SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Amoxicillin 500mg Capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains:

Amoxicillin Trihydrate 588mg equivalent to Amoxicillin 500mg.

For excipients, see 6.1.

3 PHARMACEUTICAL FORM

Size ‘0’ scarlet/ivory hard gelatin capsules.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Amoxicillin 500mg Capsules is indicated for the oral treatment of the following bacterial infections caused by amoxicillin-sensitive gram-positive and gram-negative pathogens (see section 5.1):

- Infections of the upper respiratory tract, including infections of the ears, nose and throat: Acute otitis media, acute sinusitis and bacterial pharyngitis
- Infections of the lower respiratory tract: Acute exacerbation of chronic bronchitis, community-acquired pneumonia.
- Infections of the kidneys and the genito-urinary tract: Cystitis, pyelonephritis .
- Infections associated with the gastrointestinal tract. It may be necessary to use combination therapy when treating infections caused by anaerobic organisms.
- Endocarditis: Amoxicillin 500mg Capsules may be used for the prevention of bacteraemia, associated with procedures such as dental extraction, in patients at risk of developing bacterial endocarditis. Amoxicillin 500mg Capsules may

also be used for the treatment of endocarditis as an extension of parenteral therapy.

Consideration should be given to official local guidance (e.g. national recommendations) on the appropriate use of antibacterial agents.

Susceptibility of the causative organism to the treatment should be tested (if possible), although therapy may be initiated before the results are available.

4.2 Posology and method of administration

The dosage depends on the susceptibility of the pathogens and the severity of the disease.

Standard dosage:

Adults and adolescents (> 40 kg body weight):

The usual dosage covers a range from 750 mg to 3g amoxicillin daily in three divided doses. In some areas 1500 mg amoxicillin daily in three divided doses is recommended as the upper usual dose.

Short course treatment:

Uncomplicated urinary tract infections: two 3 g doses with 10-12 hours between the doses are recommended in some areas.

Children (under 12 years)

For infants and children oral suspensions containing amoxicillin are recommended.

Dosage for the prevention of endocarditis:

For the prevention of endocarditis, in patients not having a general anaesthetic, 3 g amoxicillin are given in the hour preceding the surgical procedure, followed by (6 hours later) a further 3 g dose, if considered necessary.

Dosage in impaired renal function:

The dose should be reduced in patients with severe renal impairment. In patients with a creatinine clearance of less than 30 ml/min an increase in the dosage interval or a

reduction in the subsequent doses is recommended (see section 4.4). Short course treatments with a single dose of 3 g cannot be given in patients with renal failure.

Duration of therapy:

In general the therapy should be continued for 2 to 3 days following the disappearance of symptoms. In β-haemolytic streptococcal infections the duration of therapy should be at least 10 days in order to achieve eradication of the organism.

Method of administration:

The preparations are administered orally.

Amoxicillin 500mg Capsules should be taken unchewed with liquid (e.g. a glass of water).

The absorption of amoxicillin is not reduced by food intake.

Children weighing < 40 kg

The daily dosage for children is 40 - 90 mg/kg/day in two to three divided doses* (not exceeding 3 g/day) depending on the indication, severity of the disease and the susceptibility of the pathogen (see special dosage recommendations below and sections 4.4, 5.1 and 5.2).

*PK/PD data indicate that dosing three times daily is associated with enhanced efficacy, thus twice daily dosing is only recommended when the dose is in the upper range.

Children weighing more than 40 kg should be given the usual adult dosage.

Special dosage recommendation Tonsillitis:

50 mg/kg/day in two divided doses.

Acute otitis media: In areas with high prevalence of pneumococci with reduced susceptibility to penicillins, dosage regimens should be guided by national/local recommendations.

Early Lyme disease (isolated erythema migrans): 50 mg/kg/day in three divided doses, over 14-21days.

Prophylaxis for endocarditis: 50 mg amoxicillin/kg body weight given as a single dose one hour preceding the surgical procedure.

Dosage in impaired renal function: The dose should be reduced in patients with severe renal function impairment. In patients with a creatinine clearance of less than 30 ml/min an increase in the dosage interval and a reduction in the total daily dose is recommended (see section 4.4 and 5.2).

Renal impairment in children under 40 kg:

Creatinine clearance ml/min	Dose	Interval between administration
> 30	Usual dose	No adjustment necessary
10 – 30	Usual dose	12 h (corresponding to 2/3 of the dose)
< 10	Usual dose	24 h (corresponding to 1/3 of the dose)

4.3 Contraindications

Amoxicillin 500mg Capsules is contraindicated in patients with a previous history of hypersensitivity to amoxicillin or to any of the excipients.

Amoxicillin 500mg Capsules must not be administered to patients with a verified hypersensitivity to any beta-lactam drug (e.g. penicillins, cephalosporins, carbapenems, monobactams). Consequently a careful history should be taken in regard to any allergic reactions before commencing treatment.

Amoxicillin 500mg Capsules is also contraindicated in viral infections, acute lymphatic leukaemia, or infectious mononucleosis (due to an increased risk of erythematous skin rashes).

4.4 Special warnings and precautions for use

Patients suffering from severe gastrointestinal disturbances with diarrhoea and vomiting should not be treated with Amoxicillin 500mg Capsules, due to the risk of reduced absorption. In these cases parenteral treatment with amoxicillin is advisable.

Amoxicillin 500mg Capsules should be used with caution in patients with allergic diathesis and asthma.

In patients with renal impairment the excretion of amoxicillin will be delayed and, depending on the degree of the impairment, it may be necessary to reduce the total daily dosage (see section 4.2.).

The prolonged use of amoxicillin may occasionally result in an overgrowth of non-susceptible organisms or yeasts. Patients should therefore be watched carefully for superinfections.

The occurrence of anaphylactic shock and other severe allergic reactions is rare following the oral administration of amoxicillin. However, if such reactions occur, appropriate emergency treatment measures must be taken: I.v. administration of epinephrine, followed by antihistaminic drugs, volume substitution and administration of glucocorticoids. Patients should be kept under close observation, and further therapeutic measures (artificial respiration, oxygen) should be administered as required.

The presence of high urinary concentrations of amoxicillin can cause precipitation of the product in urinary catheters. Therefore, catheters should be visually inspected at intervals. At high doses, adequate fluid intake and urinary output must be maintained to minimise the possibility of amoxicillin crystalluria.

Amoxicillin 500mg Capsules contains sunset yellow. This may cause allergic reactions. Precaution should be taken in premature children and during the neonatal period: renal, hepatic and haematological functions should be monitored.

4.5 Interaction with other medicinal products and other forms of interaction

Concomitant use not recommended

Allopurinol

Concomitant administration of allopurinol may promote the occurrence of allergic cutaneous reactions.

Digoxin

An increase in the absorption of digoxin is possible on concurrent administration with Amoxicillin 500mg Capsules.

Anticoagulants

Concomitant administration of amoxicillin and anticoagulants, such as coumarin, may increase the incidence of bleeding.

Probenecid

By inhibiting the renal elimination of amoxicillin the concomitant administration of probenecid leads to an increase in the concentrations of amoxicillin in serum and bile.

Other antibiotics

There is a possibility that the antibacterial action of amoxicillin could be antagonised on coadministration with macrolides, tetracyclines, sulphonamides or chloramphenicol.

Caution is recommended when amoxicillin is given concomitantly with:

Oral hormonal contraceptives

Administration of amoxicillin can transiently decrease the plasma level of estrogens and progesterone, and may reduce the efficacy of oral contraceptives. Patients should be advised to use supplemental non-hormonal contraceptive measures.

Other forms of interactions:

- Forced diuresis leads to a reduction in blood concentrations by increased elimination of amoxicillin.
- The occurrence of diarrhoea may impair the absorption of other medicaments and consequently adversely affect efficacy.
- Amoxicillin may produce false positive results in glucose determination tests performed with nonenzymatic methods. Likewise the urobilinogen test can be affected.
- Amoxicillin may decrease the amount of urinary estriol in pregnant women.

4.6 Fertility, Pregnancy and lactation

Pregnancy Amoxicillin crosses the placenta and foetal plasma concentrations are approximately 25-30% of the maternal plasma concentrations. However, since there is no evidence of any embryotoxic or other adverse effects of the drug, amoxicillin may be considered appropriate for use during pregnancy when the potential benefits outweigh the potential risks.

Lactation Amoxicillin diffuses into the breast milk (approx. 10% of the corresponding serum concentration) and in rare cases this can lead to diarrhoea and/or fungal

colonisation of the mucosa in the infant. The possibility of sensitisation of the infant to beta-lactam drugs should also be considered.

4.7 Effects on ability to drive and use machines

No effects on the ability to drive and use machines have been observed.

4.8 Undesirable effects

The most commonly reported adverse drug reactions are hypersensitivity reactions:
Common (≥1 % *but < 10%)*

- Cutaneous reactions such as exanthema, pruritus, urticaria; the typical morbilliform exanthema occurs 5 - 11 days after start of therapy. Immediate appearance of urticaria indicates an allergic reaction to amoxicillin and therapy should therefore be discontinued.

Rare (≥0.01 % *but < 0.1%): (see also section 4.4)*

- Angioneurotic oedema (Quincke's oedema)
- Erythema multiforme exsudativum
- Stevens-Johnson syndrome
- Eosinophilia
- Drug fever
- Laryngeal oedema
- Serum sickness
- Haemolytic anaemia
- Allergic vasculitis
- Interstitial nephritis
- Anaphylactic shock

Blood disorders:

There have been isolated reports of leucopenia, granulocytopenia, thrombocytopenia, pancytopenia, anaemia, myelosuppression, agranulocytosis, prolongation of bleeding time, and prolongation of prothrombin time. However, these changes were reversible on discontinuation of therapy.

Gastrointestinal disorders:

Common (≥1% *but < 10%):*

Gastric complaints, nausea, loss of appetite, vomiting, flatulence, soft stools, diarrhoea, enanthemas (particularly in the region of the mouth), dry mouth, taste disturbances. These effects on the gastrointestinal system are mostly mild and frequently disappear either during the treatment or very soon after completion of therapy. The occurrence of these side-effects can generally be reduced by taking Amoxicillin 500mg Capsules during meals or with some food. If severe and persistent diarrhoea occurs, the very rare possibility of pseudomembranous colitis should be considered. The administration of anti-peristaltic drug is contraindicated.

Very rare (*<0.01%):*

Development of a black tongue. Liver disorders: *Uncommon (≥ 0.1% but* < 1%) Moderate and transient increase of liver enzymes. Rare reports of hepatitis and cholestatic jaundice.

Renal disorders

Rare (≥ 0.01% but < 0.1%):

Acute interstitial nephritis may occur in rare cases.

CNS Disorders

CNS effects have been seen rarely. They include hyperkinesia, dizziness and convulsions. Convulsions may occur in patients with impaired renal function or in those receiving high doses.

Other undesirable effects

Prolonged and repeated use of the preparation can result in superinfections and colonization with resistant organisms or yeasts such as oral and vaginal candidiasis.

4.9 Overdose

Symptoms of overdose: Amoxicillin is not generally associated with acute toxic effects, even when accidentally consumed in high doses. Overdosage can lead to symptoms such as gastrointestinal disturbances and fluid and electrolyte imbalance.

Management of overdose: There is no specific antidote for an overdose of amoxicillin. Treatment consists primarily of administration of activated charcoal (gastric lavage is usually not necessary) or symptomatic measures. Particular

attention should be paid to the water and electrolyte balance of the patients. In patients with severely impaired renal function, large overdoses can result in signs of renal toxicity; crystalluria is possible. Amoxicillin can be eliminated via haemodialysis.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Beta-lactam antibiotics, penicillins

General Properties

ATC classification
ATC-Code:J01 A04

Mode of action

Amoxicillin is an aminopenicillin that has bacterial action due to its inhibition of the synthesis of the bacterial cell wall

Mechanism (s) of resistance

Bacteria may be resistant to amoxicillin (and, thus, ampicillin) due to production of betalactamases which hydrolyse aminopenicillins, due to alteration in penicillin-binding proteins, due to impermeability to the drug, or due to drug efflux pumps. One or more of these mechanisms may co-exist in the same organism, leading to variable and unpredictable cross-resistance to other beta-lactams and to antibacterial drugs of other classes.

Breakpoints

The MIC breakpoints for susceptible organisms vary according to species.
Enterobacteriaceae are considered susceptible when inhibited at ≤ 8 mg/L amoxicillin.
From NCCLS recommendations and using NCCLS-specified methods:
M. catarrhalis (β-lactamase negative) is considered susceptible at ≤ 0.25 µg/ml and resistant at ≥ 0.5 µg/ml;
H. influenzae (β-lactamase negative) is considered susceptible at ≤ 1 µg/ml and resistant at ≥ 4 µg/ml;
S. *pneumoniae* is considered susceptible to amoxicillin at MIC ≤ 0.5 µg/ml and resistant at ≥ 2 µg/ml.

Susceptibility:

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.

SUSCEPTIBLE:

	Frequency of resistance ranges in EU (extreme values)
Gram-positive aerobes	
Bacillus anthracis	
Corynebacterium spp[§]	
Enterococcus faecalis[§]	
Listeria monocytogenes	
Streptococcus agalactiae	
Streptococcus bovis	
Streptococcus pneumoniae [#]	*4.6 – 51.4%*
Streptococcus pyogenes [#]	
Streptococcus viridans[§]	
Gram-negative aerobes:	
Brucella spp [#]	
Escherichia coli	*46.7%*
Haemophilus influenzae	*2 – 31.7%*[a]
Haemophilus parainjluenzae	*15.3%*
Neisseria gonorrhoeae[§]	*12 – 80%*
Neisseria meningitidis [#]	*28%*
Proteus mirabilis	
Salmonella spp[§]	
Shigella spp[§]	
Vibrio cholerae	
Anaerobes	
Bacteroides melaninogenicus[§]	
Clostridium spp	
Fusobacterium spp. [§]	
Peptostreptococci	

RESISTANT

Gram-positive aerobes
Staphylococci (β-lactamase producing strains)

Gram-negative aerobes
Acinetobacter spp
Citrobacter spp
Enterobacter spp
Klebsiella spp

Moraxella catarrha/is Proteus spp (indole positive)
Proteus vulgaris Providencia spp
Pseudomonas spp *Serratia* spp

Anaerobes
Bacteroides fragilis

Others
Chlamydia
Mycoplasma
Rickettsia

a) % of beta-lactamase production
b) % of penicillin-resistance (including intermediate resistance)
No β-lactamase producers have as yet been reported for these bacterial species
§ variably susceptible; susceptibility is therefore unpredictable in the absence of susceptibility testing.

5.2 Pharmacokinetic properties

Absorption:

The absolute bioavailability of amoxicillin depends on the dose and ranges between 75 and 90%. In the dose range between 250 mg and 750 mg the bioavailability (parameters: AUC and/or recovery in urine) is linearly proportional to the dose. At higher doses the extent of absorption decreases. Absorption is not affected by concomitant food intake. Oral administration of a single dose of 500 mg amoxicillin results in plasma concentrations of 6-11 mg/l. After administration of a single dose of 3 g amoxicillin, the plasma concentrations reach 27 mg/l. Peak plasma concentrations are present about 1-2 hours after administration.

Distribution:

Protein binding for amoxicillin is approximately 17%. Therapeutic drug levels are rapidly achieved in serum, lung tissue, bronchial secretions, middle ear fluid, bile and urine. Amoxicillin can penetrate inflamed meninges and enter the cerebrospinal fluid. Amoxicillin crosses the placenta and a small percentage is excreted into the breast milk.

Biotransformation and elimination:

The main route of excretion of amoxicillin is the kidney. About 60-80% of an oral dose of amoxicillin is excreted in unchanged active form in the urine within 6 hours of administration, and a small fraction is excreted in the bile. Approximately 7 - 25% of the administered dose is metabolised to inactive penicilloic acid. The serum half-life in patients with normal renal function is approximately 1 - 1.5 hour. In patients with end-stage renal failure the half-life ranges between 5 to 20 hours. The substance is haemodialysable.

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. Consequently, due to the decreased CL, the exposure is expected to be elevated in this group of patients, although this increase in exposure may in part be diminished by decreased bioavailability when given orally.

5.3 Preclinical safety data

Preclinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity and reprotoxicity.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule contents

Magnesium Stearate

Gelatin

Capsule (Body)

Erythrosine E l27

Patent Blue E l31

Sunset Yellow E 110

Titanium Dioxide E l71

Capsule (Cap)

Yellow Iron Oxide E l72

Titanium Dioxide E 171

6.2 Incompatibilities

None stated.

6.3 Shelf life

36 months.

6.4 Special precautions for storage

Do not store above 25^{o}C. Store in the original container

6.5 Nature and contents of container

Polypropylene container with pilfer proof polyethylene closure containing 100, 500 and 1000 capsules.

6.6 Special precautions for disposal

None.

7 MARKETING AUTHORISATION HOLDER

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8 MARKETING AUTHORISATION NUMBER(S)

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