NEW ZEALAND DATA SHEET

1. FLUCLOXACILLIN

Flucloxacillin 250 mg capsules.
Flucloxacillin 500 mg capsules.
Flucloxacillin Oral Solution 125 mg/5 mL powder for oral solution.
Flucloxacillin Oral Solution 250 mg/5 mL powder for oral solution.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Flucloxacillin 250 mg capsules: Each capsule contains 250 mg flucloxacillin (as sodium).
Flucloxacillin 500 mg capsules: Each capsule contains 500 mg flucloxacillin (as sodium).
Flucloxacillin Oral Solution 125 mg/5 mL powder for oral solution: Following reconstitution, each 5 mL of solution contains 125 mg flucloxacillin (as sodium).
Flucloxacillin Oral Solution 250 mg/5 mL powder for oral solution: Following reconstitution, each 5 mL of solution contains 250 mg flucloxacillin (as sodium).

Excipients with known effect:
Sodium
Sorbitol

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Capsules:
250 mg: Size ‘2’ hard gelatine capsule having an opaque caramel body fitted with opaque grey cap. Both printed 'FXN 250' in black.

500 mg: Size ‘0E’ hard gelatine capsule having an opaque caramel body fitted with opaque grey cap. Both printed 'FXN 500' in black.

Powder for oral solution:
Free-flowing white granular powder with a slight lemon odour.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Flucloxacillin is indicated for the treatment of infections due to Gram-positive organisms, including infections caused by β-lactamase producing staphylococci.

Typical indications include:

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

Oral preparations of the β-lactamase-resistant penicillins (or flucloxacillin) should not be used as initial therapy in serious, life threatening infections. Oral therapy with flucloxacillin may be used to follow up the previous use of parenteral flucloxacillin as soon as the clinical condition warrants.

4.2 Dose and method of administration

Dose

Doses should be administered 1 hour before meals.

Adults (including elderly patients)

250 mg four times a day.

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

Paediatric population

Children 2-10 years: 125 mg four times a day.

Children under 2 years: half the recommended dose for children 2-10 years.

Renal impairment

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 < 10mL/min) a reduction in dose or 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 maximum recommended dose in adults is 1 g every 8 to 12 hours.

Method of administration

Oral

4.3 Contraindications

Flucloxacillin is contraindicated in patients who have had previous experience of a major allergy or anaphylaxis to a cephalosporin or penicillin.

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

Hypersensitivity to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Flucloxacillin should be given with caution to patients who have experienced symptoms of allergy associated with a cephalosporin or penicillin.

Before initiating therapy with flucloxacillin, careful inquiry should be made concerning previous hypersensitivity reactions to beta-lactams. Cross-sensitivity between penicillins and cephalosporins is well documented.

Serious and occasionally fatal hypersensitivity reactions (anaphylaxis) have been reported in patients receiving beta-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 beta-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, intravenous steroids, and airway management, including intubation, may also be required.

Hepatitis, predominantly of a cholestatic type has been reported and, very rarely, deaths have occurred, almost always in patients with serious underlying disease. Reports have been more frequent with increasing age or following prolonged treatment (see section 4.8). Flucloxacillin should be used with caution in patients with evidence of hepatic dysfunction.

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.

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.

Dosage should be adjusted in renal impairment. (see section 4.2).

Flucloxacillin Oral Solution contains sodium benzoate (5 mg/5 mL).

Massive doses of flucloxacillin can cause hypokalaemia and sometimes hypernatraemia. Use of a potassium-sparing diuretic may be helpful. In patients undergoing high-dose treatment for more than 5 days, electrolyte balance, blood counts and renal functions should be monitored.

Pseudomembranous colitis has been reported with virtually all broad-spectrum antibiotics. It is important to consider this diagnosis in patients who develop severe and persistent diarrhoea during or after receiving flucloxacillin. In this situation, even if *Clostridium difficile* is only suspected, administration of flucloxacillin should be discontinued and appropriate treatment given.

4.5 Interaction with other medicines and other forms of interaction

Probenicid decreases the renal tubular secretion of flucloxacillin. Concurrent administration of probenicid delays the renal excretion of flucloxacillin.

Bacteriostatic agents may interfere with the bactericidal action of flucloxacillin.

Chloramphenicol, Erythromycin, Sulfonamides or Tetracyclines: Since bacteriostatic agents may interfere with the bactericidal effect of penicillins in the treatment of meningitis or other situations where a rapid bactericidal effect is necessary, it is best to avoid concurrent therapy.

Aminoglycosides: if flucloxacillin is to be used concurrently with an aminoglycoside, the two antibiotics should not be mixed.

The efficacy of oral contraceptives may be impaired under concomitant administration of flucloxacillin, which may result in unwanted pregnancy. Women taking oral contraceptives should be aware of this and should be informed about alternative methods of contraception.

Penicillins reduce the excretion of methotrexate thereby increasing the risk of methotrexate toxicity.

Penicillins may interfere with:
- Urinary glucose test
- Coomb's tests
- Tests for urinary or serum proteins
- Tests which use bacteria e.g. Guthrie test.

Doses should be administered 1 hour before meals.

4.6 Fertility, pregnancy and lactation

<u>Pregnancy</u>
Category B1
Penicillins are generally considered safe for use in pregnancy. Animal studies with flucloxacillin have shown no teratogenic effects. Limited information is available concerning the results of the use of

flucloxacillin in human pregnancy. Flucloxacillin should only be used in pregnancy when the potential benefits outweigh the potential risks associated with treatment.

Breastfeeding
Trace quantities of penicillin can be detected in breast milk with the potential for hypersensitivity reactions (e.g. drug rashes) or gastrointestinal disorders (e.g. diarrhoea or candidosis) in the breast-fed infant. Consequently, breastfeeding might have to be discontinued.

Fertility
No data.

4.7 Effects on ability to drive and use machines

During treatment with flucloxacillin, undesirable effects may occur (e.g. allergic reactions, dizziness, convulsions) which may influence the ability to drive and use machines. Patients should be cautious when driving or operating machinery.

4.8 Undesirable effects

The following convention has been utilised for the classification of undesirable effects:
Very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000), not known (cannot be estimated from the available data).

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. Eosinophilia.

Immune system disorders
Very rare: Anaphylactic shock (exceptional with oral administration) (see section 4.4), 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). 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.

There is evidence that the risk of flucloxacillin-induced liver injury is increased in subjects carrying the HLA-B*5701 allele. Despite this strong association, only 1 in 500-1000 carriers will develop liver injury. Consequently, the positive predictive value of testing the HLA-B*5701 allele for liver injury is very low (0.12%) and routine screening for this allele is not recommended.

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).
Not known: AGEP – acute generalized exanthematous pustulosis (see section 4.4), cutaneous vasculitis.

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.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://nzphvc.otago.ac.nz/reporting/

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.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Beta-lactamase resistant penicillins; ATC Code: J01CF05.

Flucloxacillin sodium, a derivative of 6-amino-penicillanic acid, is a semi-synthetic penicillin with a narrow spectrum of bactericidal activity. Flucloxacillin, by its action on the synthesis of the bacterial wall, exerts a bactericidal effect on streptococci, staphylococci, including the beta-lactamase-producing strains, clostridia and neisseria. It is not active against methicillinresistant staphylococci.

Strains of the following organisms are generally sensitive to the bactericidal action of flucloxacillin *in vitro* (the minimal inhibitory concentrations (MIC) of flucloxacillin are also quoted below).

Micro-organisms	**MIC (mg/l)**
Staphylococcus aureus	0.1 - 0.25
Staphylococcus aureus (beta-lactamase +)	0.25 - 0.5
Streptococcus pneumoniae	0.25
Streptococcus pyogenes (Group A betahaemolytic)*	0.1
Streptococcus viridans group	0.5
Clostridium tetani	0.25
Clostridium welchii	0.25
Neisseria meningitidis	0.1
Neisseria gonorrhoeae	0.1
Neisseria gonorrhoeae (beta-lactamase +)	2.5

* The Group A beta-haemolytic streptococci are less sensitive to the isoxazolyl penicillins than to penicillin G or penicillin V.

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 1 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.

Absorption is more efficient when taken on an empty stomach. The total quantity absorbed by the oral route represents approximately 79% of the quantity administered.

Distribution
Flucloxacillin diffuses well into most tissues. 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.

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

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.

Biotransformation
In normal subjects approximately 10% of the flucloxacillin administered is metabolised to penicilloic acid. The elimination half-life of flucloxacillin is 30-60 minutes.

Elimination
The drug is rapidly excreted by the kidney, about 50% within 6 hours of administration. A small portion of the dose administered is excreted in the bile. The excretion of flucloxacillin is slowed in cases of renal failure.

5.3 Preclinical safety data

No relevant information additional to that already contained elsewhere in the data sheet.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsules:
Gelatin
Magnesium stearate
Silicon dioxide

Powder for oral solution:
Citric acid
Disodium edetate
Lemon flavour
Menthol flavour
Saccharin sodium

Silicon dioxide
Sodium benzoate
Sodium citrate
Sorbitol
Strawberry flavour
Xanthan gum

6.2 Incompatibilities

As with other penicillins, flucloxacillin is incompatible with colistin polymyxin B sulphate. Loss of potency after mixing with streptomycin has also been reported.

6.3 Shelf life

Flucloxacillin 250 mg and 500 mg capsules
Blister pack: 24 months.
Plastic bottle: 36 months.

Flucloxacillin Oral Solution 125 mg/5 mL powder for oral solution
Powder: 15 months.
Reconstituted solution: 14 days when stored in a refrigerator (2–8 °C). Do not freeze.

Flucloxacillin Oral Solution 250 mg/5 mL powder for oral solution
Powder: 18 months.
Reconstituted solution: 14 days when stored in a refrigerator (2–8 °C). Do not freeze.

6.4 Special precautions for storage

Flucloxacillin 250 mg and 500 mg capsules
Store below 25 °C. Protect from light.

Flucloxacillin Oral Solution 125 mg/5 mL and 250 mg/5 mL powder for oral solution
Store below 25 °C. Protect from light.

For storage conditions after reconstitution of the medicine, see section 6.3.

6.5 Nature and contents of container

Flucloxacillin 250 mg capsules
PVC/PE/PVdC blister pack of 20 capsules, or plastic bottles of 100 or 250 capsules.

Flucloxacillin 500 mg capsules
PVC/PE/PVdC blister pack of 20 capsules, or plastic bottles of 100, 250 or 500 capsules.

Flucloxacillin Oral Solution 125 mg/5 mL powder for oral solution
HDPE plastic bottle that, when correctly prepared, will contain 100 mL of solution.

Flucloxacillin Oral Solution 250 mg/5 mL powder for oral solution
HDPE plastic bottle that, when correctly prepared, will contain 100 mL of solution.

6.6 Special precautions for disposal and other handling

Flucloxacillin Oral Solution 125 mg/5 mL powder for oral solution
To prepare solution, add 87 mL of purified water and shake well. The resulting solution should be an opaque, off-white solution with a lemon odour.

Flucloxacillin Oral Solution 250 mg/5 mL powder for oral solution
To prepare solution, add 79 mL of purified water and shake well. The resulting solution should be an opaque, off-white solution with a lemon odour.

7. MEDICINE SCHEDULE

Prescription Medicine.

8. SPONSOR

AFT Pharmaceuticals Ltd
PO Box 33-203
Takapuna
Auckland 0740
Phone: 0800 423 823
Email: customer.service@aftpharm.com

9. DATE OF FIRST APPROVAL

Flucloxacillin Capsules: 11 May 1998
Flucloxacillin Oral Solution: 14 March 2002

10. DATE OF REVISION OF THE TEXT

3 July 2017

Summary table of changes:

Section changed	Summary of new information
4.2	Revised dosing information.
4.3	Contraindications added in patients with cephalosporin or penicillin allergy,

	and hypersensitivity to excipients.
4.4	Warnings added for patients with cephalosporin/penicillin allergies, massive dose effects, and incidence of *Pseudomembranous colitis*.
4.5	Interactions with oral contraceptives, methotrexate, and laboratory tests added.
4.6	Breastfeeding statement updated.
4.7	Statement on effect on ability to drive and use machines updated.
4.8	Data updated. Cutaneous vasculitis added.