1.6 Product information:

1.6.1 Prescribing Information (Summary of Product Characteristics)

1. NAME OF THE FINISHED PHARMACEUTICAL PRODUCT

AMOXICILLIN CAPSULES USP 500 mg

1.1 Strength

500 mg

1.2 Pharmaceutical form

Solid oral Dosage hard gelatin capsule

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

2.1 Qualitative declaration

Each hard gelatin capsule contains:
Amoxicillin Trihydrate USP
Eq. to Amoxicillin…….500 mg
Excipients……..q.s.
Approved colors used in empty capsule shells.

2.2 Quantitative declaration

S. No.	Ingredients	Specification	Qty. Req. per batch in Kg	Overages	Actual Qty per Capsule (mg)	Function
1.	*Amoxicillin Trihydrate (Compacted)	USP	575.00	Nil	575.00	(Active) Penicillin antibiotic
2.	Croscarmellose Sodium	USP	3.50	Nil	3.50	Disintegrant
3.	Magnesium Stearate	USP	5.00	Nil	5.00	Lubricant
4.	Purified Talcum	USP	5.00	Nil	5.00	Glidant
5.	*Microcrystalline Cellulose PH-102	USP	16.50	Nil	16.50	Diluent
6.	EHG Capsules “0” Size	IH	1010000	Nil	q.s.	Enclosure

Note:* To be calculated on 100 % assay on anhydrous basis of active ingredient and Capsule weight to be adjusted by reducing the quantity of Microcrystalline Cellulose PH-102.

2.3 Salts and hydrates

Amoxicillin Trihydrate USP equivalent to Amoxicillin 500 mg

2.4 Esters and pro-drugs

Not Applicable

2.5 Oral powders for solution or suspension

Not Applicable.

2.6 Parenterals excluding powders for reconstitution

Not Applicable

2.7 Powders for reconstitution prior to Parenteral administration

Not Applicable

2.8 Concentrates

Not Applicable

2.9 Transdermal patches

Not Applicable

2.10 Multidose solid or semi-solid products

Not Applicable

2.11 Biological medicinal products

Not Applicable

3. PHARMACEUTICAL FORM

Capsules for oral administration.

Maroon color cap. & Yellow color body. Size '0' hard gelatin capsule containing white to off white granular powder packed in printed aluminum foil & clear PVC.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

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

Amoxicillin 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 Amoxicillin 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 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.

Adults and children ≥40 kg

Indication*	Dose*
Acute bacterial sinusitis	250mg to 500mg every 8 hours or 750mg to 1g every 12 hours For severe infections 750mg to 1g every 8 hours Acute cystitis may be treated with 3g twice daily for one day
Asymptomatic bacteriuria in pregnancy	
Acute pyelonephritis	
Dental abscess with spreading cellulitis	
Acute cystitis	
Acute otitis media	500mg every 8 hours, 750mg to 1g every 12 hours For severe infections 750mg to 1g every 8 hours for 10 days
Acute streptococcal tonsillitis and pharyngitis	
Acute exacerbations of chronic bronchitis	
Community acquired pneumonia	500mg to 1g every 8 hours
Typhoid and paratyphoid fever	500mg to 2g every 8 hours
Prosthetic joint infections	500mg to 1g every 8 hours
Prophylaxis of endocarditis	2g orally, single dose 30 to 60 minutes before procedure
Helicobacter pylori eradication	750mg to 1g 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: 500mg to 1g 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): 500mg to 2g 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 may be treated with Amoxicillin capsules, dispersible tablets, suspensions or sachets.

Amoxicillin Paediatric Suspension is recommended for children under six months of age.

Children weighing 40kg 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	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 ≥ 40kg**	**Children < 40 kg**[#]
greater than 30	No adjustment necessary	No adjustment necessary
10 to 30	Maximum 500mg twice daily	15 mg/kg given twice daily (maximum 500mg twice daily)
less than 10	Maximum 500 mg/day	15 mg/kg given as a single dose (maximum 500 mg)
[#] In the majority of cases, parenteral therapy is preferred		

In patients receiving haemodialysis

Amoxicillin may be removed from the circulation by haemodialysis

	Haemodialysis
Adults and children	500mg every 24h

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

In patients receiving peritoneal dialysis

Amoxicillin maximum 500mg/day

Hepatic impairment

Dose with caution and monitor hepatic function at regular intervals.

4.3 Method of administration

Amoxicillin is for oral use.

Absorption of amoxicillin is impaired by food.

Therapy can be started parenterally according to the dosing recommendations of the intravenous formulation and continued with an oral preparation.

Swallow with water without opening capsule.

Route of Administration: Oral

4.4 Contraindications

Hypersensitivity to the active substance, to any of the penicillins or to any of the excipients.

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

4.5 Special warnings and precautions for use

Hypersensitivity reactions

Before initiating therapy with amoxicillin, careful enquiry should be made concerning previous hypersensitivity reactions to penicillin and cephalosporins or other beta-lactam agents.

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 . 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 (AGEP). 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.

Patients with lymphatic leukaemia and possibly with HIV infection are particularly prone to developing erythematous rashes with amoxicillin. Amoxicillin should be discontinued if a skin rash occurs.

Jarisch-Herxheimer reaction

The Jarisch-Herxheimer reaction has been seen following amoxicillin treatment of Lyme disease. 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 of an anti-infective may result in the overgrowth of non-susceptible organisms (superinfection).

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, 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.

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.

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.

Interference with diagnostic tests

Elevated serum and urinary levels of amoxicillin are likely to affect certain laboratory tests. Due to 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.

4.6 Paediatric population

Not Applicable.

4.7 Interaction with other medicinal products and other forms of Interaction

Oral anticoagulants

Oral anticoagulants and penicillin antibiotics have been widely used in practice without reports of interaction. However, in the literature there are rare 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.

Probenecid

Concomitant use of probenecid is not recommended. Probencid decreases the renal tubular secretion of amoxicilin. Concurrent use with amoxicillin 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.

Methotrexate

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

4.8 Additional information on special populations

Not Applicable.

4.9 Paediatric population

Not Applicable.

4.10 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.

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.

4.11 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.

4.12 Undesirable effects

The following convention has been utilised for the classification of undesirable effects:

Very common (≥1/10),

Common (≥1/100 to <1/10),

Uncommon (≥1/1000 to <1/100),

Rare (≥1/10,000 to <1/1000),

Very rare (<1/10,000),

Not known (cannot be estimated from the available data)

The majority of side effects listed below are not unique to amoxicillin and may occur when using other penicillins.

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

Unless otherwise stated, the frequency of adverse events has been derived from more than 30 years of post-marketing reports.

Infections and infestations

Very Rare:: Muco-cutaneous candidiasis.

Blood and lymphatic system disorders

Very Rare: Reversible leucopenia (including severe neutropenia or agranulocytosis), reversible thrombocytopenia and haemolytic anaemia. Prolonged prothrombin and bleeding times

Immune system disorders

Very rare: As with other antibiotics, severe allergic reactions, including angioneurotic oedema, anaphylaxis , serum sickness and hypersensitivity vasculitis.

Not Known: Jarisch-Herxheimer reaction

If any hypersensitivity reaction occurs the treatment should be discontinued.

Nervous system disorders

Very Rare: Hyperkinesia, dizziness and convulsions. Convulsions may occur in patients with impaired renal function or in those receiving high doses.

Gastrointestinal disorders

Clinical trial data:

Common: Diarrhoea & Nausea

Uncommon: Vomiting

Post-marketing data:

Very Rare: Antibiotic associated colitis (including pseudomembraneous colitis and haemorrhagic colitis, Black hairy tongue.

Hepatobiliary disorders

Very Rare: Hepatitis and cholestatic jaundice. A moderate rise in AST and/or ALT.

The significance of a rise in AST and/or ALT is unclear

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 disorders

Very rare: Interstitial nephritis, Crystalluria.

4.13 Overdose

Symptoms and signs of overdose

Problems of overdosage with amoxicillin are unlikely to occur. Gastrointestinal symptoms (such as nausea, vomiting and diarrhoea) and disturbances 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.

Treatment of intoxication

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

Amoxicillin can 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 bactericidal 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.

5.2 Pharmacokinetic properties

Absorption:

Amoxicillin fully dissociates in aqueous solution at physiological pH. Amoxicillin is stable in the acid gastric secretion and is rapidly absorbed from the gastrointestinal tract after oral administration. Following oral administration, amoxicillin is approximately 70% bioavailable. The time to peak plasma concentration (T_{max}) is approximately one hour.

In the range 250 to 3000 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 amoxicillin.

Distribution

About 18% of total plasma amoxicillin is bound to protein and the apparent volume of distribution is around 0.3 to 0.41/kg. Following intravenous administration, amoxicillin has been found in gall bladder, abdominal tissue, skin, fat, muscle tissue, 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.

Amoxicillin has been shown to cross the placental barrier.

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 an orally administered dose is excreted unchanged in the urine during the first 6 hours after administration of a single 250mg or 500mg 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.

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. In preterm infants with gestational age 26-33 weeks, the total body clearance after intravenous dosing of amoxicillin, day 3 of life, ranged between 0.75 – 2 ml/min, very similar to the inuline clearance (GFR) in this population. Following oral administration, the absorption pattern and the bioavailability of amoxicillin in small children may be different to that of adults. 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.

Hepatic impairment

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

5.3 Preclinical safety data

Not Applicable.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Croscarmellose Sodium	USP
Magnesium Stearate	USP
Purified Talcum	USP
Microcrystalline Cellulose PH-102	USP
E.H.G Capsule Size "2"	IH

6.2 Incompatibilities

Not Applicable

6.3 Shelf life

36 Months

6.4 Special precautions for storage

Sore protected from light at a temperature not exceeding 30°C.

6.5 Nature and contents of container

10×10 Alu/PVC Blister.

6.6 Special precautions for disposal and other handling

No special requirements

7 Marketing Authorisation Holder And Manufacturing Site Addresses

Scott-Edil Advance Research Laboratories & Education Limited.
Hill Top Ind. Area, Bhatoli Kalan,
Baddi-173205, Himachal Pradesh, INDIA

MANUFACTURING SITE ADDRESS
Scott-Edil Advance Research Laboratories & Education Limited.
Hill Top Ind. Area, Bhatoli Kalan,
Baddi-173205, Himachal Pradesh, INDIA

8 MARKETING AUTHORISATION NUMBER
Not Applicable

9 DATE OF FIRST REGISTRATION/RENEWAL OF THE REGISTRATION
Not Applicable.

10 DATE OF REVISION OF THE TEXT
Not Applicable

11 DOSIMETRY
Not Applicable