SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

MOXILEN 250mg Capsule
MOXILEN 500mg Capsule

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

MOXILEN hard capsules contain the equivalent of either 250mg or 500mg amoxicillin as amoxicillin trihydrate.

Excipients with known effect:
MOXILEN 500mg capsules:
- carmoisine

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Capsule, hard
MOXILEN hard capsules are for oral administration.

Pharmaceutical form description
- 250mg capsules: pink – grey hard gelatin capsules "2", printed "MOXILEN", filled with white to off-white powder
- 500mg capsules: maroon – white hard gelatin capsules size "0" printed "MOXILEN", filled with white to off-white powder

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Amoxicillin is an aminopenicillin, which has activity against penicillin-sensitive gram-positive bacteria, as well as *Escherichia coli*, *Proteus mirabilis*, *Salmonella sp*., *Shigella sp*., and *Haemophilus influenzae.* However, many *Entero-bacteriaceae*, *H. influenzae*, *Salmonella* and *Shigella* species are resistant to this penicillin because of beta-lactamase production by these organisms. Amoxicillin can be administered orally for the following infections caused by susceptible bacterial organisms:

Bronchitis,
Biliary tract infections,
Uncomplicated Endocervical and Urethral Gonorrhoea (caused by susceptible strains of Neisseria gonorrhoea)
Acute otitis media,
Mouth infections,
Pharyngitis,
Pneumonia,
Sinusitis,
Urinary tract infections,
Gastro-enteritis (including E.coli enteritis and Salmonella enteritis),
Lyme disease (early stages, monotherapy and later stages, in combination with probenecid),
Typhoid fever.

Amoxicillin is a possible alternative to erythromycin for chlamydial infections in pregnant women. Amoxicillin is also indicated as prophylaxis for spleen disorders (pneumococcal infection) and bacterial endocarditis and adjunct for Helicobacter pylori-associated peptic ulcer.

4.2. Posology and method of administration

Usual adult dose is 250-500mg every 8 hours.

Adults:
Severe or recurrent infections of respiratory tract – 3g twice daily
Uncomplicated endocervical and urethral gonorrhea (gonococci-sensitive) – Single dose of 3g with probenecid 1g
Dental abscesses/ uncomplicated acute urinary tract infections – A dose of 3g repeated once after 8 or 10 to 12 hours.
Chlamydia (in pregnant women) – 500mg every 8 hours for 7 to 10 days.
Prophylaxis of endocarditis – 3g one hour before dental procedures under local or no anaesthesia then 1.5g 6 hours after the initial dose.

Helicobactor pylori associated gastritis or peptic ulcer – 500mg 4 times a day or 750mg 3 times a day.
Lyme disease – 250–500mg 3 or 4 times a day for 3–4 weeks

Children:
Children up to 10 years – 125–250mg every 8 hours
Children under 20kg bodyweight – 20–40mg per kg daily.
Otitis media (children 3-10 years) – 750mg twice daily for 2 days.
Uncomplicated endocervical and urethral gonorrhea – 50mg per kg of body weight and 25mg of probenecid per kg of body weight simultaneously as a single dose in pre-pubertal children
Lyme disease – 6.7–13.3mg per kg of body weight every 8 hours for 10–30 days.

Method of administration:
Swallow with water without opening capsule.

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 beta-lactam agent (eg. cephalosporins, carbapenem or monobactam).

4.4. Special warnings and precautions for use

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 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 oestriol in pregnant women.

Important information about excipients
MOXILEN 500mg hard capsules contains carmoisine.
May cause allergic reactions

4.5. Interactions with other medicinal products and other forms of interaction

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.
Allopurinol
Concurrent 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.

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. Amoxicillin may be used in pregnancy when the potential benefits outweigh the potential risks associated with treatment.
Breast-feeding
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.

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 (see section 4.8).

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 amoxicillin, presented by MedDRA System Organ Class are listed below.

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 (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). ***For oral formulations only*** Black hairy tongue ***For dispersible tablets and oral suspension formulations only*** 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 and acute generalised exanthematous pustulosis (AGEP) (see section 4.4). Drug reaction with Eosinophilia and Systemic Symptoms (DRESS)
Renal and urinary tract disorders	
Very rare	Interstitial nephritis Crystalluria (see sections 4.4 and 4.9 Overdose)
*The incidence of these AEs was derived from clinical studies involving a total of approximately 6,000 adult and paediatric patients taking amoxicillin. [#]***For oral suspension formulations only*** 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. 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).

Parenteral formulations

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).

Treatment of intoxication

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

Amoxicillin may be removed from the circulation by haemodialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1. 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.

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.

Breakpoints

MIC breakpoints for amoxicillin 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 amoxicillin. Methicillin resistant isolates are, with few exceptions, resistant to all beta-lactam agents.
[3]Susceptibility to amoxicillin 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 amoxicillin. 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 amoxicillin 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 Amoxicillin**
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 amoxicillin due to production of penicillinase. In addition, all methicillin-resistant strains are resistant to amoxicillin.

5.2. Pharmacokinetic properties

Oral

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

Cmax	Tmax*	$AUC_{(0\text{-}24h)}$	T½
(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 3000mg 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 amoxicillin.

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).

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).

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.

Gender

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

Renal impairment

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

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 conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity and toxicity to reproduction and development.

Carcinogenicity studies have not been conducted with amoxicillin.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

MOXILEN capsules 250 mg contain magnesium stearate.
The capsule shell contains:

- gelatine,
- erythrosine (E127),
- red iron oxide (E172),
- black iron oxide (E172), and
- titanium dioxide (E171).

MOXILEN capsules 500 mg contain magnesium stearate.
The capsule shell contains:

- gelatine,
- erythrosine (E127),
- brilliant blue FCF (E133),
- carmoisine (E122) and
- titanium dioxide (E171).

6.2. Incompatibilities

Not applicable.

6.3. Shelf life

36 months.

6.4. Special precautions for storage

Store below 30°C in the original package in order to protect from light and moisture.

6.5. Nature and contents of container

MOXILEN hard capsules 250mg and 500mg are packed in polyvinylchloride film-aluminium foil blisters with a leaflet, in cartons.
Cartons of MOXILEN 250mg Capsules contain 1000 capsules
Cartons of MOXILEN 500mg Capsules contain 500 capsules

6.6. Special precautions for disposal and other handling

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

7. Product Registration Holder

Komedic Sdn, Bhd. 4 Jalan PJS 11/14, Bandar Sunway 46150, Petaling Jaya

8. Manufacturer

Medochemie Ltd (Factory B), 48 Iapetou Street, Agios Athanassios Industrial Area, 4101 Agios Athanassios, Limassol, Cyprus

9. MARKETING AUTHORISATION NUMBER(S)

MOXILEN capsules 250 mg: MAL19860458AZ
MOXILEN capsules 500 mg: MAL19860465AZ

10. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

MOXILEN capsules 250 mg
Date of first authorisation: 14.12.1979/14.01.2015

MOXILEN capsules 500 mg
Date of first authorisation: 14.12.1979/14.01.2015

11. DATE OF REVISION OF THE TEXT

01/2024