SCHEDULING STATUS: S4

1 NAME OF THE MEDICINE

MACROPEN 500 (Capsules)

MACROPEN S (Powder for suspension)

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

MACROPEN 500:

Gelatine capsules containing amoxicillin trihydrate equivalent to 250 mg amoxicillin and flucloxacillin sodium equivalent to 250 mg flucloxacillin.

Sugar free.

MACROPEN S:

Powder for preparing a fruit-flavoured suspension. When dispensed as directed, each 5 mL of the yellow suspension contains amoxicillin trihydrate equivalent to 125 mg amoxicillin and flucloxacillin sodium equivalent to 125 mg flucloxacillin.

Excipients with known effect

Preservative: Sodium benzoate 0,13 % *m/m.*

Contains sugar: Sucrose 3,32 g.

Contains sweetener: Saccharin sodium 0,458 g.

For full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

MACROPEN 500: Light grey/dark grey capsules imprinted MACROPEN 500.

MACROPEN S: Free-flowing, off-white powder. Yellow suspension.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

MACROPEN 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

Posology

Adults

One 500 mg capsule three times a day.

Paediatric population

Children 2 – 12:

5 mL of suspension (containing 250 mg MACROPEN) three times a day.

Children under 2:

2,5 mL of suspension (containing 125 mg MACROPEN) three times a day.

Neonates:

No formulation is available at present.

In severe infections, these dosages may be increased.

Method of administration

For oral use.

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

4.3 Contraindications

- Hypersensitivity to the active substances, to any penicillins, or to any of the excipients (listed in section 6.1).
- Amoxicillin as contained in MACROPEN is a penicillin and should not be given to patients with a history of hypersensitivity to β-lactam antibiotics (e.g. cephalosporins, carbapenem or monobactam).
- Patients with a previous history of flucloxacillin sodium, contained in MACROPEN, associated jaundice/hepatic dysfunction.
- As there is currently no neonatal formulation, MACROPEN should not be given to neonates.

4.4 Special warnings and precautions for use

Hypersensitivity reactions

Serious, and occasionally fatal, hypersensitivity reactions (including anaphylaxis, anaphylactoid, and severe cutaneous reactions) have been reported in patients receiving beta-lactam antibiotics. Hypersensitivity reactions can also progress to Kounis syndrome, a serious allergic reaction that can result in myocardial infarction (see section 4.8). These reactions are more likely to occur in individuals with a history of penicillin hypersensitivity and in atopic individuals.

Although anaphylaxis is more frequent following parenteral therapy, it has occurred in patients on oral therapy. Before commencing therapy with any penicillin as contained in MACROPEN, careful enquiry should be made concerning previous hypersensitivity reactions to penicillins, cephalosporins or other allergens. If an allergic reaction occurs, appropriate therapy should be instituted and MACROPEN therapy discontinued.

Drug-induced enterocolitis syndrome (DIES) has been reported mainly in children receiving amoxicillin (see section 4.8). DIES is an allergic reaction with the leading symptom of protracted vomiting (1 to 4 hours after administration of amoxicillin) in the absence of allergic skin or respiratory symptoms. Further symptoms could comprise abdominal pain, diarrhoea, hypotension or leucocytosis with neutrophilia. There have been severe cases including progression to shock.

Skin reactions

The occurrence at the treatment initiation of a feverish generalised erythema associated with pustula may be a symptom of acute generalised exanthematous pustulosis (AGEP). This reaction requires MACROPEN discontinuation and contraindicates any subsequent administration.

MACROPEN 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 MACROPEN.

Severe cutaneous adverse reactions (SCAR), such as Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS), and acute generalised exanthematous pustulosis (AGEP) have been reported in patients taking beta-lactam antibiotics. When SCAR is suspected, flucloxacillin sodium as contained in MACROPEN should be discontinued immediately and an alternative treatment should be considered.

Lymphatic leukaemia

MACROPEN should be given with caution to patients with lymphatic leukaemia, as they are susceptible to amoxicillin-induced skin rashes.

Non-susceptible microorganisms

The use of MACROPEN 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.

MACROPEN is not suitable for the treatment of some types of infection unless the pathogen is already documented and known to be susceptible or there is a very high likelihood that the pathogen would be suitable for treatment with MACROPEN. This particularly applies when considering the treatment of patients with urinary tract infections and severe infections of the ear, nose and throat.

Amoxicillin, an aminopenicillin, is not the treatment of choice in patients presenting with sore throat or pharyngitis because of the possibility that the underlying cause is infectious mononucleosis, in the presence of which there is a high incidence of rash if MACROPEN is used (see sub-header Skin reactions).

Overgrowth of non-susceptible microorganisms

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

Antibiotic-associated pseudomembranous colitis has been reported with MACROPEN.

A toxin produced by *Clostridium difficile* appears to be the primary cause. The severity of the colitis may range from mild to life-threatening.

Clostridium difficile associated diarrhoea (CDAD) has been reported with the use of nearly all antibacterial medicines and may range in severity from mild diarrhoea to fatal colitis.

It is important to consider this diagnosis in patients who develop diarrhoea or colitis in association with MACROPEN use (this may occur up to several weeks after cessation of MACROPEN therapy).

If prolonged or significant diarrhoea occurs or the patient experiences abdominal cramps, treatment should be discontinued immediately.

Convulsions

Convulsions may occur in patients with impaired renal function or in those receiving high doses or in patients with predisposing factors (e.g. history of seizures, treated epilepsy or meningeal

disorders (see section 4.8).

Anticoagulants

Abnormal prolongation of prothrombin time (increased INR) has been reported in patients receiving MACROPEN and oral anticoagulants.

Appropriate monitoring should be undertaken when anticoagulants are prescribed concurrently.

Prolonged therapy

Periodic assessment of renal, hepatic and haematopoietic function should be made during prolonged therapy. Elevated liver enzymes and changes in blood counts have been reported.

Supra-infections with non-susceptible organisms may occur, particularly with prolonged use.

The possibility of superinfection with mycotic or bacterial pathogens should be kept in mind. If superinfection occurs (usually involving *Aerobacter, Pseudomonas* or *Candida*), discontinue the medicine and/or institute appropriate therapy.

Jarisch-Herxheimer reaction

Jarisch-Herxheimer reaction may occur when treating patients with syphilis.

The Jarisch-Herxheimer reaction may occur with MACROPEN treatment of Lyme disease. Patients should be reassured that this is a common and usually self-limiting consequence of antibiotic treatment of Lyme disease.

Urinary tract infections

Following single dose therapy of acute lower urinary tract infections, the urine should be cultured. A positive culture may be evidence of a complicated or upper urinary tract infection, and higher dose or prolonged course of treatment may be appropriate.

Crystalluria

In patients with reduced urine output, crystalluria has been observed.

The presence of high urinary concentrations of MACROPEN can cause precipitation of MACROPEN in urinary catheters. Therefore, catheters should be visually inspected at intervals.

In patients with bladder catheters, a regular check of patency should be maintained (see sections 4.8 and 4.9). At high doses, adequate fluid intake and urinary output must be maintained to minimise the possibility of crystalluria.

Impaired Renal Function

The use of flucloxacillin as in MACROPEN (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 MACROPEN, 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.

Hepatic impairment

Hepatitis:

- Hepatitis, predominantly of cholestatic jaundice has been reported.
- Jaundice may appear several weeks after therapy.

MACROPEN should be used with caution in patients with evidence of hepatic dysfunction.

Effects on laboratory tests

Since high urine concentrations of MACROPEN may result in false positive reactions when testing for the presence of glucose in urine, it is recommended that glucose tests based on enzyme-based glucose oxidase reactions be used.

Following administration of ampicillin to pregnant women, a transient decrease in plasma concentration of total conjugated oestriol, oestriol-glucuronide, conjugated oestrone and oestradiol has been noted. This effect may also occur with MACROPEN.

Allopurinol

Patients with hyperuricaemia being treated with allopurinol may also be at increased risk of developing skin rashes (see section 4.5).

Oral contraceptives

MACROPEN may decrease the efficacy of oestrogen-containing oral contraceptives.

High anion gap metabolic acidosis

Caution is advised when flucloxacillin sodium as contained in MACROPEN is administered concomitantly with paracetamol due to the increased risk of high anion gap metabolic acidosis (HAGMA). Patients at high risk for 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 MACROPEN and paracetamol, close monitoring is recommended in order to detect the appearance of acid–base disorders, namely HAGMA, including testing for urinary 5-oxoproline.

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

Hypokalaemia

Hypokalaemia (potentially life threatening) can occur with the use of flucloxacillin, as in MACROPEN, 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).

Sucrose warning for MACROPEN S suspension

MACROPEN contains sucrose which may have an effect on the glycaemic control of patients with diabetes mellitus. Patients with rare hereditary conditions such as fructose intolerance, glucose-galactose mal-absorption or sucrase-isomaltase insufficiency should not take MACROPEN.

Important information about excipients of MACROPEN S suspension

MACROPEN S suspension contains 5 mg sodium benzoate in each 5 mL.

This medicine contains less than 1 mmol sodium (23 mg) per mL that is to say essentially 'sodium-free'. The sodium content in MACROPEN S suspension must be taken into account in patients on a sodium-restricted diet if the administration of high doses is necessary.

4.5 Interaction with other medicines and other forms of interaction

Paracetamol

Caution should be taken when flucloxacillin sodium as contained in MACROPEN 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

The concurrent administration of allopurinol and ampicillin substantially increases the incidence of rashes. It is not known whether this potentiation of ampicillin rashes is due to allopurinol or the hyperuricemia present in these patients. Similar reactions can be expected with MACROPEN.

Digoxin

An increase in the absorption of digoxin is possible on concurrent administration with MACROPEN. A dose adjustment of digoxin may be necessary.

Anticoagulants

Concomitant administration of MACROPEN and anticoagulants from the coumarin class may prolong the bleeding time. A dose adjustment of anticoagulants may be necessary (see section 4.4). If co-administration is necessary, the prothrombin time or international normalised ratio should be carefully monitored with the addition or withdrawal of MACROPEN.

Probenecid

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

Tetracyclines

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

Piperacillin

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

Oral typhoid vaccine

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

Methotrexate

Penicillins may reduce the excretion of methotrexate causing a potential increase in toxicity. Serum methotrexate levels should be closely monitored in patients who receive MACROPEN and methotrexate simultaneously (see section 4.4).

Sugammadex

Flucloxacillin may reduce the response to sugammadex.

Voriconazole

Flucloxacillin has been reported to significantly decrease plasma voriconazole concentrations. If concomitant administration of flucloxacillin and voriconazole cannot be avoided, monitor patient for potential loss of voriconazole effectiveness. An increased dose of voriconazole may be required.

Oral hormonal contraceptives

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

Administration of MACROPEN can transiently decrease the plasma level of oestrogens and progesterone and may reduce the efficacy of oral contraceptives. It is therefore recommended to take supplemental non-hormonal contraceptive measures.

Effect on laboratory tests

At high concentrations, MACROPEN may diminish the results of serum glycemia levels.

Other forms of interactions

- Forced diuresis leads to a reduction in blood concentrations by increased elimination of amoxicillin as contained in MACROPEN.
- MACROPEN may decrease the amount of urinary estriol in pregnant women (see section 4.4).
- MACROPEN may interfere with protein testing when colorimetric methods are used.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential/ Contraception in males and females

MACROPEN can transiently decrease the plasma level of oestrogens and progesterone and may reduce the efficacy of oral contraceptives. It is therefore recommended to take supplemental non-hormonal contraceptive measures (see section 4.4).

Pregnancy

Safety in pregnancy has not been established.

Breastfeeding

MACROPEN is excreted in breast milk. Caution should be exercised when MACROPEN is administered to a nursing woman.

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.

MACROPEN may cause allergic reactions, dizziness or convulsions and thus have a moderate influence on mental and/or physical abilities to perform or execute tasks or activities requiring mental alertness, judgment and/or sound coordination and vision (see section 4.4 and section 4.8). 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

Summary of the safety profile

The most common adverse effects associated with penicillins are allergic reactions. These skin rashes occur most frequently and are either urticarial or maculopapular.

Administration of penicillins to a hypersensitive patient may occasionally result in anaphylactic shock with collapse and sometimes death. Angioedema or bronchospasm may also occur.

Gastrointestinal adverse effects, particularly diarrhoea, nausea and vomiting, occur quite frequently.

Tabulated list of adverse reactions

Body System	Undesirable effects		
	Frequent	Less frequent	Frequency not known
Infections and infestations		Mucocutaneous candidiasis	

Body System	Undesirable effects		
	Frequent	**Less frequent**	**Frequency not known**
Blood and lymphatic system disorders [3]			Haemolytic anaemia, reversible thrombocytopenia, thrombocytopenic purpura, eosinophilia, agranulocytosis, reversible leukopenia (including severe neutropenia or agranulocytosis), prolongation of bleeding time and prothrombin time (see section 4.4)
Immune system disorders (see section 4.3 and 4.4)		Serum sickness-like syndrome, hypersensitivity vasculitis, anaphylaxis (see section 4.4) [4], severe allergic reactions including angioneurotic oedema	

Body System	Undesirable effects		
	Frequent	**Less frequent**	**Frequency not known**
Metabolism and nutrition disorders		High anion gap metabolic acidosis, when MACROPEN is used concomitantly with paracetamol, has been reported (see section 4.5).	Hypokalaemia
Nervous system disorders	Headache	Dizziness, convulsions (see section 4.4) [5], hyperkinesia	Aseptic meningitis
Cardiac disorders			Kounis syndrome
Gastrointestinal disorders	Diarrhoea, nausea, vomiting	Black hairy tongue, antibiotic-associated colitis (including pseudomembranous colitis and haemorrhagic colitis) (see section 4.4), dyspepsia, abdominal pain, tooth discolouration [1]	Drug-induced enterocolitis syndrome (see section 4.4), oesophageal pain and related events [6]
Hepato-biliary disorders		Hepatitis and cholestatic jaundice	Rises in AST and/or ALT

Body System	Undesirable effects		
	Frequent	**Less frequent**	**Frequency not known**
Skin and subcutaneous tissue disorders [2]	Skin rashes	Erythematous maculopapular rash, pruritus, urticaria, erythema multiforme, bullous exfoliative dermatitis, toxic epidermal necrolysis (TEN), Stevens-Johnson syndrome (SJS), Lyell's syndrome, acute generalised exanthematous pustulosis (AGEP) (see section 4.4), drug reaction with eosinophilia and systemic symptoms (DRESS), Jarisch-Herxheimer reaction (see section 4.4), symmetrical drug-related intertriginous and flexural exanthema (SDRIFE) (baboon syndrome)	Linear IgA disease

Body System	Undesirable effects		
	Frequent	**Less frequent**	**Frequency not known**
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, crystalluria (including acute renal injury) (see section 4.9)	
General disorders and administration site conditions		Fever sometimes develops more than 48 hours after the start of the treatment	

[1] Usually the discoloration can be removed by teeth brushing.

[2] Whenever such reactions occur treatment should be discontinued.

[3] These reactions are usually reversible on discontinuation of therapy and are believed to be hypersensitivity phenomena.

[4] Anaphylaxis is the most serious reaction experienced.

[5] Convulsions may occur with impaired renal function or in those receiving high doses.

[6] 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. Health care providers are requested to report any suspected adverse drug reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

4.9 Overdose

In overdose, side effects can be precipitated and/or be of increased severity (see section 4.8).

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.

Amoxicillin crystalluria, in some cases leading to renal failure, has been observed (see section 4.4 and 4.8).

Treatment

Treatment should be symptomatic and supportive.

Gastrointestinal symptoms may be treated symptomatically, with attention to the water/electrolyte balance. MACROPEN 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 with extended spectrum; Beta-lactamase resistant penicillins

ATC code: J01CA04; J01CF05

Bacteriology

MACROPEN exhibits *in vitro* and in experimental animals *in vivo*, bactericidal activity against some Gram-positive and Gram-negative bacteria. *In vitro* sensitivity does not necessarily imply *in vivo* efficacy.

5.2 Pharmacokinetic properties

Absorption

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

Excretion

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

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

MACROPEN 500:

Magnesium stearate

Size 0 hard gelatin capsule:

Red iron oxide

Black iron oxide

Titanium dioxide

MACROPEN S:

Capsaroma DC 100 (orange flavour)

Capsaroma DC 117 (peppermint)

Colour spectracol quinolene yellow CI 47005

Disodium edetate

Glycamil (monoammonium glycyrrhizinate)

Lemon DC 101

Peach apricot

Raspberry DC 107

Saccharin sodium (dried)

Sodium benzoate

Sodium citrate anhydrous

Sucrose

Xanthan gum

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

MACROPEN 500:

36 months

MACROPEN S:

Dry powder: 36 months

Reconstituted suspension: 7 days or 14 days. Once reconstituted, MACROPEN S must be used within 7 days kept at 25 °C, or used within 14 days and kept in a refrigerator at 5 °C.

6.4 Special precautions for storage

MACROPEN 500:

Store at or below 25 °C.

Keep the container tightly closed.

Store in a cool, dry place.

MACROPEN S:

Powder:

Store at or below 25 °C.

Keep the container tightly closed.

Keep in a cool, dry place.

Reconstituted medicine:

For storage conditions of the reconstituted medicine, see section 6.3.

6.5 Nature and contents of container

MACROPEN 500: HDPE bottle and screw cap with induction sealing containing 15 or 100 capsules.

MACROPEN S: Glass bottles containing powder for the preparation of 100 mL of 250 mg/5 mL suspension.

6.6 Special precautions for disposal and other handling

Any unused product or waste material should be disposed of in accordance with local requirements.

7 HOLDER OF CERTIFICATE OF REGISTRATION

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8 REGISTRATION NUMBER(S)

MACROPEN 500: 27/20.1.2/0106

MACROPEN S: 27/20.1.2/0107

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

MACROPEN 500: 29 January 1993

MACROPEN S: 01 June 1993

10 DATE OF REVISION OF TEXT

30 January 2026