1.5.5.1 Clean Professional Information for medicines for human use

SCHEDULING STATUS

S4

1 NAME OF THE MEDICINE

MACROPEN 500 (capsules)

MACROPEN S (powder for suspension)

2 QUALITIVE AND QUANTITIVE COMPOSITION

MACROPEN 500:

Gelatin capsules containing amoxycillin trihydrate equivalent to 250 mg amoxycillin 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 amoxycillin trihydrate equivalent to 125 mg amoxycillin 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 sweeteners: Saccharin sodium 0,458 g

For full list of excipients, see section 6.1.

1.5.5.1 Clean Professional Information for medicines for human use

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.

1.5.5.1 Clean Professional Information for medicines for human use

Method of administration

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

4.3 Contraindications

- Hypersensitivity to the active substances or to any of the 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 monohydrate 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 (anaphylaxis) reactions 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.
- 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.

Skin reactions:

- The occurrence at the treatment initiation of a feverish generalised erythema associated with pustula may be a symptom of acute generalised exanthemous pustulosis (AEGP). 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 monohydrate 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. 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's 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.
- At high doses, adequate fluid intake and urinary output must be maintained to minimise the possibility of crystalluria.

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 monohydrate 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)*.

Sucrose warning for MACROPEN 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 suspension:

- MACROPEN 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 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 monohydrate 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 increases substantially 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 coadministration 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. Concomitant 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.

Methotrexate

- Interaction between MACROPEN and methotrexate leading to methotrexate toxicity has been reported. Serum methotrexate levels should be closely monitored in patients who receive MACROPEN and methotrexate simultaneously *(see section 4.4*).

Oral hormonal 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.

1.5.5.1 Clean Professional Information for medicines for human use

4.7 Effects on ability to drive and use machines

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 & section 4.8*).

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**	
	Less frequent	**Frequency not known**
Infections and Infestations:	*Mucocutaneous candidosis*	
Blood and the lymphatic system disorders [3]:		Anaemia Thrombocytopenia Thrombocytopenic purpura Eosinophilia Agranulocytosis

		Leucopenia (including severe neutropenia or agranulocytosis) Prolongation of bleeding time and prothrombin time *(see section 4.4)*
Immune system disorders (*see section 4.3 & 4.4*)	Serum sickness-like syndrome Hypersensitivity vasculitis Anaphylaxis (*see section 4.4*)[4] Angioneurotic oedema	
Nervous system disorders:	Dizziness Convulsions *(see section 4.4)*[5] Hyperkinesia	Aseptic meningitis
Gastrointestinal disorders:	Diarrhoea Nausea Vomiting Black hairy tongue Antibiotic-associated colitis (including pseudomembranous colitis and haemorrhagic colitis) (*see section 4.4)* Tooth discolouration[1]	

Hepato-biliary disorders	Hepatitis and cholestatic jaundice	Rises in AST and/or ALT
Skin and subcutaneous tissue disorders [2]	Erythematous maculopapular rash Pruritis Urticaria Erythema multiforme Bullous exfoliative dermatitis Toxic epidermal necrolysis Stevens-Johnson syndrome Acute generalised pustulosis Lyell's syndrome Acute generalised exanthemous pustulosis (AGEP) (*see section 4.4*) Drug reaction with eosinophilia and systemic symptoms (DRESS) Jarisch-Herxheimer reaction (*see section 4.4*)	
Renal and urinary disorders:	Interstitial nephritis Crystalluria (*see section 4.9*)	

[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.

Post marketing disorders:

Metabolism and nutrition disorders:

- High anion gap metabolic acidosis, when MACROPEN is used concomitantly with paracetamol, has been reported (*see section 4.5*).

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.

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.

Treatment:

1.5.5.1 Clean Professional Information for medicines for human use

Treatment should be symptomatic and supportive.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

A. 20.1.2 Penicillins

Pharmacotherapeutic group: Penicillins with extended spectrum; ATC code: J01CA04

(a) **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.

(b) **Absorption**

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

(c) **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

MACROPEN S:

Sucrose

Sodium citrate anhydrous

Disodium edetate

Sodium benzoate

Xantham gum

Saccharin sodium (dried)

Capsaroma DC 117 (peppermint)

Capsaroma DC 100 (orange)

Lemon DC 101

Raspberry DC 107

Glycamil (monoammonium glycyrrhizinate)

Peach apricot

Colour spectracol Quinolene yellow CI 47005

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

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

6.4 Special precautions for storage

MACROPEN 500:

Store at or below 25 ºC.

1.5.5.1 Clean Professional Information for medicines for human use

Keep the container tightly closed.

Store in a cool, dry place.

MACROPEN S:

Powder:

Store at or below 25 ºC.

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:

Glass bottles 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 of a used medicine or waste materials derived from such medicine and other handling of the product

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

7 HOLDER OF THE CERTIFICATE OF REGISTRATION

Viatris South Africa (Pty) Ltd.

4 Brewery Street,

Isando, Johannesburg

1.5.5.1 Clean Professional Information for medicines for human use

Gauteng

1609

Republic of South Africa

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

29 January 1993

10 DATE OF REVISION OF TEXT

04 November 2024