National Agency for Food & Drug Administration & Control (NAFDAC)

Registration & Regulatory Affairs (R & R) Directorate

SUMMARY OF PRODUCT CHARACTERISTICS (SmPC) BIOMOX 500MG

1.3.1 SUMMARY OF PRODUCT CHARACTERISTICS (SmPC)

1.3.1.1 Name of the product

BIOMOX INJECTION

(AMOXICILLIN SODIUM for INJECTION 500 mg)

1.3.1.2 Qualitative and Quantitative Composition

Each vial contains amoxicillin sodium equivalent to 500mg amoxicillin.

1.3.1.3 Pharmaceutical Form

Powder for injection.

1.3.1.4 Clinical Particular

1.Therapeutic indications

Amoxicillin is indicated for the treatment of the following infections in adults and children (see section 4.2, 4.4 and 5.1):

• Severe infections of the ear, nose and throat (such as mastoiditis, peritonsillar infections, epiglottitis, and sinusitis when accompanied by severe systemic signs and symptoms)
• Acute exacerbations of chronic bronchitis
• Community acquired pneumonia
• Acute cystitis
• Acute pyelonephritis
• Severe dental abscess with spreading cellulitis
• Prosthetic joint infections
• Lyme disease
• Bacterial meningitis
• Bacteremia that occurs in association with, or is suspected to be associated with, any of the infections listed above

Amoxicillin is also indicated for the treatment and prophylaxis of endocarditis.

Consideration should be given to official guidance on the appropriate use of antibacterial agents.

2.Posology and method of administration

Posology

The dose of amoxicillin that is selected to treat an individualinfection should take into account:

• The expected pathogens and their likely susceptibility to antibacterial agents (see section 4.4)

• The severity and the site of the infection

• The age, weight and renal function of the patient; as shown below

The duration of therapy should be determined by the type of infection and the response of the patient, and should generally be as short as possible. Some infections require longer periods of treatment (see section 4.4 regarding prolonged therapy).

Adults and children ≥ 40 kg

Indication*	**Dose***
Severe infections of the ear, nose and throat	750 mg to 2 g every 8 hours, or 2 g every

(such as mastoiditis, peritonsillar infections, epiglottis and sinusitis when accompanied by severe systemic signs and symptoms	12 hours, maximum of 12 g/day
Acute exacerbations of chronic bronchitis	
Community acquired pneumonia	
Acute cystitis	
Acute pyelonephritis	
Severe dental abscess with spreading cellulitis	
Prosthetic joint infections	750 mg to 2 g every 8 hours, or 2 g every 12 hours, maximum of 12 g/day
Prophylaxis of endocarditis	2 g single dose 30 to 60 minutes before procedure.
Treatment of endocarditis	1 g to 2 g every 4 to 6 hours, maximum of 12 g/day
Bacterial meningitis	1 g to 2 g every 4 to 6 hours, maximum of 12 g/day
Lyme disease (see section 4.4)	Late stage (systemic involvement): 2 g every 8 hours
Bacteraemia that occurs in association with, or is suspected to be associated with, any of the infections listed in section 4.1	1 g to 2 g every 4, 6 or 8 hours, maximum of 12 g/day
*Consideration should be given to the official treatment guidelines for each indication.	

Intramuscular

Maximum daily dosage: 4 g/day.

Maximum single dose: 1 g.

Paediatric population

Infants and toddlers >3 months and children <40 kg **Indication***	**Dose***
Severe infections of the ear, nose and throat (such as mastoiditis, peritonsillar infections, epiglottis and sinusitis when accompanied by severe systemic signs and symptoms	20 to 200 mg/kg/day given in 2 to 4 equally divided doses of up to 25 mg/kg or infusions of up to 50 mg/kg
Community acquired pneumonia	
Acute cystitis	
Acute pyelonephritis	
Severe dental abscess with spreading cellulitis	
Prophylaxis of endocarditis	50 mg/kg single dose 30 to 60 minutes before procedure
Treatment of endocarditis	200 mg/kg/day in 3 to 4 equally divided does of up to 25 mg/kg or infusions of up to 50 mg/kg
Bacterial meningitis	100 to 200 mg/kg/day in 3 to 4 equally divided doses of up to 25 mg/kg or

	infusions of up to 50 mg/kg
Lyme disease (see section 4.4)	Early stage: 25 to 50 mg/kg/day in three divided doses for 10 days (range 10 to 21 days) Late stage (systemic involvement): 50 mg/kg/day in three divided doses
Bacteraemia that occurs in association with, or is suspected to be associated with, any of the infections listed in section 4.1	50 to 150 mg/kg/day given in 3 equally divided doses of up to 25 mg/kg or infusions of up to 50 mg/kg
*Consideration should be given to the official treatment guidelines for each indication.	
Neonates ≥ 4 kg and infants up to 3 months **Indication***	**Dose***
Most infections	Usual daily dose of 20 to 150 mg/kg/day given in 3 equally divided doses of up to 25 mg/kg or infusions of up to 50 mg/kg
Treatment of endocarditis	150 mg/kg/day given in 3 equally divided does of up to 25 mg/kg or infusions of up to 50 mg/kg
Bacterial meningitis	150 mg/kg/day given in three divided doses
Lyme disease (see section 4.4)	Early stage: 25 to 50 mg/kg/day in three divided doses for 10 days (range 10 to 21 days) Late stage (systemic involvement): 50 mg/kg/day in three divided doses
Bacteraemia that occurs in association with, or is suspected to be associated with, any of the infections listed in section 4.1	Usual daily dose of 50 to 150 mg/kg/day given in 3 equally divided doses of up to 25 mg/kg or infusions of up to 50 mg/kg
*Consideration should be given to the official treatment guidelines for each indication.	
Premature Neonates ≤ 4 kg **Indication***	**Dose***
Most infections	Usual daily dose of 20 to 100 mg/kg/day given in 2 equally divided doses of up to 25 mg/kg or infusions of up to 50 mg/kg
Treatment of endocarditis	100 mg/kg/day given in two divided does
Bacterial meningitis	100 mg/kg/day given in two divided doses
Lyme disease (see section 4.4)	Early stage: 25 to 50 mg/kg/day in two divided doses for 10 days (range 10 to 21 days) Late stage (systemic involvement): 50 mg/kg/day in two divided doses
Bacteraemia that occurs in association with, or is suspected to be associated with, any of the infections listed in section 4.1	Usual daily dose of 50 to 100 mg/kg/day given in 2 equally divided doses of up to 25 mg/kg or infusions of up to 50 mg/kg
*Consideration should be given to the official treatment guidelines for each indication.	

Intramuscular:

Maximum daily dosage: 120 mg/kg/day as 2 to 6 equally divided doses.

Elderly

No adjustment needed; as for adults.

Renal impairment

	Adults and children ≥ 40 kg		**Children < 40 kg**	
GFR (ml/min)	**Intravenous**	**Intramuscular**	**Intravenous**	**Intramuscular**
Greater than 30	No adjustment	No adjustment	No adjustment	No adjustment
10 to 30	1g stat, then 500 mg to 1g twice daily	500mg every 12 hours	25mg/kg twice daily	15 mg/kg every 12 hours
Less than 10	1g stat, then 500mg/day	500mg/day given as a single dose	25mg/kg/day given as a single dose	15mg/kg/day given as a single dose

In patients receiving haemodialysis and peritoneal dialysis:

Amoxicillin may be removed from the circulation by haemodialysis.

	Haemodialysis		**Peritoneal dialysis**	
	Intravenous	**Intramuscular**	**Intravenous**	**Intramuscular**
Adults and children ≥ 40 kg	1 g at the end of dialysis, then 500 mg every 24 hours	500 mg during dialysis, 500 mg at the end, then 500 mg every 24 hours	1 g stat, then 500 mg/day	500 mg/day given as a single dose
Children < 40 kg	25 mg/kg stat and 12.5 mg/kg at the end of the dialysis, then 25 mg/kg/day	15 mg/kg during and at the end of dialysis, then 15 mg/kg every 24 hours	25 mg/kg/day given as a single dose	15 mg/kg/day given as a single dose

Method of administration

The standard recommended route of administration is by intravenous injection or intravenous infusion. Intramuscular administration should only be considered when the intravenous route is not possible or less appropriate for the patient.

Intravenous

Amoxicillin may be administered either by slow intravenous injection over a period of 3 to 4 minutes directly into a vein or via a drip tube or by infusion over 20 to 30 minutes.

Intramuscular

The maximum single dose is1 g in adults and children > 40 kg.

Do not inject more than 60 mg/kg at one time in children < 40 kg.

3. Contraindications

Hypersensitivity to the active substance or to any of the penicillins.
History of a severe immediate hypersensitivity reaction (e.g. anaphylaxis) to another beta-lactam

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

4.Special warnings and precautions foruse

Hypersensitivity reactions

Before initiating therapy with amoxicillin, careful enquiry should be made concerning previous hypersensitivity reactions to penicillins, cephalosporins or other beta-lactam agents (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, amoxicillin therapy must be discontinued and appropriate alternative therapy instituted.

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 (AEGP, see section 4.8). This reaction requires amoxicillin discontinuation and contra-indicates 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 seen 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 also occasionally result in overgrowth of non-susceptible organisms. Antibiotic-associated colitis has been reported with nearly all antibacterial agents 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 physician consulted and an appropriate therapy initiated. Anti-peristaltic medicinal products are contra-indicated 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 rarely 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 very rarely, 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 sections 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 oestriol in pregnant women.
Important information about excipients
Amoxicillin 500 mg contains 38 mg sodium per vial, equivalent to 1.9% of the WHO recommended maximum daily intake of 2 g sodium for an adult. This should be taken into consideration by patients on a sodium controlled diet.
Lidocaine or benzyl alcohol may be used only when administering amoxicillin by the intramuscular route.

a) Interaction with other medicinal products and other forms ofinteraction

Probenecid
Concomitant use of probenecid is not recommended. Probenecid decreases the renal tubular secretion of amoxicillin. Concomitant use of probenecid may result in increased and prolonged blood levels of amoxicillin.
AllopurinolConcurrent administration of allopurinol during treatment with amoxicillin can increase the likelihood of allergic skin reactions.
Tetracyclines
Tetracyclines and other bacteriostatic drugs 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 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
Penicillins may reduce the excretion of methotrexate causing a potential increase in toxicity.

b) Fertility, pregnancy andlactation

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. Amoxicillin may be used in pregnancy when the potential benefits outweigh the potential risks associated with treatment.
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 breast-fed infant, so that breast-feeding might have to be discontinued. Amoxicillin should only be used during breast-feeding after benefit/risk assessment by the physician in charge.

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

5. Effects on ability to drive and use machines
No studies on the effects on the ability to drive and use machines have been performed. However, undesirable effects may occur (e.g. allergic reactions, dizziness, convulsions), which may influence the ability to drive and use machines (see section 4.8).

6. Undesirableeffects
The most commonly reported adverse drug reactions (ADRs) are diarrhoea, nausea and skin rash. The ADRs derived from clinical studies and post-marketing surveillance with amoxicillin, presented by MedDRA System Organ Class are listed below.
The following terminologies have been used in order to classify the occurrence of undesirable effects.
Very common (≥1/10)
Common (≥1/100, <1/10)
Uncommon (≥1/1000, <1/100)
Rare (≥1/10,000, <1/1000)
Very rare (<1/10,000)
Not known (cannot be estimated from the available data).
Infections and infestations
Very rare: Mucocutaneous candidiasis
Blood and lymphatic system disorders
Very rare: Reversible leucopenia (including severe neutropenia or agranulocytosis), reversible thrombocytopenia and haemolytic anaemia.
Prolongation of bleeding time and prothrombin (see section 4.4)
Immune system disorders
Very rare: Severe allergic reactions, including angioneurotic oedema, anaphylaxis, serum sickness and hypersensitivity vasculitis (see section 4.4).
Not known: Jarisch-Herxheimer reaction (see section 4.4)
Nervous system disorders
Very rare: Hyperkinesia, dizziness and convulsions (see section 4.4).
Gastrointestinal disorders
Clinical Trial Data
*Common: Diarrhoea and nausea.
*Uncommon: Vomiting
Post-marketing Data
Very rare: Antibiotic associated colitis including pseudomembraneous colitis and haemorrhagic colitis (see section 4.4).
Hepato-biliary disorders
Very rare: Hepatitis and cholestatic jaundice; a moderate rise in AST and/or ALT.
Skin and subcutaneous tissue disorders
Clinical Trial Data
*Common: Skin rash
*Uncommon: Urticaria and pruritus
Post-marketing Data
Very rare: 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) and drug reaction with eosinophilia and systemic symptoms (DRESS).
Renal and urinary disorders
Very rare: Interstitial nephritis, crystalluria (see sections 4.4 and 4.9).

* The incidence of these AEs was derived from clinical studies involving a total of approximately 6,000 adult and paediatric patients taking amoxicillin.
Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.

7. Overdose

Symptoms and signs

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).
Amoxicillin has been reported to precipitate in bladder catheters, predominantly after intravenous administration of large doses. A regular check of patency should be maintained (see section 4.4)

Management

Gastrointestinal symptoms may be treated symptomatically, with attention to the water/electrolyte balance.
Amoxicillin can be removed from the circulation by haemodialysis.

1.3.1.5 Pharmacological properties

1.Pharmacodynamic properties

Pharmacotherapeutic group: Penicillins with extended spectrum

ATC code: J01CA04

Mechanism of action

Amoxicillin is a semisynthetic penicillin (beta-lactam antibiotic) that inhibits 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.

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.

2.Pharmacokinetic properties

Absorption

The pharmacokinetic results for studies in which amoxicillin was administered to groups of healthy volunteers given as a bolus intravenous injection are presented below.

Mean pharmacokinetic parameters

Bolus intravenous injection				
Dose administered	Peak serum conc (µg/ml)	T ½ (h)	AUC (µg.h/ml)	Urinary recovery (%, 0 to 6h)
500 mg	32.2	1.07	25.5	66.5
1000 mg	105.4	0.9	76.3	77.4

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.
From animal studies there is no evidence for significant tissue retention of drug-derived material.
Amoxicillin, like most penicillins, can be detected in breast milk (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 dose of amoxicillin. Various studies have found the urinary excretion to be 50 to 85% for amoxicillin over a 24 hour period.
Concomitant use of probenecid delays amoxicillin excretion (see section 4.5).
Gender
Following oral administration of amoxicillin to healthy males and female subjects, gender has no significant impact on the pharmacokinetics of amoxicillin.
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 section 4.2).
Hepatic impairment
Hepatically impaired patients should be dosed with caution and hepatic function monitored at regular intervals.
Pharmacokinetic/pharmacodynamic relationship
The time above the minimum inhibitory concentration (T>MIC) is considered to be the major determinant of efficacy for amoxicillin.

1.3.1.6 Pharmaceutical particulars

1.3.1.6.1:List of excipients

None

1.3.1.6.2:Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

Amoxicillin should not be mixed with blood products, other proteinaceous fluids such as protein hydrolysates, or with intravenous lipid emulsions. If prescribed concomitantly with an aminoglycoside, the antibiotics should not be mixed in the syringe, intravenous fluid container or giving set because loss of activity of the aminoglycoside under these conditions.

Amoxicillin solutions should not be mixed with infusions containing dextran or bicarbonate

1.3.1.6.3:Shelf life

3 years.

Reconstituted vials (for intravenous injection or before dilution for infusion), see section 6.6.

1.3.1.6.4:Special precaution for storage

Store in a cool and dry place below 25℃. Protect from light.

Keep out of reach of children.

1.3.1.6.5:Nature contents of container

Clear glass vials with chlorobutyl rubber closure.

Clear glass ampoule

1.3.1.6.6 Special precautions for disposal and other handling

The reconstituted solution should be used immediately after preparation. Any remaining part should be discarded after reconstituted.