PROFESSIONAL INFORMATION - APPROVED

SCHEDULING STATUS:

S4

1. NAME OF THE MEDICINE:

ULTRAMOX 500 capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION:

Each capsule contains amoxicillin trihydrate equivalent to 500 mg amoxicillin.

Sugar free

For full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Capsules

Pink/burgundy capsules overprinted "ULTRAMOX 500".

4. CLINICAL PARTICULARS:

4.1 Therapeutic indications

Infections caused by susceptible, non-penicillinase-producing organisms including:

- Upper respiratory tract infections
- Lower respiratory tract infections
- Otitis media
- Upper urinary tract infections
- Lower urinary tract infections
- Skin and soft tissue infections
- Gonorrhoea

- Non-specific urethritis
- Typhoid Fever
- Gastro-intestinal tract infections

4.2 Posology and method of administration

Posology

The average adult dose for ULTRAMOX is 750 mg - 1,5 g per day, but in serious infections up to 6 g daily has been administered without harmful effects.

(a) General dosages:

Adults: 250 mg (1 x 250 mg capsule) three times a day.

In severe infections these dosages may safely be increased.

(b) Specific Dosages:

Indications	Daily Dosages		Duration
	Adults	Children	4 – 5 days
Gastro intestinal tract infections	1 – 2 g	-	
Acute Typhoid Fever	4 g	-	14 days
	-	100 mg/kg	21 days
Gonorrhoea	2 – 3 g	-	stat

** Gonorrhoea: Some venereologists have found that greater clinical success has been achieved by using probenecid in conjunction with ULTRAMOX therapy.

Renal impairment:

Patients with renal insufficiency may possibly require a reduced dose.

During treatment with high doses of ULTRAMOX, an adequate fluid intake and urinary output must be maintained (see section 4.4).

In-dwelling catheters should be checked regularly since the presence of high urinary concentrations of ULTRAMOX can cause precipitation of the product in urinary catheters (see section 4.4).

Method of administration

ULTRAMOX 500 is for oral administration. It is not affected by food. Swallow with water without opening the capsule.

4.3 Contraindications

Hypersensitivity to the penicillins or any of the cephalosporins or to any of the excipients listed in section 6.1.

Amoxicillin as contained in ULTRAMOX is penicillin and should not be given to patients with a history of hypersensitivity to β-lactam antibiotics (e.g. carbapenem or monobactam). Potential cross allergy to other beta-lactams such as cephalosporins should be taken into account.

4.4 Special warnings and precautions for use

Hypersensitivity reactions:

- Serious and occasionally fatal hypersensitivity (anaphylactoid) reactions have been reported in patients on penicillin therapy. Although anaphylaxis is more frequent following parenteral therapy, it has occurred in patients on oral penicillins.
- Hypersensitivity reactions can also progress to Kounis syndrome, a serious allergic reaction that can result in myocardial infarction *(see section 4.8).*

- Before commencing therapy with any penicillin as contained in ULTRAMOX, careful inquiry should be made concerning previous hypersensitivity reactions to penicillins, cephalosporins, or other allergies *(see section 4.3*).
- If an allergic reaction occurs, appropriate therapy should be instituted and ULTRAMOX 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 (1-4 hours after medicine intake) 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:

- ULTRAMOX should be avoided if infectious mononucleosis and glandular fever is suspected since the occurrence of a morbilliform rash has been associated with this condition following the use of amoxicillin.

Lymphatic leukaemia:

- ULTRAMOX should preferably not be used in patients with lymphatic leukaemia, since they are especially susceptible to ampicillin-induced skin rashes.
- 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 ULTRAMOX discontinuation and contraindicates any subsequent administration.

Overgrowth of non-susceptible microorganisms:

- Prolonged use may also occasionally result in overgrowth of non-susceptible organisms.
- Antibiotic associated *Pseudomembranous colitis* has been reported. 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 ULTRAMOX use (this may occur up to several weeks after cessation of ULTRAMOX therapy). If prolonged or significant diarrhoea occurs or the patient experiences abdominal cramps, treatment with ULTRAMOX should be discontinued immediately.

- Anti-peristaltic medicines are contraindicated in this situation.

Anticoagulants:

- Prolongation of prothrombin time has been reported rarely in patients receiving ULTRAMOX. Appropriate monitoring should be undertaken when anticoagulants are prescribed concurrently.

Hepatic impairment:

- ULTRAMOX should be used with caution in patients with evidence of hepatic dysfunction.
- Changes in liver function tests have been observed in some patients receiving ULTRAMOX.
- Transient hepatitis and cholestatic jaundice have been reported.

Renal impairment:

- The dose should be reduced in patients with renal failure.

Prolonged therapy:

- Periodic assessment of renal, hepatic, and haematopoietic functions should be made during prolonged therapy.
- The possibility of superinfections with mycotic or bacterial pathogens should be kept in mind during therapy. If superinfections occur ULTRAMOX should be discontinued and/or appropriate therapy instituted.

Jarisch-Herxheimer reaction:

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

Allopurinol:

- ULTRAMOX should preferably not be used in patients treated with allopurinol since they are especially susceptible to ampicillin-induced skin rashes (*see section 4.5*).

Crystalluria:

- In patients with reduced urine output, crystalluria (including acute renal injury) has been observed. The presence of high urinary concentrations of ULTRAMOX can cause precipitation of the product in urinary catheters. Therefore, catheters should be visually inspected at intervals. When high doses are administered, adequate fluid intake and urinary output must be maintained *(see section 4.8 and 4.9).*

Convulsions:

- Convulsions may occur in patients with impaired renal function, 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*).

Non-susceptible microorganisms:

- The use of ULTRAMOX may lead to the appearance of resistant strains of organisms and sensitivity testing should therefore be carried out wherever possible, to ensure the appropriateness of the therapy.
- ULTRAMOX 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 ULTRAMOX. 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 amoxicillin is used (see sub-header ‘Skin reactions’).

- There is insufficient evidence at present to show that ULTRAMOX penetrates into the cerebrospinal fluid in therapeutic quantities and it should, therefore, not be used in the treatment of cerebrospinal infections.

Effects on laboratory tests:

- Since high urine concentrations of amoxicillin as contained in ULTRAMOX 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 (*see section 4.5*).

Oral contraceptives:

- 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 amoxicillin as contained in ULTRAMOX.

Oral hormonal contraceptives:

- ULTRAMOX may reduce the efficacy of oral contraceptives and patients should be warned accordingly *(see section 4.5*).

Use in lactation:

- ULTRAMOX is excreted in breast milk and should be used with caution when administered to lactating women (*see section 4.6)*.

4.5 Interaction with other medicines and other forms of interaction

Due to amoxicillin's effect on intestinal flora, the absorption of other medicines may be affected.

Allopurinol:

The concomitant administration of allopurinol and ampicillin substantially increases the incidence of skin rashes in patients receiving both medicines as compared to patients receiving

ampicillin alone (*see section 4.4)*. It is not known whether this potentiation of ampicillin rashes is due to allopurinol or the hyperuricaemia present in these patients.

Digoxin:

The absorption of concurrently administered digoxin may be increased during treatment with ULTRAMOX.

Anticoagulants:

Concomitant administration of ULTRAMOX and anticoagulants e.g. coumarin 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 internationally normalised ratio should be carefully monitored with the addition or withdrawal of ULTRAMOX.

Probenecid:

Probenecid decreases the renal tubular secretion of ULTRAMOX.

Concurrent use with ULTRAMOX may result in increased and prolonged blood concentrations of ULTRAMOX.

Tetracyclines:

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

Interaction with Laboratory tests:

It is recommended that when testing for the presence of glucose in urine during ULTRAMOX treatment, enzymatic glucose oxidase methods should be used. Due to the high urinary concentrations of ULTRAMOX, false positive readings are common with chemical methods (*see section 4.4*).

Methotrexate:

Interaction between ULTRAMOX and methotrexate leading to methotrexate toxicity has been reported.

Serum methotrexate levels should be closely monitored in patients who receive ULTRAMOX and methotrexate simultaneously (*see section 4.4*). ULTRAMOX decreases the renal clearance of methotrexate, probably by competition at the common tubular secretion system.

Oral hormonal contraceptives:

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

Other forms of interactions:

Forced diuresis leads to a reduction in blood concentrations by increased elimination of ULTRAMOX.

ULTRAMOX 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

ULTRAMOX may reduce the efficacy of oral contraceptives and patients should be warned accordingly (*see section 4.5*).

Pregnancy

Safety in pregnancy has not been established.

Breastfeeding

ULTRAMOX is excreted in breast milk and should be used with caution when administered to lactating women.

4.7 Effects on ability to drive and use machines

ULTRAMOX may cause allergic reactions, dizziness or convulsions and may thus have an effect 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 4.8*).

4.8 Undesirable effects

Summary of the safety profile

The most frequently reported adverse side effects are diarrhoea, nausea, vomiting, indigestion, abdominal pain, skin rashes, urticaria and erythema multiforme, vaginitis, abnormal taste, headache, dizziness, tiredness and hot flushes.

Tabulated list of adverse reactions

System Organ Class	**Undesirable effects**	
	Less frequent	**Frequency not known**
Infections and Infestations:	Mucocutaneous candidosis	
Blood and lymphatic system disorders[3]:		Haemolytic anaemia, Reversible thrombocytopenia, Thrombocytopenic purpura, Eosinophilia, Reversible leucopenia Agranulocytosis Leucopenia (including severe neutropenia or agranulocytosis) Prolongation of bleeding time and prothrombin time (see section 4.4)[6]

Immune system disorders (*see section 4.3 & 4.4*) [8] **:**	Serum sickness-like syndrome, Hypersensitivity vasculitis, Anaphylaxis Angioneurotic oedema	
Nervous system disorders:	Dizziness, Headache, Reversible hyperactivity, Convulsions (see section 4.4)[9] Hyperkinesia	Aseptic meningitis
Cardiac disorders		Kounis syndrome (see section 4.4)
Gastrointestinal disorders[1]:	Diarrhoea, Nausea, Vomiting, Gastritis Stomatitis, Glossitis, Enterocolitis Black hairy tongue, Antibiotic-associated colitis (including pseudomembranous colitis and haemorrhagic colitis) (see section 4.4), Tooth discolouration[7]	Drug-induced enterocolitis syndrome (see section 4.4)

Hepatobiliary disorders[4]:	Hepatitis and cholestatic jaundice.	Rises in AST and/or ALT [5]
Skin and subcutaneous tissue disorders[2]:	Skin rash, 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)	Linear IgA disease
Renal and urinary tract disorders:	Interstitial nephritis	Crystalluria (including acute renal injury) (see section 4.9)

[1] If gastro-intestinal reactions are evident, they may be reduced by taking ULTRAMOX at the start of a meal.

[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. A slight thrombocytosis was noted in less than 1 % of the patients treated with ULTRAMOX.

[4] The events may be severe and occur predominantly in adult or elderly patients. Signs and symptoms usually occur during or shortly after treatment, but in some cases may not become apparent until several weeks after treatment has ceased.

The hepatic effects are usually reversible. However, in extremely rare circumstances, death has been reported. These have almost always been cases associated with serious underlying disease or concomitant medication.

[5] A moderate rise in Aspartate transaminase (AST) or SGOT and/or Alanine transaminase (ALT) or SGPT has been noted in patients treated with ULTRAMOX, but the significance of these findings is unknown.

[6] Appropriate monitoring should be undertaken when anticoagulants are prescribed concomitantly.

[7] It can be removed by brushing.

[8] Serious and occasional fatal hypersensitivity (anaphylactic) reactions and angioneurotic oedema can occur. In the event of an anaphylactic reaction, immediate treatment with adrenalin, oxygen, corticosteroids and antihistamines should be initiated.

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

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 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:

- Oral administration can cause gastro-intestinal symptoms such as transient diarrhoea, nausea and colic which are dose-related and a result of local irritation and not toxicity.

Treatment:

- If encountered, gastro-intestinal symptoms and disturbances of the fluid and electrolyte balance may be evident.
- They may be treated symptomatically and supportive with attention to the water/electrolyte balance.
- In the absence of an adequate fluid intake and urinary output, crystalluria, in some cases leading to renal failure, is a possibility.
- Amoxicillin may be removed from the circulation by haemodialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

A 20.1.2 Penicillins

Pharmacotherapeutic group: Penicillins with extended spectrum;

ATC code: J01CA04

(a) Bacteriology

(i) Spectrum

Amoxicillin is a penicillinase-susceptible penicillin and is, therefore, contraindicated in infections caused by penicillinase-producing organisms. ULTRAMOX exhibits *in vitro*, and in experimental animals *in vivo*, bactericidal activity against a wide range of Gram-negative and Gram-positive organisms including:

Gram-positive bacteria:	Gram-negative bacteria
Staphylococcus aureus	*Neisseria gonorrhoeae*
(penicillin-sensitive)	*Neisseria meningitidis*
Streptococcus pyogenes	*Haemophilus influenzae*
Streptococcus viridans	*Bordetella pertussis*
Streptococcus faecalis	*Escherichia coli*
Diplococcus pneumoniae	*Salmonella typhi*
Corynebacterium species	*Salmonella species*
Clostridium species	*Shigella species*
Bacillus anthracis	*Brucella species*
	Proteus mirabilis

(ii) Bactericidal Action

In vitro: ULTRAMOX exerts a more rapid bactericidal action than other beta-lactam antibiotics against susceptible Escherichia coli. At similar inhibitory concentrations, ULTRAMOX results in a greater degree of bacterial cell lysis than other beta-lactam antibiotics against susceptible *E. coli*.

In vivo: ULTRAMOX has been shown to exert greater therapeutic activity than ampicillin at similar blood levels in certain experimental infections.

5.2 Pharmacokinetic properties

Absorption

ULTRAMOX is extremely well absorbed orally. After oral administration, there is no significant difference between the peak serum levels in fasting and non-fasting subjects. The presence of food does not interfere with the absorption of ULTRAMOX. ULTRAMOX may, therefore, be taken with meals.

There is a linear/dose response in peak serum levels after oral administration.

Distribution

i) Sputum: The concentration of amoxicillin is sputum does not decrease as occurs with ampicillin as purulence subsides.

ii) Bile: ULTRAMOX is present in bile obtained from a common bile duct drain of a healthy gall-bladder, however biliary levels are lower when the gall-bladder is diseased and absent in the presence of biliary tract obstruction.

iii) Urine: The average concentration of ULTRAMOX in urine collected during the first six hours after a 250 mg oral dose, is 580 µg/ml.

(iv) CSF: There is insufficient evidence at present to show that ULTRAMOX penetrates into the cerebra-spinal fluid in therapeutic quantities and it should, therefore, not be used in the treatment of cerebra-spinal infections.

Elimination

i) Renal: Approximately 60 % of an oral dose of ULTRAMOX is excreted unchanged in the active form into the urine within six hours.

(ii) Biliary: A variable percentage of ULTRAMOX is excreted into the bile.

Probenecid

Even higher ULTRAMOX serum levels may be achieved after oral administration to patients with normal renal function, by the simultaneous administration of a renal blocking agent such as probenecid. Probenecid should not be given in the presence of abnormal renal function.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule contents

Sodium lauryl sulphate

Pregelatinised maize starch

Magnesium stearate

Capsule shell:

Gelatine

Erythrosine (CI no. 45430)

Quinoline yellow (CI no. 47005)

Titanium dioxide (CI no. 77891)

Sunset yellow (15985)

Brilliant blue (CI no. 42090).

6.2 Incompatibilities

Not applicable

6.3 Shelf life

2 years

6.4 Special precautions for storage

Store at or below 25 °C in a dry place.

6.5 Nature and contents of container

Blister or patient ready pack containing 15 or 100 capsules.

HDPE containers containing 15 or 100 or 500 capsules.

6.6 Special precautions for disposal

No special requirements.

7 HOLDER OF CERTIFICATE OF REGISTRATION

Oethmaan Biosims (Pty) Ltd

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