1. NAME OF THE MEDICINAL PRODUCT

Dramoxillin® powder for Oral suspension

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Amoxycillin 125mg/5ml Powder for Oral Suspension contains Amoxycillin Trihydrate BP 125mg.

3. PHARMACEUTICAL FORM

Dry Powder for Oral suspension

4. Clinical particulars

4.1 Therapeutic indications

DrAmoxycillin is indicated for the treatment of the following infections in adults and children:

- Acute bacterial sinusitis
- Acute otitis media
- Acute streptococcal tonsillitis and pharyngitis
- Acute exacerbations of chronic bronchitis
- Community acquired pneumonia
- Acute cystitis
- Asymptomatic bacteriuria in pregnancy
- Acute pyelonephritis
- Typhoid and paratyphoid fever
- Dental abscess with spreading cellulitis
- Prosthetic joint infections
- *Helicobacter pylori* eradication
- Lyme disease

Amoxycillin Powder for Oral Suspension Sugar Free is also indicated for the prophylaxis of endocarditis.
Consideration should be given to official guidance on the appropriate use of antibacterial agents.

4.2 Posology and method of administration

Posology

Posology

The dose of Amoxycillin Powder for Oral Suspension that is selected to treat an individual infection should take into account:

- The expected pathogens and their likely susceptibility to antibacterial agents
- 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***
Acute bacterial sinusitis Asymptomatic bacteriuria in pregnancy	250 mg to 500 mg every 8 hours or 750 mg to 1g every 12 hours
Acute pyelonephritis Dental abscess with spreading cellulitis	For severe infections 750 mg to 1 g every 8 hours
Acute cystitis	Acute cystitis may be treated with 3 g twice daily for one day
Acute otitis media Acute streptococcal tonsillitis and pharyngitis Acute exacerbations of chronic bronchitis	500 mg every 8 hours, 750 mg to 1 g every 12 hours For severe infections 750 mg to 1 g every 8 hours for 10 days
Community acquired pneumonia	500 mg to 1 g every 8 hours
Typhoid and paratyphoid fever	500 mg to 2 g every 8 hours
Prosthetic joint infections	500 mg to 1 g every 8 hours
Prophylaxis of endocarditis	2 g orally, single dose 30 to 60 minutes before procedure
Helicobacter pylori eradication	750 mg to 1 g twice daily in combination with a proton pump inhibitor (e.g. omeprazole, lansoprazole) and another antibiotic (e.g. clarithromycin, metronidazole) for 7 days
Lyme disease	Early stage: 500 mg to 1 g every 8 hours up to a maximum of 4 g/day in divided doses for 14 days (10 to 21 days) Late stage (systemic involvement): 500 mg to 2 g every 8 hours up to a maximum of 6 g/day in divided doses for 10 to 30 days
*Consideration should be given to the official treatment guidelines for each indication	

<u>Children weighing < 40 kg</u>

Amoxycillin Powder for Oral Suspension is recommended for children under six months of age.

Children weighing 40 kg or more should be prescribed the adult dosage.

Recommended doses:

Indication⁺	**Dose⁺**
Acute bacterial sinusitis Acute otitis media Community acquired pneumonia Acute cystitis Acute pyelonephritis Dental abscess with spreading cellulitis	20 to 90 mg/kg/day in divided doses*

Acute streptococcal tonsillitis and pharyngitis	40 to 90 mg/kg/day in divided doses*
Typhoid and paratyphoid fever	100 mg/kg/day in three divided doses
+ Consideration should be given to the official treatment guidelines for each indication. *Twice daily dosing regimens should only be considered when the dose is in the upper range.	

Elderly

No dose adjustment is considered necessary.

Renal impairment

GFR (ml/min)	Adults and children ≥ 40 kg	Children < 40 kg#
greater than 30	no adjustment necessary	no adjustment necessary
10 to 30	maximum 500 mg twice daily	15 mg/kg given twice daily
less than 10	maximum 500 mg/day.	15 mg/kg given as a single daily dose
# In the majority of cases, parenteral therapy is preferred.		

In patients receiving haemodialysis

Amoxycillin may be removed from the circulation by haemodialysis.

	Haemodialysis
Adults and children over 40 kg	500 mg every 24 h Prior to haemodialysis one additional dose of 500 mg should be administered. In order to restore circulating drug levels, another dose of 500 mg should be administered after haemodialysis.
Children under 40 kg	15 mg/kg/day given as a single daily dose (maximum 500 mg). Prior to haemodialysis one additional dose of 15 mg/kg should be administered. In order to restore circulating drug levels, another dose of 15 mg/kg should be administered after haemodialysis.

In patients receiving peritoneal dialysis

Amoxycillin maximum 500 mg/day.

Hepatic impairment

Dose with caution and monitor hepatic function at regular intervals (see sections 4.4 and 4.8).

Method of administration

Amoxycillin Powder for Oral Suspension is for oral use.

Absorption of Amoxycillin Powder for Oral Suspension is unimpaired by food. Therapy can be started parenterally according to the dosing recommendations of the intravenous formulation and continued with an oral preparation.

For instructions on reconstitution of the medicinal product before administration.

4.3 Contraindications

Hypersensitivity to the active substance, to any of the penicillins or to any of the excipients listed in section 6.1.

History of a severe immediate hypersensitivity reaction (e.g. anaphylaxis) to another betalactam agent (e.g. a cephalosporin, carbapenem or monobactam).

4.4 Special warnings and precautions for use

Hypersensitivity reactions

Before initiating therapy with any penicillin, 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, Amoxycillin therapy must be discontinued and appropriate alternative therapy instituted.

Non-susceptible microorganisms

Amoxycillin 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 Amoxycillin. 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.

Renal impairment

In patients with renal impairment, the dose should be adjusted according to the degree of impairment.

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. This reaction requires Amoxycillin discontinuation and contra-indicates any subsequent administration.

Amoxycillin 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 Amoxycillin.

Jarisch-Herxheimer reaction

The Jarisch-Herxheimer reaction has been seen following Amoxycillin treatment of Lyme disease. It results directly from the bactericidal activity of Amoxycillin 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 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. 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, Amoxycillin 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 Amoxycillin. 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.
Crystalluria
In patients with reduced urine output, crystalluria has been observed very rarely, predominantly with parenteral therapy. During the administration of high doses of Amoxycillin, it is advisable to maintain adequate fluid intake and urinary output in order to reduce the possibility of Amoxycillin crystalluria. In patients with bladder catheters, a regular check of patency should be maintained.
Interference with diagnostic tests
Elevated serum and urinary levels of Amoxycillin are likely to affect certain laboratory tests. Due to the high urinary concentrations of Amoxycillin, false positive readings are common with chemical methods.
It is recommended that when testing for the presence of glucose in urine during Amoxycillin treatment, enzymatic glucose oxidase methods should be used.
The presence of Amoxycillin may distort assay results for oestriol in pregnant women.

4.5 Interaction with other medicinal products and other forms of interaction

Probenecid
Concomitant use of probenecid is not recommended. Probenecid decreases the renal tubular secretion of Amoxycillin. Concomitant use of probenecid may result in increased and prolonged blood levels of Amoxycillin.
Allopurinol
Concurrent administration of allopurinol during treatment with Amoxycillin can increase the likelihood of allergic skin reactions.
Tetracyclines
Tetracyclines and other bacteriostatic drugs may interfere with the bactericidal effects of Amoxycillin.
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 Amoxycillin. If co- administration is necessary, the prothrombin time or international normalised ratio should be carefully monitored with the addition or withdrawal of Amoxycillin. Moreover, adjustments in the dose of oral anticoagulants may be necessary.

Methotrexate

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

Oral typhoid vaccine

The oral typhoid vaccine is inactivated by antibacterials.

Important Information about excipients

This medicinal product contains sorbitol. Patients with rare hereditary problems of fructose intolerance should not take this medicine.

This medicinal product contains sodium benzoate which is a mild irritant to the eyes, skin and mucous membrane. May increase the risk of jaundice in newborn babies.

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 Amoxycillin during pregnancy in humans do not indicate an increased risk of congenital malformations.

Amoxycillin may be used in pregnancy when the potential benefits outweigh the potential risks associated with treatment.

Breastfeeding

Amoxycillin 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. Amoxycillin 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 Amoxycillin on fertility in humans.

Reproductive studies in animals have shown no effects on fertility.

4.7 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.

4.8 Undesirable effects

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 amoxycillin, 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 to <1/10)
Uncommon (≥1/1,000 to <1/100)
Rare (≥1/10,000 to <1/1,000)
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 time.
Immune system disorders	
Very rare	Severe allergic reactions, including angioneurotic oedema, anaphylaxis, serum sickness and hypersensitivity vasculitis.
Not known	Jarisch-Herxheimer reaction.
Nervous system disorders	
Very rare	Hyperkinesia, dizziness and convulsions.
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. Black hairy tongue Superficial tooth discolouration[#]

Hepatobiliary 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) and drug reaction with eosinophilia and systemic symptoms (DRESS).
Renal and urinary tract disorders	
Very rare:	Interstitial nephritis Crystalluria
* The incidence of these AEs was derived from clinical studies involving a total of approximately 6,000 adult and paediatric patients taking Amoxycillin. #Superficial tooth discolouration has been reported in children. Good oral hygiene may help to prevent tooth discolouration as it can usually be removed by brushing	

4.9 Overdose

Symptoms and signs of overdose

Gastrointestinal symptoms (such as nausea, vomiting and diarrhoea) and disturbance of the fluid and electrolyte balances may be evident. Amoxycillin 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.

Treatment of intoxication

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

Amoxycillin can be removed from the circulation by haemodialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: penicillins with extended spectrum; ATC code: J01CA04.

Mechanism of action

Amoxycillin 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.

Amoxycillin is susceptible to degradation by beta-lactamases produced by resistant bacteria and therefore the spectrum of activity of Amoxycillin 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 Amoxycillin.

Mechanisms of resistance

The main mechanisms of resistance to Amoxycillin 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.

Breakpoints

MIC breakpoints for Amoxycillin are those of the European Committee on Antimicrobial Susceptibility Testing (EUCAST) version 5.0.

Organism	**MIC breakpoint (mg/L)**	
	Susceptible ≤	**Resistant >**
Enterobacteriaceae	8[1]	8
Staphylococcus spp.	Note[2]	Note [2]
Enterococcus spp.[3]	4	8
Streptococcus groups A, B, C and G	Note [4]	Note [4]
Streptococcus pneumoniae	Note [5]	Note [5]
Viridans group steprococci	0.5	2
Haemophilus influenzae	2[6]	2[6]
Moraxella catarrhalis	Note [7]	Note [7]
Neisseria meningitidis	0.125	1
Gram positive anaerobes except *Clostridium difficile*[8]	4	8
Gram negative anaerobes[8]	0.5	2

Helicobacter pylori	0.125[9]	0.125[9]
Pasteurella multocida	1	1
Non- species related breakpoints[10]	2	8

[1]Wild type Enterobacteriaceae are categorised as susceptible to aminopenicillins. Some countries prefer to categorise wild type isolates of *E. coli* and *P. mirabilis* as intermediate. When this is the case, use the MIC breakpoint S ≤ 0.5 mg/L
[2]Most staphylococci are penicillinase producers, which are resistant to Amoxycillin. Methicillin resistant isolates are, with few exceptions, resistant to all beta-lactam agents.
[3]Susceptibility to Amoxycillin can be inferred from ampicillin
[4]The susceptibility of streptococcus groups A, B, C and G to penicillins is inferred from the benzylpenicillin susceptibility.
[5]Breakpoints relate only to non-meningitis isolates. For isolates categorised as intermediate to ampicillin avoid oral treatment with Amoxycillin. Susceptibility inferred from the MIC of ampicillin.
[6]Breakpoints are based on intravenous administration. Beta-lactamase positive isolates should be reported resistant.
[7]Beta lactamase producers should be reported resistant
[8]Susceptibility to Amoxycillin can be inferred from benzylpenicillin.
[9]The breakpoints are based on epidemiological cut-off values (ECOFFs), which distinguish wild-type isolates from those with reduced susceptibility.
[10]The non-species related breakpoints are based on doses of at least 0.5 g x 3or 4 doses daily (1.5 to 2 g/day).

The prevalence of resistance may vary geographically and with time for selected species, and local information on resistance is desirable, particularly when treating severe infections. As necessary, expert advice should be sought when the local prevalence of resistance is such that the utility of the agent in at least some types of infections is questionable.

***In vitro* susceptibility of micro-organisms to Amoxycillin**
Commonly Susceptible Species
Gram-positive aerobes: *Enterococcus faecalis* Beta-hemolytic streptococci (Groups A, B, C and G) *Listeria monocytogenes*
Species for which acquired resistance may be a problem
Gram-negative aerobes: *Escherichia coli* *Haemophilus influenzae* *Helicobacter pylori* *Proteus mirabilis* *Salmonella* typhi *Salmonella* paratyphi *Pasteurella multocida*
Gram-positive aerobes: Coagulase negative staphylococcus *Staphylococcus aureus*[£] *Streptococcus pneumoniae* Viridans group streptococcus

Gram-positive anaerobes: *Clostridium* spp.
Gram-negative anaerobes: *Fusobacterium* spp.
Other: *Borrelia burgdorferi*
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. £ Almost all *S.aureus* are resistant to amoxilcillin due to production of penicillinase. In addition, all methicillin-resistant strains are resistant to Amoxycillin.

5.2 Pharmacokinetic properties

Absorption

Amoxycillin fully dissociates in aqueous solution at physiological pH. It is rapidly and well absorbed by the oral route of administration. Following oral administration, Amoxycillin is approximately 70% bioavailable. The time to peak plasma concentration (Tmax) is approximately one hour.

The pharmacokinetic results for a study, in which an Amoxycillin dose of 250 mg three times daily was administered in the fasting state to groups of healthy volunteers are presented below.

C_{max}	T_{max} *	AUC $_{(0\text{-}24h)}$	T ½
(µg/ml)	(h)	(µg.h/ml)	(h)
3.3 ± 1.12	1.5 (1.0-2.0)	26.7 ± 4.56	1.36 ± 0.56
*Median (range)			

In the range 250 to 3000 mg the bioavailability is linear in proportion to dose (measured as Cmax and AUC). The absorption is not influenced by simultaneous food intake. Haemodialysis can be used for elimination of Amoxycillin.

Distribution

About 18% of total plasma Amoxycillin is bound to protein and the apparent volume of distribution is around 0.3 to 0.4 l/kg.

Following intravenous administration, Amoxycillin has been found in gall bladder,

abdominal tissue, skin, fat, muscle tissues, synovial and peritoneal fluids, bile and pus. Amoxycillin does not adequately distribute into the cerebrospinal fluid.
From animal studies there is no evidence for significant tissue retention of drug- derived material. Amoxycillin, like most penicillins, can be detected in breast milk. Amoxycillin has been shown to cross the placental barrier.

Biotransformation
Amoxycillin 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 Amoxycillin is via the kidney.
Amoxycillin 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 Amoxycillin is excreted unchanged in urine during the first 6 hours after administration of a single 250 mg or 500 mg dose of Amoxycillin. Various studies have found the urinary excretion to be 50-85% for Amoxycillin over a 24 hour period.
Concomitant use of probenecid delays Amoxycillin excretion (see section 4.5).

Age
The elimination half-life of Amoxycillin 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.

Gender
Following oral administration of Amoxycillin/ to healthy males and female subjects, gender has no significant impact on the pharmacokinetics of Amoxycillin.

Renal impairment
The total serum clearance of Amoxycillin decreases proportionately with decreasing renal function.

Hepatic impairment
Hepatically impaired patients should be dosed with caution and hepatic function monitored at regular intervals.

5.3 Preclinical safety data
Non-clinical data reveal no special hazard for humans based on studies of safety pharmacology, repeated dose toxicity, genotoxicity and toxicity to reproduction and development.
Carcinogenicity studies have not been conducted with Amoxycillin.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Dextrose Monohydrate
Corn Starch
Sodium Carboxy Methyl cellulose
Vanilla Powder
Sodium citrate

Aerosil 200
Aspartame
Benzoic Acid
Sunset Yellow

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

48 months

6.4 Special precautions for storage

Store below 30°C in tight container protected from light and moisture.

6.5 Nature and contents of container and special equipment for use, administration or implantation

Dramoxilin® (125mg/5ml) Powder for oral suspension is presented in 100ml bottle, packed in hardboard carton with leaflet and measuring cup enclosed.

6.6 Special precautions for disposal and other handling

No special requirements.

7. APPLICANT/MANUFACTURER

Drugfield Pharmaceuticals Limited
Lynson Chemical Avenue Km38,
Lagos-Abeokuta Expressway
Sango-Otta, Ogun State, Nigeria
Tel: +2348033513989
Email:Info@drugfieldpharma.com

8.0 DATE OF REVISION OF THE TEXT

09/2023