1. NAME OF THE MEDICINAL PRODUCT

PAKCILLINE

(Ampicilin Capsules BP 250 mg)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Sr. No.	Ingredients	Spec	Unit Formula (mg)	Batch Formula(kg) for 5,000 Capsule	Function
1	Ampicillin Trihydrate eq. to Ampicillin B.P	BP	250.0	1.509*	Active
2	Talcum	BP	10.000	0.050	Diluent
3	Magnesium stearate BP	BP	8.000	0.040	Diluent
4	Silicon dioxide USP/NF	BP	2.000	0.010	Diluent
5	E.H.G. Capsules, black/Red size "2" Printed with **"PAKCILLINE – 250"** on body and on cap	IH	NA	5,200	E.H.G. Capsules

* 5% overages added.

Net Content 321.8mg per Capsule

3. PHARMACEUTICAL FORM

Capsules for oral administration

Description: Black cap & Red body empty hard gelatin capsules of size "2" printed with **"Pakcilline-250"** on body & on cap.

4. Clinical particulars

4.1 Therapeutic indications

Treatment of infection:

Ampicillin capsules 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

Ampicillin 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

The dose of Ampicillin that is selected to treat an individual infection 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***
Acute bacterial sinusitis	250 mg to 500 mg every 8 hours or 750 mg to 1 g every 12 hours For severe infections 750 mg to 1 g every 8 hours Acute cystitis may be treated with 3 g twice daily for one day
Asymptomatic bacteriuria in pregnancy	
Acute pyelonephritis	
Dental abscess with spreading cellulitis	
Acute cystitis	
Acute otitis media	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
Acute streptococcal tonsillitis and pharyngitis	
Acute exacerbations of chronic bronchitis	
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 (see section 4.4)	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	

Children <40 kg

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

Recommended doses:

Indication+	**Dose+**
Acute bacterial sinusitis	20 to 90 mg/kg/day in divided doses*
Acute otitis media	
Community acquired pneumonia	
Acute cystitis	
Acute pyelonephritis	
Dental abscess with spreading cellulitis	
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
Prophylaxis of endocarditis	50 mg/kg orally, single dose 30 to 60 minutes before procedure
Lyme disease (see section 4.4)	Early stage: 25 to 50 mg/kg/day in three divided doses for 10 to 21 days Late stage (systemic involvement): 100 mg/kg/day in three divided doses for 10 to 30 days
+ 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 (maximum 500 mg twice daily)
less than 10	maximum 500 mg/day.	15 mg/kg given as a single daily dose (maximum 500 mg)
# In the majority of cases, parenteral therapy is preferred.		

In patients receiving haemodialysis
Ampicillin 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

Ampicillin 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

Oral:

Ampicillin is for oral use.

Absorption of Ampicillin is unimpaired by food.

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

4.4 Special warnings and precautions for use

Hypersensitivity reactions

Before initiating therapy with Ampicillin, careful enquiry should be made concerning previous hypersensitivity reactions to penicillins, cephalosporins or other beta-lactam agencts (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 hypersensitivity and in atopic individuals. If an allergic reaction occurs, Ampicillin therapy must be discontinued and appropriate alternative therapy instituted.

Non-susceptible microorganisms

Ampicillin 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 Ampicillin (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 rate of excretion of Ampicillin will be reduced depending on the degree of impairment and it may be necessary to reduce the total daily unit Ampicillin dosage accordingly (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 Ampicillin discontinuation and contra-indicates any subsequent administration.

Ampicillin 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 Ampicillin.

Jarisch-Herxheimer reaction

The Jarisch-Herxheimer reaction has been seen following Ampicillin treatment of Lyme disease (see section 4.8). It results directly from the bactericidal activity of Ampicillin 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, Ampicillin 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 Ampicillin. 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 Ampicillin, it is advisable to maintain adequate fluid intake and urinary output in order to reduce the possibility of Ampicillin 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 Ampicillin are likely to affect certain laboratory tests. Due to the high urinary concentrations of Ampicillin, false positive readings are common with chemical methods.

It is recommended that when testing for the presence of glucose in urine during Ampicillin treatment, enzymatic glucose oxidase methods should be used.

The presence of Ampicillin may distort assay results for oestriol in pregnant women.

Important information about excipients

The capsules contain sunset yellow, E110 which can cause allergic-type reactions including asthma.

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 Ampicillin. Concomitant use of probenecid may result in increased and prolonged blood levels of Ampicillin.

Allopurinol:

Concurrent administration of allopurinol during treatment with Ampicillin can increase the likelihood of allergic skin reactions.

Tetracyclines :

Tetracyclines and other bacteriostatic drugs may interfere with the bactericidal effects of Ampicillin.

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 Ampicillin. If co-administration is necessary, the prothrombin time or international normalised ratio should be carefully monitored with the addition or withdrawal of Ampicillin. 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 Ampicillin during pregnancy in humans do not indicate an increased risk of congenital malformations. Ampicillin may be used in pregnancy when the potential benefits outweigh the potential risks associated with treatment.

Breastfeeding

Ampicillin 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. Ampicillin 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 Ampicillin 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 Ampicillin, 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 (see section 4.4 – Special Warnings and Precautions for Use.

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).
Black hairy tongue

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 generalized exanthematous pustulosis (AGEP) (See section 4.4) and 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 Ampicillin.

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.

Healthcare professionals are asked to report any suspected adverse reactions via Yellow Card Scheme.

Website: www.mhra.gov.uk/yellowcard.

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. Ampicillin 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 of intoxication:

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

Ampicillin may be removed from the circulation by haemodialysis.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: penicillins with extended spectrum; ATC code: J01C A04

Mechanism of action

Ampicillin 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.

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

Mechanisms of resistance

The main mechanisms of resistance to Ampicillin 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 Ampicillin 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 Ampicillin. Methicillin resistant isolates are, with few exceptions, resistant to all beta-lactam agents.
[3]Susceptibility to Ampicillin 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 Ampicillin. 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 Ampicillin 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 Ampicillin
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[7]
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 Ampicillin due to production of penicillinase. In addition, all methicillin-resistant strains are resistant to Ampicillin.

5.2 Pharmacokinetic properties

Oral

Absorption

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

The pharmacokinetic results for a study, in which an Ampicillin 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 $_{(0-24h)}$	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 C_{max} and AUC). The absorption is not influenced by simultaneous food intake.

Haemodialysis can be used for elimination of Ampicillin.

Distribution

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

Following intravenous administration, Ampicillin has been found in gall bladder, abdominal tissue, skin, fat, muscle tissues, synovial and peritoneal fluids, bile and pus. Ampicillin does not adequately distribute into the cerebrospinal fluid.

From animal studies there is no evidence for significant tissue retention of drug-derived material. Ampicillin, like most penicillins, can be detected in breast milk (see section 4.6).

Ampicillin has been shown to cross the placental barrier (see section 4.6).

Biotransformation

Ampicillin 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 Ampicillin is via the kidney.

Ampicillin 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 Ampicillin is excreted unchanged in urine during the first 6 hours after administration of a single 250 mg or 500 mg dose of Ampicillin. Various studies have found the urinary excretion to be 50-85% for Ampicillin over a 24 hour period.

Concomitant use of probenecid delays Ampicillin excretion (see section 4.5).

Age

The elimination half-life of Ampicillin 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 Ampicillin/ to healthy males and female subjects, gender has no significant impact on the pharmacokinetics of Ampicillin.

Renal impairment

The total serum clearance of Ampicillin 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 studies of safety pharmacology, repeated dose toxicity, genotoxicity and toxicity to reproduction and development.

Carcinogenicity studies have not been conducted with Ampicillin.

6. Pharmaceutical particulars

6.1 List of excipients
Each gelatin capsule contains:

Gelatin (capsule body and cap)

Magnesium stearate

Colloidal anhydrous silica

Purified Talcum

6.2 Incompatibilities
Not applicable

6.3 Shelf life
24 months.

6.4 Special precautions for storage
Do not store above 25°C. Store in the original package.

6.5 Nature and contents of container
Blister pack of 10 capsules.

6.6 Special precautions for disposal and other handling
No special instructions for use/handling.

7. APPLICANT/MANUFACTURER

Name: **Charles Mekus Pharmaceutical & Stores Nig. Ltd**.

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