1. Name of the medicinal product

Medifloxil Powder for Reconstitution

2 Qualitative and quantitative composition

Each 5ml contains: Amoxicillin Trihydrate BP equivalent to Amoxicillin 125 mg; Flucloxacillin Sodium BP equivalent to Flucloxacillin 125 mg.

For the full list of excipients, see section 6.1

3 Pharmaceutical form Dosage form

Dry Syrup

4 Clinical particulars

4.1 Therapeutic indication(s)

Amoxicillin and Flucloxacillin offer broad spectrum antibiotic therapy across a wide range of infections including: Pelvic inflammatory disease, Respiratory tract infections, Skin and soft tissue infections, upper respiratory tract infections, urinary tract infections.

4.2 Posology and method of administration

Adults
500mg every 8 hours ½ to 1 hour before meals.
Children
Up to 2 years:
125mg every 8 hours ½ to 1 hour before meals.
2-10 years
250mg every 8 hours ½ to 1 hour before meals

Method of administration

Reconstitution of dry syrup

Shake the bottle to loosen the powder. To make up to 100ml syrup, add water to just below the mark, invert the bottle and shake until all the powder is dispersed. Finally add water to make the volume to the mark and mix.

4.3 Contra-indications

Patients with a history of sensitivity to penicillin should not take Medifloxil

4.4 Special warnings and precautions for use

Medifloxil should be discontinued and appropriate alternative therapy instituted. Medifloxil should be avoided if infectious mononucleosis is suspected since the occurrence of a morbilliform rash has been associated with hepatitis, predominantly of a cholestatic type.

4.5 Interactions with other medicinal products and other forms of interaction

Amoxicillin Trihydrate

Probenecid

Concomitant use of probenecid is not recommended. Probenecid decreases the renal tubular secretion of amoxicillin. Concomitant use of probenecid may result in increased and prolonged levels of amoxicillin.

Allopurinol

Concurrent administration of allopurinol during treatment with amoxicillin can increase the likelihood of allergic skin reactions.

Tetracyclines

Tetracyclines and other bacteriostatic drugs may interfere with the bactericidal effects of amoxicillin.

Methotrexate

Penicillins may reduce the excretion of methotrexate causing a potential increase in toxicity.

Oral typhoid vaccine

The oral typhoid vaccine is inactivated by antibacterials.

Oral Anticoagulants

Oral anticoagulants and penicillin antibiotics have been widely used in practice without reports of interaction. However, in the literature there are cases of increased international normalized ratio in patients maintained on acenocoumarol or warfarin and prescribed a course of amoxicillin. If co-administration is necessary, the prothrombin time or international normalized ratio should be carefully monitored with the addition or withdrawal of amoxicillin. Moreover, adjustments in the dose of oral anticoagulants may be necessary.

Flucloxacillin

Probenecid and sulfinpyrazone slow down the excretion of flucloxacillin by decreasing tubular secretion.

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.

There are rare cases of altered international normalized ratio (INR) in patients taking warfarin and prescribed a course of flucloxacillin. If co-administration is necessary, the prothrombin time or international normalized ratio should be carefully monitored during addition or withdrawal of flucloxacillin.

Bacteriostatic drugs may interfere with the bactericidal action of flucloxacillin.

Caution should be taken when flucloxacillin is used concomitantly with paracetamol as concurrent intake has been associated with high anion gap metabolic acidosis, especially in patients with risk factors.

4.6 Pregnancy and lactation

Pregnancy

Amoxicillin Trihydrate

Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity. Limited data on the use of amoxicillin during pregnancy in humans do not indicate an increased risk of congenital malformations. Amoxicillin may be used in pregnancy when the potential benefits outweigh the potential risks associated with treatment.

Flucloxacillin

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 has shown no evidence of untoward effect. The use of flucloxacillin in pregnancy should be reserved for cases considered essential by the clinician. Flucloxacillin should only be used in pregnancy when the potential benefits outweigh the risks associated with treatment.

Breastfeeding

Amoxicillin Trihydrate

Amoxicillin is excreted into the breast milk in small quantities with the possible risk of sensitization. Consequently, diarrhea and fungus infection of the mucous membranes are possible in the breast-fed infant, so that breast-feeding might have to be discontinued. Amoxicillin should only be used during breast-feeding after benefit/risk assessment by the physician in charge.

Flucloxacillin

Flucloxacillin is secreted into mother's milk and may occasionally cause sensitization of the infant. 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 the ability to drive and operate machinery

No studies on the effects on the ability to drive and use machines have been performed. However, undesirable effects may occur (e.g. allergic reactions, dizziness, convulsions), which may influence the ability to drive or use machines.

Flucloxacillin has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Side effects as with other antibiotics, severe allergic reactions including anaphylaxis, angioneurotic oedema, serum sickness and allergic vasculitis have been reported rarely. Rash, purpura, fever, eosinophilia, pruritis and urticarial have been reported. Rarely skin reactions such as erythema multiform, Stevens-Johnson syndrome bullous and exfoliative dermatitis have been reported. Minor gastrointestinal disturbances may occur during

treatment, including nausea, vomiting and diarrhea. As with other antibiotics, pseudomembranous colitis and intestinal candidiasis have been reported rarely. As with other penicillin and cephalosporins, hepatitis and cholestatic jaundice have been reported. Intestinal nephritis may occur. In patients suffering from renal failure, neurological disorders with convulsions are possible with use of high intravenous doses. As with other beta lactams, hematological effects including reversible leucopenia, reversible thrombocytopenia and hemolytic anemia have been reported rarely.

Reporting of suspected adverse reactions

Healthcare professionals are requested to report any suspected adverse reactions via national Pharmacovigilance Electronic Reporting Systems to the respective national regulatory authorities.

4.9 Overdose

Flucloxacillin

With high doses (mainly parenteral) neurotoxicity may develop.

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

Flucloxacillin is not removed from the circulation by hemodialysis.

Amoxicillin Trihydrate

Symptoms and signs of overdose

Gastrointestinal symptoms (such as nausea, vomiting and diarrhea) and disturbance of the fluid and electrolyte balances may be evident. Amoxicillin crystalluria, in some cases leading to renal failure, has been observed. Convulsions may occur in patients with impaired renal function or in those receiving high doses (see Sections 4.4 and 4.8).

Treatment of intoxication

Gastrointestinal symptoms may be treated symptomatically, with attention to the water/electrolyte balance.

Amoxicillin can be removed from the circulation by hemodialysis.

5 Pharmacological properties

5.1 Pharmacodynamic properties

ATC code: J01C

Amoxicillin Trihydrate

Mechanism of action

Amoxicillin is a semisynthetic penicillin (beta-lactam antibiotic) that inhibits one or more enzymes (often referred to as penicillin-binding proteins, PBPs) in the biosynthetic pathway of bacterial peptidoglycan, which is an integral structural component of the bacterial cell wall. Inhibition of peptidoglycan synthesis leads to weakening of the cell wall, which is usually followed by cell lysis and death.

Amoxicillin is susceptible to degradation by beta-lactamases produced by resistant bacteria and therefore the spectrum of activity of amoxicillin alone does not include organisms which produce these enzymes.

Pharmacokinetic/pharmacodynamic relationship

The time above the minimum inhibitory concentration (T>MIC) is considered to be the major determinant of efficacy for amoxicillin.

Mechanisms of resistance

The main mechanisms of resistance to amoxicillin are:

• Inactivation by bacterial beta-lactamases.

• Alteration of PBPs, which reduce the affinity of the antibacterial agent for the target.

Impermeability of bacteria or efflux pump mechanisms may cause or contribute to bacterial resistance, particularly in Gram-negative bacteria.

Breakpoints

MIC breakpoints for amoxicillin are those of the European Committee on Antimicrobial Susceptibility Testing (EUCAST) version 5.0.

Organism	**MIC breakpoint (mg/L)**	
	Susceptible ≤	**Resistant >**
Enterobacteriaceae	8[1]	8
Staphylococcus spp.	Note[2]	Note [2]
Enterococcus spp.[3]	4	8
Streptococcus groups A, B, C and G	Note [4]	Note [4]
Streptococcus pneumoniae	Note [5]	Note [5]
Viridans group steprococci	0.5	2
Haemophilus influenzae	2[6]	2[6]
Moraxella catarrhalis	Note [7]	Note [7]
Neisseria meningitidis	0.125	1
Gram positive anaerobes except *Clostridium difficile*[8]	4	8
Gram negative anaerobes[8]	0.5	2
Helicobacter pylori	0.125[9]	0.125[9]
Pasteurella multocida	1	1
Non- species related breakpoints[10]	2	8

[1]Wild type Enterobacteriaceae are categorised as susceptible to aminopenicillins. Some countries prefer to categorise wild type isolates of *E. coli* and *P. mirabilis* as intermediate. When this is the case, use the MIC breakpoint S ≤ 0.5 mg/L
[2]Most staphylococci are penicillinase producers, which are resistant to amoxicillin. Methicillin resistant isolates are, with few exceptions, resistant to all beta-lactam agents.
[3]Susceptibility to amoxicillin can be inferred from ampicillin
[4]The susceptibility of streptococcus groups A, B, C and G to penicillins is inferred from the benzylpenicillin susceptibility.
[5]Breakpoints relate only to non-meningitis isolates. For isolates categorised as intermediate to ampicillin avoid oral treatment with amoxicillin. Susceptibility inferred from the MIC of ampicillin.
[6]Breakpoints are based on intravenous administration. Beta-lactamase positive isolates should be reported resistant.
[7]Beta lactamase producers should be reported resistant
[8]Susceptibility to amoxicillin can be inferred from benzylpenicillin.

[9]The breakpoints are based on epidemiological cut-off values (ECOFFs), which distinguish wild-type isolates from those with reduced susceptibility.
[10]The non-species related breakpoints are based on doses of at least 0.5 g x 3or 4 doses daily (1.5 to 2 g/day)

The prevalence of 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.

***In vitro* susceptibility of micro-organisms to Amoxicillin**
Commonly Susceptible Species
Gram-positive aerobes:
Enterococcus faecalis Beta-hemolytic streptococci (Groups A, B, C and G) *Listeria monocytogenes*
Species for which acquired resistance may be a problem
Gram-negative aerobes: *Escherichia coli* *Haemophilus influenzae* *Helicobacter pylori* *Proteus mirabilis* *Salmonella* typhi *Salmonella* paratyphi *Pasteurella multocida*
Gram-positive aerobes: Coagulase negative staphylococcus *Staphylococcus aureus*[£] *Streptococcus pneumoniae* Viridans group streptococcus
Gram-positive anaerobes: *Clostridium* spp.
Gram-negative anaerobes: *Fusobacterium* spp.
Other: *Borrelia burgdorferi*
Inherently resistant organisms[†]
Gram-positive aerobes: *Enterococcus faecium*[†]
Gram-negative aerobes: *Acinetobacter* spp. *Enterobacter* spp. *Klebsiella* spp. *Pseudomonas* spp.
Gram-negative anaerobes: *Bacteroides* spp. (many strains of *Bacteroides fragilis* are resistant).
Others: *Chlamydia* spp. *Mycoplasma* spp. *Legionella* spp.

† Natural intermediate susceptibility in the absence of acquired mechanism of resistance.
£ Almost all *S.aureus* are resistant to amoxicillin due to production of penicillinase. In addition, all methicillin-resistant strains are resistant to amoxicillin.

Flucloxacillin
Pharmacotherapeutic 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.

Risk of hepatic injury

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.

5.2 Pharmacokinetic properties
Amoxicillin Trihydrate

Absorption

Amoxicillin fully dissociates in aqueous solution at physiological pH. It is rapidly and well absorbed by the oral route of administration. Following oral administration, amoxicillin is approximately 70% bioavailable. The time to peak plasma concentration (T_{max}) is approximately one hour.

The pharmacokinetic results for a study, in which an amoxicillin dose of 250 mg three times daily was administered in the fasting state to groups of healthy volunteers are presented below.

Cmax	Tmax *	AUC (0-24h)	T ½
(µg/ml)	(h)	((µg.h/ml)	(h)
3.3 ± 1.12	1.5 (1.0-2.0)	26.7 ± 4.56	1.36 ± 0.56
*Median (range)			

In the range of 250 to 3000 mg the bioavailability is linear in proportion to dose (measured as C_{max} and AUC). The absorption in not influenced by simultaneous food intake.

Haemodialysis can be used for elimination of amoxicillin.

Distribution

About 18% of total plasma amoxicillin is bound to protein and the apparent volume of distribution is around 0.3 to 0.4 l/kg.

Following intravenous administration, amoxicillin has been found in gall bladder, abdominal tissue, skin, fat, muscle tissues, synovial and peritoneal fluids, bile and pus. Amoxicillin does not adequately distribute into the cerebrospinal fluid.

From animal studies there is no evidence for significant tissue retention of drug-derived material. Amoxicillin, like most penicillins, can be detected in breast milk (see section 4.6).

Amoxicillin has been shown to cross the placental barrier (see section 4.6).

Biotransformation

Amoxicillin is partly excreted in the urine as the inactive penicilloic acid in quantities equivalent to up to 10 to 25% of the initial dose.

Elimination

The major route of elimination for amoxicillin is via the kidney.

Amoxicillin has a mean elimination half-life of approximately one hour and a mean total clearance of approximately 25 l/hour in healthy subjects. Approximately 60 to 70% of the amoxicillin is excreted unchanged in urine during the first 6 hours after administration of a single 250 mg or 500 mg dose of amoxicillin. Various studies have found the urinary excretion to be 50-85% for amoxicillin over a 24 hour period

Concomitant use of probenecid delays amoxicillin excretion (see section 4.5).

Age

The elimination half-life of amoxicillin is similar for children aged around 3 months to 2 years and older children and adults. For very young children (including preterm newborns) in the first week of life the interval of administration should not exceed twice daily administration due to immaturity of the renal pathway of elimination. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function.

Gender

Following oral administration of amoxicillin to healthy males and female subjects, gender has no significant impact on the pharmacokinetics of amoxicillin.

Renal impairment

The total serum clearance of amoxicillin decreases proportionately with decreasing renal function (see sections 4.2 and 4.4).

Hepatic impairment

Hepatically impaired patients should be dosed with caution and hepatic function monitored at regular intervals.

Flucloxacillin

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 8.8mg/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: 11.6mg/l (compact bone) and 15.6mg/l (spongy bone), with a mean serum level of 8.9mg/l.

Crossing the meningeal barrier: Flucloxacillin diffuses in only small proportion in to 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 in the order of 53 minutes.

Elimination: 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 additional preclinical data of relevance to the prescriber.

6 Pharmaceutical particulars

6.1 List of excipients

- Citric Acid
- Sucrose
- Sucrose (Crushed –Fine)
- Sodium benzoate
- Sodium Saccharin
- Disodium Edetate (EDTA)
- Sodium citrate
- Vanilla Flavour Dry
- Sunset Yellow FD & C Yellow 6 Colour (E110)
- Magnesium stearate

6.2 Incompatibilities
As for penicillins. Incompatibilities with colistin polymyxin B sulphate. Loss of potency after mixing with streptomycin has also been reported.

6.3 Shelf-life
In the original unopened container; 24 months
After reconstitution (where appropriate) NA
Shelf-life after first opening: Not applicable

6.4 Special precautions for storage:
Medifloxil powder for reconstitution Do not store above 30^0 C, in a dry and dark place.
Keep out of the reach of children

6.5 **Nature and contents of container**
Pack Size: 500 capsules, 10X10 B/P, 2X10B/P
Medifloxil powder for reconstitution Leaflets,
Medifloxil powder for reconstitution Unit carton

6.6 Special precautions for disposal and other handling
For internal use only

7. **Marketing Authorization Holder**

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8. Marketing Authorization Number

CTD8925

9. Date of first registration/ last Renewal

2022 March 21

10. 10. Date of Revision of the text

2022 March 21