oral typhoid vaccine may be inactivated by flucloxacillin.

Flucloxacillin reduces the excretion of methotrexate which can cause methotrexate toxicity.

Flucloxacillin may reduce the response to sugammadex.

Bacteriostatic drugs may interfere with the bactericidal action of flucloxacillin.

4.6 Fertility, pregnancy and lactation

Pregnancy: Animal studies with flucloxacillin have shown no teratogenic effects. Limited data is available on the use of flucloxacillin in pregnancy. 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

None known.

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. Eosinophilia. Haemolytic anaemia.

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)

Nervous system disorders

Very rare: In patients suffering from renal failure, neurological disorders with convulsions are possible with the I.V. injection of high doses.

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 laboratory 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. Hepatic events may be severe and in very rare circumstances a fatal outcome has been reported. Most reports of deaths have been in patients ≥ 50 years and 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

Pharmacotherapeutic classification: Beta-lactamase resistant penicillins

ATC code: J01C F05

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 (*Enterococcus faecalis*) staphylococci. It is not active against methicillin-resistant staphylococci.

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 14.5mg/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: Serum protein binding rate is 95%. Flucloxacillin diffuses well into most tissue. Crossing the meningeal barrier: Flucloxacillin diffuses in only small proportion into the cerebrospinal fluid of subjects whose meninges are not inflamed.

Crossing into mother's milk: Flucloxacillin is excreted in small quantities in mother's 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. 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 excretion of flucloxacillin is slowed in cases of renal failure.

Following oral administration Flucloxacillin is almost completely absorbed achieving blood levels comparable to those achieved after intramuscular injection

5.3 Preclinical safety data

No further information of relevance to add

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule content:

Sodium starch glycollate
Magnesium stearate

Capsule shell:

Gelatin
Black iron oxide (E172)
Red iron oxide (E172)
Titanium dioxide (E171)
Yellow iron oxide (E172)

Printing Ink:

Shellac
Propylene glycol
Black Iron oxide E172

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Do not store above 25°C. Keep the container tightly closed. Store in the original container to protect from moisture.

6.5 Nature and contents of container

Polypropylene securitainers with polyethylene air-proof security caps.

Securitainers are available in pack sizes of 40, 100 & 500 capsules. Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements

7. MARKETING AUTHORISATION HOLDER

Athlone Laboratories Limited
Ballymurray

Co. Roscommon
Ireland

8. MARKETING AUTHORISATION NUMBER(S)

PA 298/17/2

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 14th October 2011

10. DATE OF REVISION OF THE TEXT

14th October 2011