1.3.1.1 PROFESSIONAL INFORMATION FOR MEDICINES FOR HUMAN USE

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

MEGAPEN 500 250mg/250mg capsules

MEGAPEN S 125mg/125mg / 5ml syrup

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Capsule:

Each capsule of MEGAPEN 500 contains amoxycillin trihydrate equivalent to 250mg amoxycillin and flucloxacillin sodium equivalent to 250mg flucloxacillin.

Sugar free

Syrup:

Each 5ml of MEGAPEN S contains amoxycillin trihydrate equivalent to 125mg amoxycillin and flucloxacillin sodium equivalent to 125mg flucloxacillin.

Preservative: 0,13 % m/m sodium benzoate.

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Capsules

MEGAPEN 500 is a Light grey/standard grey capsules imprinted “Garec 500”.

Syrup

MEGAPEN S is a free-flowing off-white powder. After reconstitution, it turns to yellow syrup.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

MEGAPEN is indicated for:

- the treatment of bacterial infections, caused by susceptible organisms; in particular infections of mixed origin where penicillin-resistant staphylococci may be implicated.

4.2. Posology and method of administration

In severe infections these dosages may be increased.

To ensure maximal absorption MEGAPEN should be given in the fasting state, i.e., approximately 1 hour before a meal.

Adults

One 500 mg capsule 3 times a day.

Paediatric

Children 2 - 12

5 ml of syrup (containing 250 mg MEGAPEN) three times a day.

Children under 2

2.5 ml of syrup (containing 125 mg MEGAPEN) three times a day.

Neonates

No formulation is available at present.

Method of administration

For oral administration.

4.3. Contraindications

MEGAPEN should not be given:

- Patients with hypersensitivity to penicillin or to any excipients in MEAGPEN.
- As there is currently no neonatal formulation, MEGAPEN should not be given to neonates.

4.4. Special warnings and precautions for use

Hypersensitivity

Administration of penicillins to a hypersensitive patient may occasionally result in anaphylactic shock with collapse and sometimes death.

Angioedema or bronchospasm may also occur.

Before initiating therapy with MEGAPEN, careful enquiry should be made concerning previous hypersensitivity reactions to penicillins, cephalosporins or other allergens. Although anaphylaxis is more frequent following parenteral therapy, it has occurred in patients on oral penicillins. These reactions are more likely to occur in individuals with a history of penicillin hypersensitivity and/or a history of sensitivity to multiple allergens. There have been reports of individuals with a history of penicillin hypersensitivity, who have experienced severe reactions when treated with cephalosporins.

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

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

Feverish Generalised Erythema

The occurrence at the treatment initiation of a feverish generalised erythema associated with pustula may be a symptom of acute generalised exanthematous pustulosis (AGEP) (see section 4.8). In case of AGEP diagnosis, flucloxacillin, as in MEGAPEN, should be discontinued and any subsequent administration of flucloxacillin contraindicated.

Superinfections

The possibility of superinfections with mycotic or bacterial pathogens should be kept in mind during therapy. If superinfections occur, MEGAPEN should be discontinued and/or appropriate therapy instituted.

Drug-induced enterocolitis syndrome (DIES)

Drug-induced enterocolitis syndrome (DIES) has been reported mainly in children receiving amoxicillin, as in MEGAPEN. DIES is an allergic reaction with the leading symptom of protracted vomiting (1 to 4 hours after intake) in the absence of allergic skin or respiratory symptoms. Further symptoms could comprise abdominal pain, diarrhoea, hypotension or leukocytosis with neutrophilia. There have been severe cases including progression to shock.

Resistant strains

The use of this antibiotic may lead to the appearance of resistant strains of organisms and sensitivity testing should therefore be carried out whenever possible, to ensure the appropriateness of the therapy.

Infectious mononucleosis

MEGAPEN should be avoided if infectious mononucleosis is suspected since the occurrence of a morbilliform rash has been associated with this condition following the use of amoxicillin, as in MEGAPEN.

Anticoagulants

Prolongation of prothrombin time has been reported rarely in patients receiving amoxycillin, as in MEGAPEN. Appropriate monitoring should be undertaken when anticoagulants are prescribed concurrently.

Crystalluria

In patients with reduced urine output, crystalluria (including acute renal injury) has been observed very rarely, predominantly with parenteral therapy. During the administration of high doses of amoxicillin, it is advisable to maintain adequate fluid intake and urinary output in order to reduce the possibility of amoxicillin crystalluria. In patients with bladder catheters, a regular check of patency should be maintained.

Impaired Renal Function

The use of flucloxacillin as in MEGAPEN (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 10 mL/min), however, a reduction in dose or an extension of dose interval should be considered because of the risk of neurotoxicity.

Patients on Dialysis

Flucloxacillin, as in MEGAPEN 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.

Impaired Hepatic Function

Hepatitis and cholestatic jaundice have been reported. These reactions are related neither to the dose nor to the route of administration. MEGAPEN 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).

Prolonged use

Prolonged use of an anti-infective medicine may occasionally result in overgrowth of non-susceptible organisms. Pseudomembranous enterocolitis has been reported.

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

Patients with syphilis

Caution is needed when administering MEAGAPEN to patients with syphilis, as the Jarisch-Herxheimer reaction may occur in these patients.

Lymphatic leukaemia

Amoxycillin as in MEGAPEN should be given with caution to patients with lymphatic leukaemia since they are especially susceptible to amoxicillin induced skin rashes.

Patients taking Paracetamol

Caution is advised when flucloxacillin, as in MEGAPEN is administered concomitantly with paracetamol due to the increased risk of high anion gap metabolic acidosis (HAGMA). Patients at high risk of HAGMA are in particular those with severe renal impairment, sepsis or malnutrition especially if the maximum daily doses of paracetamol are used.
After co-administration of flucloxacillin and paracetamol, a close monitoring is recommended in order to detect the appearance of acid-base disorders, namely HAGMA, including the search of urinary 5-oxoproline.

If flucloxacillin is continued after cessation of paracetamol, it is advisable to ensure that there are no signals of HAGMA, as there is a possibility of flucloxacillin maintaining the clinical picture of HAGMA (see section 4.5).

Hypokalaemia

Hypokalaemia (potentially life threatening) can occur with the use of flucloxacillin, as in MEGAPEN, especially in high doses. Hypokalaemia caused by flucloxacillin can be resistant to potassium supplementation. Regular measurements of potassium levels are recommended during the therapy with higher doses of flucloxacillin. Attention for this risk is warranted also when combining flucloxacillin with hypokalaemia-inducing diuretics or when other risk factors for the development of hypokalaemia are present (e.g. malnutrition, renal tubule disfunction).

Interference with diagnostic tests

Elevated serum and urinary levels of amoxicillin, as in MEGAPEN are likely to affect certain laboratory tests. Due to the high urinary concentrations of amoxicillin, false positive readings are common with chemical methods.

It is recommended that when testing for the presence of glucose in urine during amoxicillin treatment, enzymatic glucose oxidase methods should be used.

The presence of amoxicillin may distort assay results for oestriol in pregnant women.

4.5. Interaction with other medicines and other forms of interaction

Probenecid and sulfinpyrazone

Probenecid and sulfinpyrazone slow down the excretion of flucloxacillin, as in MEGAPEN by decreasing tubular secretion.

Piperacillin

Medicines such as piperacillin, which are excreted via renal tubular secretion, may interfere with flucloxacillin, as in MEGAPEN elimination.

Oral typhoid vaccine

The oral typhoid vaccine is inactivated by flucloxacillin and amoxycillin as in MEGAPEN.

Methotrexate

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

Sugammadex

Flucloxacillin may reduce the response to sugammadex.

Oral contraceptives

MEGAPEN may reduce the efficacy of oral contraceptives and patients should be warned accordingly.

Paracetamol

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. (See section 4.4.)

Allopurinol

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

Tetracyclines

Tetracyclines and other bacteriostatic medicines may interfere with the bactericidal effects of MEGAPEN.

Oral Anticoagulants

There are rare cases of altered international normalised ration (INR) in patients taking warfarin and prescribed flucloxacillin and amoxycillin as in MEGAPEN. If co-administration is necessary, the prothrombin time or international normalised ratio should be carefully monitored with the addition or withdrawal of MEGAPEN. Moreover, adjustments in the dose of oral anticoagulants may be necessary.

Voriconazole

Flucloxacillin (CYP450 inducer) has been reported to significantly decrease plasma voriconazole concentrations. If concomitant administration of flucloxacillin with voriconazole cannot be avoided, monitor for potential loss of voriconazole effectiveness (e.g. by therapeutic drug monitoring); increasing the dose of voriconazole may be needed.

4.6. Fertility, pregnancy and lactation

Pregnancy

Safety and efficacy have not been established in pregnant women taking MEGAPEN and should not be used by pregnant women.

Animal studies with flucloxacillin and amoxicillin 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.

Breastfeeding

Safety and efficacy have not been established in women who are breastfeeding and taking MEGAPEN.

MEGAPEN should not be used by women who are breastfeeding.

Amoxicillin and flucloxacillin are excreted into breast milk in small quantities with the possible risk of sensitisation. Consequently, diarrhoea and fungus infection of the mucous membranes are possible in the breastfed infant, so breastfeeding might have to be discontinued.

Fertility

There are no data on the effects of MEGAPEN on fertility in humans. Reproductive studies in animals have shown no effects on fertility.

4.7. Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed.

Patients should be instructed that if they experience sedation or dizziness, they should avoid potentially hazardous tasks such as driving or operating machinery.

4.8. Undesirable effects

a) Tabulated list of adverse reactions

Amoxycillin

System organ class	**Frequent**	**Less frequent**	**Frequency unknown** (cannot be estimated from the available data)
Infections and infestations		Mucocutaneous candidiasis	
Blood and the lymphatic system disorders		Haemolytic anaemia, reversible thrombocytopenia, thrombocytopenic purpura, eosinophilia, reversible leucopenia and agranulocytosis. Prolongation of bleeding time and prothrombin time	
Immune system disorders		Severe allergic reactions including angioneurotic oedema, anaphylaxis, serum sickness and hypersensitivity vasculitis	Jarisch-Herxheimer reaction
Nervous system disorders	Headache	Hyperkinesia, Reversible hyperactivity dizziness and convulsions	Aseptic meningitis
Cardiac disorders			Kounis syndrome
Gastrointestinal disorders	Nausea, vomiting, diarrhoea	Gastritis, stomatitis, glossitis, black 'hairy' tongue, enterocolitis, mucocutaneous candidiasis and antibiotic-associated colitis (including pseudomembranous colitis and haemorrhagic colitis). Indigestion, abdominal pain,	Drug-induced enterocolitis syndrome

		abnormal taste, superficial tooth discolouration#	
Hepato-biliary disorders		Hepatitis and cholestatic jaundice.	
Skin and subcutaneous tissue disorders	Skin rashes	Pruritus and urticaria erythema multiforme, Stevens-Johnson syndrome (SJS), exfoliative dermatitis, acute generalised exanthematous pustulosis (AGEP), drug reaction with eosinophilia and systemic symptoms (DRESS). and toxic epidermal necrolysis (TEN)	
Renal and urinary disorders		Interstitial nephritis	Crystalluria
Reproductive system and Breast Disorders		Vaginitis	
General disorders and administration site conditions		Hot flushes, tiredness	
Investigations			A moderate raise in Aspartate transaminase (AST) and/or Alanine transaminase (ALT
#Superficial tooth discolouration has been reported in children. Good oral hygiene may help to prevent tooth discolouration as it can usually be removed by brushing			

Flucloxacillin

System organ class	**Frequent**	**Less frequent**	**Frequency unknown** (cannot be estimated from the available data)
Blood and the lymphatic system disorders		Neutropenia (including agranulocytosis) and thrombocytopenia. These are reversible when treatment is discontinued. Eosinophilia, haemolytic anaemia.	

Immune system disorders		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.	
Metabolism and nutrition disorders		Very rare cases of high anion gap metabolic acidosis, when flucloxacillin is used concomitantly with paracetamol, generally in the presence of risk factors (see section 4.4.)	Hypokalaemia
Gastrointestinal disorders	*Minor gastrointestinal disturbances.	Pseudomembranous colitis. If pseudomembranous colitis develops, treatment should be discontinued and appropriate therapy, e.g. oral vancomycin should be initiated.	Oesophageal pain and related events
Hepato-biliary disorders		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. Hepatitis and cholestatic jaundice 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		Rash, urticaria and purpura. Erythema multiforme, Stevens-Johnson syndrome and toxic epidermal necrolysis.	AGEP – acute generalised exanthematous pustulosis
Musculoskeletal and connective tissue disorders		Arthralgia and myalgia sometimes develop more than 48 hours after the start of the treatment.	
Renal and urinary disorders		Interstitial nephritis. This is reversible when treatment is discontinued.	
General disorders and administration site conditions		Fever sometimes develops more than 48 hours after the start of the treatment.	

* oesophagitis, burn oesophageal, throat irritation, oropharyngeal pain or oral pain

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 providers are asked to report any suspected adverse reactions to **SAHPRA** via the "6.04 Adverse Drug Reactions Reporting Form", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8

Aspen Pharmacare:

E-mail: Drugsafety@aspenpharma.com

Tel: 0800 118 088

4.9. Overdose

Symptoms

No known symptoms of overdosage.

As with all penicillins, oral administration can cause gastrointestinal symptoms such as transient diarrhoea, nausea and colic which are dose related and a result of local irritation not toxicity. Disturbances in fluid and electrolyte balance may be evident.

Treatment

They may be treated symptomatically with attention to water/electrolyte balance. MEGAPEN cannot be removed from circulation by haemodialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Category and Class: A 20.1.2 Penicillins

Pharmacotherapeutic group: Penicillins

ATC code: J01CF04-5

Mechanism of action

Flucloxacillin is a semi-synthetic penicillin derived from 6-amino-penicillanic acid and is a penicillinase stable penicillin. Flucloxacillin exhibits bactericidal activity against all Gram-

positive organisms (with the exception of Streptococcus faecalis), including organisms sensitive to penicillin e.g. Haemolytic Streptococci, Staphylococci, Streptococcus pneumoniae and N. gonorrhoeae. In vitro efficacy does not imply in vivo efficacy. Flucloxacillin's anti-staphylococcal activity is not affected by penicillinase.

Resistant organisms

Group D (Enterococcus faecalis) staphylococci

Methicillin-resistant staphylococci

Amoxicillin is a semisynthetic penicillinase-susceptible penicillin of the beta-lactam group of antibiotics. It has a broad spectrum of antibacterial activity against non-penicillinase producing Gram positive, and Gram negative microorganisms, acting through the inhibition of biosynthesis of cell wall mucopeptide. The spectrum of activity does not include those organisms that produce beta-lactamases, namely resistant staphylococci, and all strains of *Pseudomonas, Klebsiella* and *Enterobacter.*

Strains of the following organisms are generally sensitive to the bactericidal action of amoxicillin *in vitro*:

Gram-positive bacteria: *Staphylococcus aureus* (penicillin-sensitive)*, *Streptococcus pyogenes, Streptococcus viridans*, *Streptococcus faecalis*, *Streptococcus pneumoniae*, *Corynebacterium* species*, *Clostridium* species*, *Bacillus anthracis*, *Listeria monocytogenes.*

Gram-negative bacteria: *Neisseria gonorrhoeae*, *Neisseria meningitides, Haemophilus influenza***, *Bordetella pertussis, Escherichia coli*, *Salmonella* species, *Shigella* species, *Proteus mirabilis, Pasteurella multocida, Helicobacter pylori, Leptospira* spp., *Fusobacterium* spp.

Other: *Borrelia burgdorferi*

*Sensitivity tests must be performed

**except type b strains causing meningitis in children

5.2. Pharmacokinetic properties

Absorption

MEGAPEN is well absorbed orally. Peak serum levels are achieved 1 to 2 hours after dosing.

Elimination

Approximately 50% of the dose is excreted unchanged into the urine within 6 hours, resulting in high urine level of active drug.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

MEGAPEN CAPSULES

Amoxycillin trihydrate, flucloxacillin sodium, magnesium stearate

MEGAPEN S

Amoxycillin trihydrate, flucloxacillin sodium, apricot dry flavour, blood orange dry flavour, disodium edetate, lemon dry flavour, menthol dry flavour, quinoline yellow, raspberry dry flavour, sodium benzoate, sodium citrate anhydrous, sodium saccharin, sucrose, xanthan gum.

6.2. Incompatibilities

Not applicable.

6.3. Shelf life

MEGAPEN S: 24 Months

MEGAPEN 500: 24 Months

6.4. Special precautions for storage

Containers should be kept tight closed in a cool dry place below (below 25 ^{0}C).

Once dispensed, MEAGPEN S must be used within 7 days if stored in a cool place (below 25 ^{0}C) or 14 days if stored in a refrigerator.

6.5. Nature and contents of container

MEGAPEN 500

Glass bottles containing 15 or 100 capsules.

MEGAPEN S

Glass bottles containing powder for the preparation of 100 ml of 250 mg/5 ml syrup.

Not all packs or pack sizes may be marketed.

6.6. Special precautions for disposal

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

PHARMACARE LIMITED

Healthcare Park

Woodlands Drive

Woodmead 2191

8. REGISTRATION NUMBER

MEGAPEN 500: Z/20.1.2/353

MEGAPEN S: Z/20.1.2/354

9. DATE OF FIRST AUTHORISATION

24 May 2005

10. DATE OF REVISION OF TEXT

22 APRIL 2024

Die Afrikaanse Professionele Inligting is op versoek beskikbaar. Mediese Blitslyn: 0800 118 088.

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