1.5.5 Proposed Professional Information for Medicines for Human Use

SCHEDULING STATUS

S4

1.NAME OF MEDICINE

ALLMOX S powder for oral suspension

ALLMOX SF powder for oral suspension

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

ALLMOX S 125 mg/5ml

Each 5 ml of reconstituted suspension contains amoxycillin trihydrate equivalent to 125 mg amoxycillin.

Contains sugar: sorbitol 12 mg per 5 ml

Contains sweetener: saccharin sodium 9mg/5 ml

ALLMOX SF 250 mg/5ml

Each 5 ml of reconstituted suspension contains amoxycillin trihydrate equivalent to 250 mg amoxycillin.

Contains sugar: sorbitol 12 mg per 5 ml

Contains sweetener: saccharin sodium 9mg/5 ml

For full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Powder for oral suspension

ALLMOX is a white to off-white powder forming an orange suspension on constitution with water. The resulting suspension has a characteristic flavour.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Infections due to susceptible non-penicillinase producing organisms including (see sections 4.4 and 5.1):

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 gastroenteritis 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

Children under 12 years

• The normal dose for children 6 months to 10 years of age is equivalent of 125 mg (i.e. 5 ml of 125 mg/5 ml) three times a day.

• 0 – 6 months: 62,5 mg three times a day.

Adults and children over 12 years

• **ALLMOX S** 125 mg/5 ml every 8 hours (three times a day).

• Severe infections: **ALLMOX SF** 250 mg/ 5 ml every 8 hours (three times a day).

• Gonorrhoea: 3 g amoxicillin 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.

Method of administration

ALLMOX oral suspension is for oral use. For instructions on reconstitution of the medicine before administration, see section 6.6.

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 agent (e.g. a cephalosporin, carbapenem or monobactam).

ALLMOX should not be given to patients with infectious mononucleosis, since they are especially susceptible to amoxycillin-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

Before initiating therapy with **ALLMOX**, careful enquiry should be made concerning previous hypersensitivity reactions to penicillins, cephalosporins or other beta-lactam medicines (see sections 4.3 and 4.8). 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. If an allergic reaction occurs, **ALLMOX** therapy must be discontinued and appropriate alternative therapy instituted.

Non-susceptible microorganisms

ALLMOX 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 **ALLMOX** (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 **ALLMOX** discontinuation and contraindicates any subsequent administration. **ALLMOX** 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 **ALLMOX**. 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, **ALLMOX** should immediately be discontinued, a medical

practitioner consulted and an appropriate therapy initiated.

Antiperistaltic medicines are contraindicated in this situation.

Prolonged therapy

Periodic assessment of organ system functions; including renal, hepatic and haematopoietic 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 **ALLMOX**, 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 **ALLMOX** treatment, enzymatic glucose oxidase methods should be used.

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

ALLMOX contains sorbitol

Sorbitol may cause gastrointestinal discomfort and mild laxative effect.

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

Concomitant use of allopurinol during treatment with **ALLMOX** can increase the likelihood of allergic skin reactions.

Tetracyclines

Tetracyclines and other bacteriostatic medicines may interfere with the bactericidal effects of **ALLMOX**. 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 **ALLMOX**. If co-administration is necessary, the prothrombin time or international normalised ratio should be carefully monitored with the

addition or withdrawal of **ALLMOX**. Moreover, adjustments in the dose of oral anticoagulants may be necessary (see sections 4.4 and 4.8).

Methotrexate

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

Oral contraceptives

ALLMOX may decrease the efficacy of oestrogen-containing oral contraceptives. **ALLMOX** may affect the absorption of other medicines due to its effect on the gastro-intestinal 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 **ALLMOX** 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 teratogenic effects on fertility.

4.7 Effects on ability to drive and use machines

ALLMOX 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.

4.8 Undesirable effects

a. Summary of the safety profile

The most commonly reported adverse reactions (ADRs) are diarrhoea, nausea and skin rash.

b. Tabulated summary of adverse reactions

The ADRs derived from clinical studies and post-marketing surveillance with amoxicillin, presented by MedDRA System Organ Class are listed below:

MedDRA system organ class	**Frequency**	**Adverse reactions**
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
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)
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. Healthcare professionals are asked to report any suspected adverse reactions to SAHPRA via the “6.04 Adverse

Drug Reaction Reporting Form", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8

4.9 Overdose Symptoms

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.

Amoxicillin can be removed from the circulation by hemodialysis.

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 agent 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.
Gram-negative anaerobes: *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

Colloidal anhydrous silica (E551)

Colour Sunset Yellow Supra CI15985 (E110)

Saccharin sodium (E954)

Sodium citrate (E331)

Sorbitol

Tutti Fruitti Flavour AP0551

Xanthan gum (E415)

6.2 Incompatibilities

No data available.

6.3 Shelf life

Dry powder: 2 years.

Reconstituted suspension: 14 days (stored at 2 °C to 8°C in a refrigerator)

6.4 Special precautions for storage

Dry powder: Store at or below 25 °C, protected from moisture. After reconstitution the product must be stored at 2-8 °C in a refrigerator.

KEEP OUT OF REACH OF CHILDREN

6.5 Nature and contents of container

ALLMOX is packed in a 75 ml and 100 ml HDPE bottle with a white polypropylene child resistant closure with an induction sealing liner in an outer carton.

6.6 Special precautions for disposal and other handling

For reconstitution:

• Check cap seal is intact before use.

• Invert and shake bottle to loosen powder.

Add 64 ml and 85 ml water for 75 ml and 100 ml pack respectively in two portions to the dry mixture in the bottle. Shake well after each addition.

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

7. NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION

Innovata Pharmaceuticals (Pty) Ltd

Crownwood Office Park

100 Northern Parkway

Ormonde

Johannesburg

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South Africa

8. Registration numbers:

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