SCHEDULING STATUS:

S4

1. NAME OF THE MEDICINE:

ALLMOX 250 CAPSULES

ALLMOX 500 CAPSULES

2. QUALITATIVE AND QUANTITATIVE COMPOSITION:

ALLMOX 250 contains amoxicillin trihydrate the equivalent of 250 mg amoxicillin per capsule.

ALLMOX 500 contains amoxicillin trihydrate the equivalent of 500 mg amoxicillin per capsule.

3. PHARMACEUTICAL FORM:

ALLMOX 250: Purple/blue hard, size 2, gelatine capsules containing a white granular powder.

ALLMOX 500: Purple/blue hard, size 0, gelatine capsules containing a white granular powder.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

- Respiratory tract infections (upper and lower): sinusitis, pharyngitis, epiglottitis, acute and chronic bronchitis and acute typical pneumonia.
- Otitis media;
- Urinary tract infections;
- Uncomplicated gonococcal infections;
- Meningitis (sensitivity tests must be performed);
- Gastrointestinal infections including salmonella and typhoid;
- Uncomplicated gastro-enteritis and enteric fever;
- Miscellaneous: Skin and soft tissue infections, bacteraemia and as adjunct in the treatment of sepsis caused by gram-negative bacteria.

4.2 Posology and method of administration

Posology

Adults and children over 12 years

- 250 mg to 500 mg every 8 hours depending on the severity of the infection.
- Gonorrhoea: 3 g amoxicillin (e.g. six ALLMOX 500 capsules) as a single dose usually combined with 1 g probenecid.
- In the treatment of beta-haemolytic streptococcal infections, a therapeutic dose should be administered for at least 10 days.

Special Populations

Renal impairment.

Patients with renal insufficiency should have their dosage adapted according to creatinine clearance.

Creatinine clearance dosage of amoxicillin (Allmox)

Creatinine clearance	**Dosage**
> 30 ml / min	Usual dosage
11 – 30 ml / min	2/3 of usual dose
>10 ml / min	1/3 of usual dose

Method of administration

ALLMOX is for oral use.

Swallow with water without opening capsule.

Absorption of ALLMOX is unimpaired by food.

4.3 Contraindications

- Hypersensitivity to amoxicillin, to any of the penicillins or to any of the excipients (see section 6.1)
- History of a severe immediate hypersensitivity reaction (e.g. anaphylaxis) to another beta-lactam medicine (e.g. a cephalosporin, carbapenem or monobactam).
- ALLMOX should not be given to patients with infectious mononucleosis, since they are especially susceptible to amoxicillin-induced skin rashes, patients with lymphatic leukaemia and patients with hyperuricaemia being treated with allopurinol, may be at increased risk of developing skin rashes.

4.4 Special warnings and precautions for use

Hypersensitivity reactions

Serious and occasionally fatal hypersensitivity reactions (including anaphylactoid and severe cutaneous adverse reactions) have been reported in patients on penicillin therapy. These reactions are more likely to occur in individuals with a history of penicillin hypersensitivity and in atopic individuals. Hypersensitivity reactions can also progress to Kounis syndrome, a serious allergic reaction that can result in myocardial infarction (see section 4.8). Presenting symptoms of such reactions can include chest pain occurring in association with an allergic reaction to amoxicillin (see section 4.8). If an allergic reaction occurs, ALLMOX therapy must be discontinued, and appropriate alternative therapy instituted.

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 drug 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.

Non-susceptible microorganisms

Amoxicillin 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 amoxicillin (see section 5.1). This particularly applies when considering the treatment of patients with urinary tract infections and severe infections of the ear, nose and throat.

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).

Renal impairment

In patients with renal impairment, the dose should be adjusted according to the degree of impairment (see section 4.2).

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 (AGEP, see section 4.8). This reaction requires amoxicillin discontinuation and contraindicates any subsequent administration.

Amoxicillin 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.

Jarisch-Herxheimer reaction

The Jarisch-Herxheimer reaction has been reported following amoxicillin treatment of syphilis (see section 4.8). Caution should be used when treating syphilis with amoxicillin.

The Jarisch-Herxheimer reaction has been reported following amoxicillin treatment of Lyme disease (see section 4.8). It results directly from the bactericidal activity of amoxicillin on the causative bacteria of Lyme disease, the spirochaete Borrelia burgdorferi. Patients should be reassured that this is a common and usually self-

limiting consequence of antibiotic treatment of Lyme disease.

Overgrowth of non-susceptible microorganisms

Prolonged use may result in overgrowth of non-susceptible organisms. Antibiotic-associated colitis has been reported with nearly all antibacterial medicines and may range in severity from mild to life threatening (see section 4.8). Therefore, it is important to consider this diagnosis in patients who present with diarrhoea during, or subsequent to, the administration of any antibiotics. Should antibiotic-associated colitis occur, amoxicillin should immediately be discontinued, a medical practitioner consulted, and an appropriate therapy initiated. Anti-peristaltic medicines are contraindicated in this situation.

Prolonged therapy

Periodic assessment of organ system functions; including renal, hepatic and hematopoietic function is advisable during prolonged therapy. Elevated liver enzymes and changes in blood counts have been reported (see section 4.8).

Anticoagulants

Prolongation of prothrombin time has been reported in patients receiving amoxicillin. Appropriate monitoring should be undertaken when anticoagulants are prescribed concomitantly. Adjustments in the dose of oral anticoagulants may be necessary to maintain the desired level of anticoagulation (see section 4.5 and 4.8).

Crystalluria

In patients with reduced urine output, crystalluria has been observed, 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 (see section 4.8 and 4.9).

Interference with diagnostic tests

Elevated serum and urinary levels of amoxicillin 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 estriol in pregnant women.

4.5 Interaction with other medicines and other forms of interaction

Probenecid

Probenecid decreases the renal tubular secretion of amoxicillin. Concomitant use of probenecid may result in increased and prolonged blood levels of amoxicillin.

Allopurinol

Concurrent use 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 amoxicillin.

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 normalised ratio (INR) in patients maintained on acenocoumarol or warfarin and prescribed a course of amoxicillin. If co-administration is necessary, the prothrombin time or international normalised ratio should be carefully monitored with the addition or withdrawal of amoxicillin. Moreover, adjustments in the dose of oral anticoagulants may be necessary (see sections 4.4 and 4.8).

Methotrexate

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

Oral contraceptives

Amoxicillin may decrease the efficacy of oestrogen-containing oral contraceptives. Amoxicillin may affect the absorption of other medicines, due to its effect on the gastrointestinal flora.

4.6 Fertility, pregnancy and lactation

Pregnancy

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.

Breastfeeding

Amoxicillin is 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 that breastfeeding might have to be discontinued.

Fertility

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

4.7 Effects on ability to drive and use machines

Amoxicillin may be associated with allergic reactions, dizziness, and convulsions. Therefore, patients must be cautious when driving or using machines and should be advised not to drive or operate machinery if they experience these symptoms (see section 4.8).

4.8 Undesirable effects

Infections and infestations

Less frequent: Mucocutaneous candidiasis

Blood and lymphatic system disorders

Less frequent: Reversible leukopenia (including severe neutropenia or agranulocytosis), reversible thrombocytopenia and haemolytic anaemia, prolongation of bleeding time and prothrombin time (see section 4.4).

Immune system disorders

Less frequent: Severe allergic reactions, including angioedema, anaphylaxis, serum sickness and hypersensitivity vasculitis (see section 4.4)

Frequency unknown: Jarisch-Herxheimer reaction (see section 4.4)

Nervous system disorders

Less frequent: Hyperkinesia, dizziness and convulsions (see section 4.4)

Gastrointestinal disorders

Frequent: Diarrhoea, nausea

Less frequent: Vomiting, antibiotic associated colitis (including pseudomembraneous colitis and haemorrhagic colitis see section 4.4), black hairy tongue.

Frequency unknown: Drug-induced enterocolitis syndrome

Hepato-biliary disorders

Less frequent: Hepatitis and cholestatic jaundice, a moderate rise in AST and/or ALT

Skin and subcutaneous tissue disorders

Frequent: Skin rash

Less frequent: Urticaria, pruritus, skin reactions such as erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis, bullous and exfoliative dermatitis, acute generalised exanthematous pustulosis (AGEP) (see section 4.4), drug reaction with eosinophilia and systemic symptoms (DRESS)

Frequency unknown: Linear IgA disease

Cardiac Disorders

Frequency unknown: Kounis syndrome

Renal and urinary disorders

Less frequent: Interstitial nephritis, crystalluria (see sections 4.4 and 4.9)

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 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

Symptoms

Gastrointestinal symptoms (such as nausea, vomiting and diarrhoea) 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

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

ALLMOX can be removed from the circulation by haemodialysis (see section 4.2).

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: penicillins with extended spectrum.

ATC code: J01CA04

Mechanism of action

Amoxicillin is a penicillinase-susceptible semisynthetic penicillin (beta-lactam antibiotic). It is bactericidal in vitro against a broad spectrum of gram-positive and gram-negative pathogens that inhibit 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 medicine for the target.

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

Inherently resistant organisms†
Gram-positive aerobes: *Enterococcus faecium*†
Gram-negative aerobes: *Acinetobacter spp.* *Enterobacter spp.* *Klebsiella spp.* *Pseudomonas spp.* *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

5.2 Pharmacokinetic properties

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 (Tmax) is approximately one hour.

The absorption is not influenced by simultaneous food intake.

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.

Amoxicillin 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).

Haemodialysis can be used for elimination of amoxicillin (see section 4.2).

Special populations

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.

Renal impairment

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

Hepatic impairment

Hepatic impaired patients should be dosed with caution and hepatic function monitored at regular intervals (see section 4.2).

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule content:

Magnesium stearate

Capsule shell:

Purple Indigo Carmine,

Erythrosine ,

Blue Indigo Carmine

Gelatine

6.2 Incompatibilities

Not applicable

6.3 Shelf life

24 months

6.4 Special precautions for storage

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

KEEP OUT OF REACH OF CHILDREN

6.5 Nature and contents of container

ALLMOX is packed in:

15's: HDPE containers and in LDPE patient ready packs

100's: HDPE containers with screw caps

500's HDPE containers with screw caps

1000's HDPE containers with screw caps

6.6 Special precautions for disposal

No special requirements for destruction

7. HOLDER OF CERTIFICATE OF REGISTRATION

Innovata Pharmaceuticals

Crownwood Office Park

100 Northern Parkway

Ormonde

Johannesburg

2091

South Africa

8.REGISTRATION NUMBERS

Allmox 250: Y/20.1.2/161

Allmox 500: Y/20.1.2/162

9. DATE OF FIRST AUTHORIZATION/RENEWAL OF THE AUTHORIZATION

Date of registration: 22 October 1991

10.Date of revision of the text

02/09/2024