

1. NAME OF THE MEDICINAL PRODUCT

Curam® 625 mg film-coated tablets.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 500 mg amoxicillin and 125 mg clavulanic acid.

3. PHARMACEUTICAL FORM

Film-coated tablet.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

For the treatment of common bacterial infections where oral therapy is indicated, including:

- Upper respiratory tract infections (including ENT): sinusitis, tonsillitis, otitis media.
- Skin and soft tissue infections: boils/abscesses, cellulitis, wound infections, intra-abdominal sepsis
- Lower respiratory tract infections: acute and chronic bronchitis, pneumonia, lung abscess
- Genito-urinary tract infections: cystitis, urethritis, pyelonephritis, septic abortion, pelvic infection
- Other infections: osteomyelitis, peritonitis, postoperative infections.

4.2 Posology and method of administration

Adults and children over 12 years:

Mild and moderate infections: one Curam 625 mg tablet twice daily.

More severe infections and respiratory tract infections: one Curam 625 mg tablet, three times a day.

Treatment with Curam should not be extended beyond 14 days without review.

Elderly

No dose adjustment is considered necessary.

Dose in renal impairment

Age	Creatinine Clearance	Dose
Adults	Mild impairment (>30ml/min)	No change of dose
	Moderate impairment (10-30 ml/min)	Curam 625 mg 12 hourly
	Severe impairment (<10ml/min)	Not more than Curam 625 mg 24 hourly
Children over 12 years old	Similar reductions in dose should be made.	

Dose in hepatic functional impairment

Dose with caution and monitor hepatic function at regular intervals (see sections 4.3 and 4.4).

Method of administration

For oral use.

Curam is well absorbed whether taken with or before meals. Administer at the start of a meal to minimise potential gastrointestinal intolerance.

4.3 Contraindications

- Hypersensitivity to the active substances, 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).
- History of jaundice/hepatic impairment due to amoxicillin/clavulanic acid (see section 4.8).

4.4 Special warnings and precautions for use

Before initiating therapy with amoxicillin/clavulanic acid, 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 (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/clavulanic acid therapy must be discontinued and appropriate alternative therapy instituted.

In the case that an infection is proven to be due to an amoxicillin-susceptible organisms(s) then consideration should be given to switching from amoxicillin/clavulanic acid to amoxicillin in accordance with official guidance.

This presentation of amoxicillin/clavulanic acid is not suitable for use when there is a high risk that the presumptive pathogens have reduced susceptibility or resistance to beta-lactam agents that is not mediated by beta-lactamases susceptible to inhibition by clavulanic acid. It should not be used to treat penicillin-resistant *S. pneumoniae*.

Convulsions may occur in patients with impaired renal function or in those receiving high doses (see section 4.8).

Amoxicillin/clavulanic acid 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.

Concomitant use of allopurinol during treatment with amoxicillin can increase the likelihood of allergic skin reactions.

Prolonged use may occasionally result in overgrowth of non-susceptible organisms.

The occurrence at the treatment initiation of a feverish generalised erythema associated with pustula may be a symptom of acute generalised exanthemous pustulosis (AGEP) (see Section 4.8). This reaction requires Amoxicillin/clavulanic acid discontinuation and contraindicates any subsequent administration of amoxicillin.

Amoxicillin/clavulanic acid should be used with caution in patients with evidence of hepatic impairment (see sections 4.2, 4.3 and 4.8).

Hepatic events have been reported predominantly in males and elderly patients and may be associated with prolonged treatment. These events have been very rarely reported in children. In all populations, signs and symptoms usually occur during or shortly after treatment but in some cases may not become apparent until several weeks after treatment has ceased. These are usually reversible. Hepatic events may be severe and, in extremely rare circumstances, deaths have been reported. These have almost always occurred in patients with serious underlying disease or taking concomitant medications known to have the potential for hepatic effects (see section 4.8).

Antibiotic-associated colitis has been reported with nearly all antibacterial agents including amoxicillin 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/clavulanic acid should immediately be discontinued, a physician be consulted and an appropriate therapy initiated. Anti-peristaltic medicinal products are contraindicated in this situation.

Periodic assessment of organ system functions, including renal, hepatic and haematopoietic function is advisable during prolonged therapy.

Prolongation of prothrombin time has been reported rarely in patients receiving amoxicillin/clavulanic acid. 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).

In patients with renal impairment, the dose should be adjusted according to the degree of impairment (see section 4.2).

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 4.9).

During treatment with amoxicillin, enzymatic glucose oxidase methods should be used whenever testing for the presence of glucose in urine because false positive results may occur with non-enzymatic methods.

The presence of clavulanic acid in Curam may cause a non-specific binding of IgG and albumin by red cell membranes leading to a false positive Coombs test.

There have been reports of positive test results using the Bio-Rad Laboratories Platelia *Aspergillus* EIA test in patients receiving amoxicillin/clavulanic acid who were subsequently found to be free of *Aspergillus* infection. Cross-reactions with non-*Aspergillus* polysaccharides and polyfuranoses with Bio-Rad Laboratories Platelia *Aspergillus* EIA test have been reported. Therefore, positive test results in patients receiving amoxicillin/clavulanic acid should be interpreted cautiously and confirmed by other diagnostic methods.

NPRA Directive

Serious and occasionally fatal hypersensitivity (including anaphylactoid and severe cutaneous adverse reactions) have been reported in patients receiving therapy with beta-lactams. Before initiating therapy with Curam, careful inquiry should be made concerning previous hypersensitivity reactions to penicillins, cephalosporins, carbapenems or other beta-lactam agents. If an allergic reaction occurs, Curam must be discontinued immediately and appropriate alternative therapy instituted.

4.5 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 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.

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 but not of clavulanic acid.

Mycophenolate mofetil

In patients receiving mycophenolate mofetil, reduction in pre-dose concentration of the active metabolite mycophenolic acid (MPA) of approximately 50% has been reported following commencement of oral amoxicillin plus clavulanic acid. The change in pre-dose level may not accurately represent changes in overall MPA exposure. Therefore, a change in the dose of mycophenolate mofetil should not normally be necessary in the absence of clinical evidence of graft dysfunction. However, close clinical monitoring should be performed during the combination and shortly after antibiotic treatment.

4.6 Pregnancy and lactation

Pregnancy

Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/foetal development, parturition or postnatal development (see section 5.3). Limited data on the use of amoxicillin/clavulanic acid during pregnancy in humans do not indicate an increased risk of congenital malformations. In a single study in women with preterm, premature rupture of the foetal membrane it was reported that prophylactic treatment with amoxicillin/clavulanic acid may be associated with an increased risk of necrotising enterocolitis in neonates. Use should be avoided during pregnancy, unless considered essential by the physician.

Breast-feeding

Both substances are excreted into breast milk (nothing is known of the effects of clavulanic acid on the breast-fed infant).

Consequently, diarrhoea and fungus infection of the mucous membranes are possible in the breast-fed infant, so that breastfeeding might have to be discontinued. The possibility of sensitisation should be taken into account.

Amoxicillin/clavulanic acid should only be used during breast-feeding after benefit/risk assessment by the physician in charge.

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 vomiting.

The ADRs derived from clinical studies and post-marketing surveillance with amoxicillin/clavulanic acid, sorted 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 ($\geq 1/10$)

Common ($\geq 1/100$ to $< 1/10$)

Uncommon ($\geq 1/1,000$ to $< 1/100$)

Rare ($\geq 1/10,000$ to $< 1/1,000$)

Very rare ($< 1/10,000$)

Not known (cannot be estimated from the available data)

Infections and infestations

Common: Mucocutaneous candidosis

Not known: Overgrowth of non-susceptible organism

Blood and lymphatic system disorders

Rare: Reversible leucopenia (including neutropenia), thrombocytopenia

Not known: Reversible agranulocytosis, haemolytic anaemia, prolongation of bleeding time and prothrombin time¹

Immune system disorders¹⁰

Not known: Angioneurotic oedema, anaphylaxis, serum sickness-like syndrome, hypersensitivity vasculitis

Nervous system disorders

Uncommon: Dizziness, headache

Not known: Reversible hyperactivity, convulsions², aseptic meningitis

Gastrointestinal disorders

Very common: Diarrhoea

Common: Nausea³, vomiting
Uncommon: Indigestion
Not known: Antibiotic-associated colitis⁴, black hairy tongue

Hepatobiliary disorders

Uncommon: Rises in AST and/or ALT⁵
Not known: Hepatitis⁶, cholestatic jaundice⁶

Skin and subcutaneous tissue disorders⁷

Uncommon: Skin rash, pruritus, urticaria
Rare: Erythema multiforme
Not known: Stevens-Johnson syndrome, toxic epidermal necrolysis, bullous exfoliative-dermatitis, acute generalized exanthematous pustulosis (AGEP)⁹ and drug reaction with eosinophilia and systemic symptoms (DRESS)

NPRA Directive

Very rare: Drug reaction with eosinophilia and systemic symptoms (DRESS)

Renal and urinary disorders

Not known: Interstitial nephritis, crystalluria⁸

¹ See section 4.4

² See section 4.4

³ Nausea is more often associated with higher oral doses. If gastrointestinal reactions are evident, they may be reduced by taking amoxicillin/clavulanic acid at the start of a meal.

⁴ Including pseudomembranous colitis and haemorrhagic colitis (see section 4.4)

⁵ A moderate rise in AST and/or ALT has been noted in patients treated with beta-lactam class antibiotics, but the significance of these findings is unknown.

⁶ These events have been noted with other penicillins and cephalosporins (see section 4.4).

⁷ If any hypersensitivity dermatitis reaction occurs, treatment should be discontinued (see section 4.4).

⁸ See section 4.9

⁹ See section 4.4

¹⁰ See sections 4.3 and 4.4

4.9 Overdose

Symptoms and signs of overdose

Gastrointestinal symptoms and disturbance of the fluid and electrolyte balances may be evident. Amoxicillin crystalluria, in some cases leading to renal failure, has been observed (see section 4.4).

Convulsions may occur in patients with impaired renal function or in those receiving high doses.

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/clavulanic acid can be removed from the circulation by haemodialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antibacterials for systemic use; beta-lactam antibacterials, penicillins; combinations of penicillins, incl. beta-lactamase inhibitors

ATC code: J01CR02.

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.

Clavulanic acid is a beta-lactam structurally related to penicillins. It inactivates some beta-lactamase enzymes thereby preventing inactivation of amoxicillin. Clavulanic acid alone does not exert a clinically useful antibacterial effect.

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 two main mechanisms of resistance to amoxicillin/clavulanic acid are:

- Inactivation by those bacterial beta-lactamases that are not themselves inhibited by clavulanic acid, including class B, C and D.
- 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/clavulanic acid are those of the European Committee on Antimicrobial Susceptibility Testing (EUCAST)

Organism	Susceptibility breakpoints (µg/ml)	
	Susceptible ≤	Resistant >
Enterobacteriaceae	8 ^{1,2}	8 ²
	32 ^{1,2,3}	32 ^{1,2,3}
<i>Staphylococcus spp</i>	Note ^{4,5}	Note ^{4,5}
<i>Enterococcus</i> ⁶	4 ²	8 ²
<i>Streptococcus A, B, C, G</i> ⁷	Note ⁸	Note ⁸
<i>Streptococcus pneumoniae</i> ³	Note ^{9,10,11}	Note ^{9,10,11}
Viridans group <i>streptococci</i>	Note ¹²	Note ¹²
<i>Haemophilus influenzae</i> ¹³	2 ²	2 ²
<i>Moraxella catarrhalis</i> ¹⁴	1 ²	1 ²
<i>Neisseria gonorrhoeae</i>	Note ¹⁵	Note ¹⁵
Gram-positive anaerobes except <i>Clostridium difficile</i>	4 ²	8 ²
Gram-negative anaerobes	4 ²	8 ²
<i>Pasteurella multocida</i>	1 ²	1 ²
<i>Kingella kingae</i>	Note ¹⁶	Note ¹⁶
PK/PD (non-species related) breakpoints	2 ²	8 ²

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 and the corresponding zone diameter breakpoint S ≥50 mm.

- ² For susceptibility testing purposes, the concentration of clavulanic acid is fixed at 2 mg/l.
- ³ Amoxicillin-clavulanic acid (uncomplicated UTI only)
- ⁴ Most staphylococci are penicillinase producers, which are resistant to benzylpenicillin, phenoxymethylpenicillin, ampicillin, amoxicillin, piperacillin and ticarcillin. Isolates negative for penicillinase and susceptible to methicillin can be reported susceptible to these agents. Isolates positive for penicillinase and methicillin susceptible are susceptible to beta-lactamase inhibitor combinations and isoxazolympenicillins (oxacillin, cloxacillin, dicloxacillin and flucloxacillin). Methicillin resistant isolates are, with few exceptions, resistant to all beta-lactam agents.
- ⁵ Ampicillin susceptible *S. saprophyticus* are mecA -negative and susceptible to ampicillin, amoxicillin and piperacillin (without or with a beta-lactamase inhibitor).
- ⁶ Susceptibility to ampicillin, amoxicillin and piperacillin with and without beta-lactamase inhibitor can be inferred from ampicillin.
- ⁷ Streptococcus groups A, B, C and G do not produce beta-lactamase. The addition of a beta-lactamase inhibitor does not add clinical benefit.
- ⁸ The susceptibility of streptococcus groups A, B, C and G to penicillins is inferred from the benzylpenicillin susceptibility with the exception of phenoxymethylpenicillin and isoxazolympenicillins for streptococcus group B.
- ⁹ Breakpoints for penicillins other than benzylpenicillin relate only to non-meningitis isolates. Isolates fully susceptible to benzylpenicillin (MIC ≤ 0.06 mg/l and/or susceptible by oxacillin disk screen, see note) can be reported susceptible to beta-lactam agents for which clinical breakpoints are listed (including those with "Note").
- ¹⁰ For isolates categorised as intermediate to ampicillin avoid oral treatment with ampicillin, amoxicillin or amoxicillin-clavulanic acid
- ¹¹ Susceptibility inferred from the MIC of ampicillin.
- ¹² For isolates susceptible to benzylpenicillin, susceptibility can be inferred from benzylpenicillin or ampicillin. For isolates resistant to benzylpenicillin, susceptibility is inferred from ampicillin.
- ¹³ Breakpoints are based on intravenous administration.
- ¹⁴ Most *M. catarrhalis* produce beta-lactamase, although beta-lactamase production is slow and may give weak results with *in vitro* tests. Beta-lactamase producers should be reported resistant to penicillins and aminopenicillins without inhibitors.
- ¹⁵ Always test for beta-lactamase. If positive, report resistant to benzylpenicillin, ampicillin and amoxicillin. Tests based on a chromogenic cephalosporin can be used to detect the beta-lactamase. The susceptibility of beta-lactamase negative isolates to ampicillin and amoxicillin can be inferred from benzylpenicillin.
- ¹⁶ The intrinsic activity of clavulanic acid in *K. kingae* is such that the organism is inhibited by ≤ 2 mg/l clavulanic acid. Therefore no MIC breakpoints for amoxicillin-clavulanic acid can be given

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.

Commonly susceptible species

Aerobic Gram-positive microorganisms

Enterococcus faecalis

Gardnerella vaginalis

Staphylococcus aureus (methicillin-susceptible)^f

Streptococcus agalactiae

*Streptococcus pneumoniae*¹

Streptococcus pyogenes and other beta-haemolytic streptococci

Streptococcus viridans group

Aerobic Gram-negative microorganisms

Capnocytophaga spp.

Eikenella corrodens

*Haemophilus influenzae*²

Moraxella catarrhalis

Pasteurella multocida

Anaerobic microorganisms

Bacteroides fragilis
Fusobacterium nucleatum
Prevotella spp.

Species for which acquired resistance may be a problem

Aerobic Gram-positive microorganisms

Enterococcus faecium §

Aerobic Gram-negative microorganisms

Escherichia coli
Klebsiella oxytoca
Klebsiella pneumoniae
Proteus mirabilis
Proteus vulgaris

Inherently resistant organisms

Aerobic Gram-negative microorganisms

Acinetobacter sp.
Citrobacter freundii
Enterobacter sp.
Legionella pneumophila
Morganella morganii
Providencia spp.
Pseudomonas sp.
Serratia sp.
Stenotrophomonas maltophilia

Other microorganisms

Chlamydophila pneumoniae
Chlamydophila psittaci
Coxiella burnetti
Mycoplasma pneumoniae

§ Natural intermediate susceptibility in the absence of acquired mechanism of resistance.

£ All methicillin-resistant staphylococci are resistant to amoxicillin/clavulanic acid.

¹*Streptococcus pneumoniae* that is fully susceptible to penicillin may be treated with this presentation of amoxicillin/clavulanic acid (see sections 4.4).

²Strains with decreased susceptibility have been reported in some countries in the EU with a frequency higher than 10%.

5.2 Pharmacokinetic properties

Absorption

Amoxicillin and clavulanic acid, are fully dissociated in aqueous solution at physiological pH. Both components are rapidly and well absorbed by the oral route of administration. Following oral administration, amoxicillin and clavulanic acid are approximately 70% bioavailable. The plasma profiles of both components are similar and the time to peak plasma concentration (T_{max}) in each case is approximately one hour.

The pharmacokinetic results for a study, in which amoxicillin/clavulanic acid (875 mg/125 mg tablets two times daily) was administered in the fasting state to groups of healthy volunteers are presented below.

Mean (\pm SD) pharmacokinetic parameters					
Active substance(s) administered	Dose (mg)	C_{max} (μ g/ml)	T_{max}^* (h)	AUC _(0-24h) (μ g.h/ml)	$T_{1/2}$ (h)

Amoxicillin					
AMX/CA 875 mg/125 mg	875	11.64 ± 2.78	1.5 (1.0-2.5)	53.52 ± 12.31	1.19 ± 0.21
Clavulanic acid					
AMX/CA 875 mg/125 mg	125	2.18 ± 0.99	1.25 (1.0-2.0)	10.16 ± 3.04	0.96 ± 0.12
AMX - amoxicillin, CA - clavulanic acid *Median (range)					

Amoxicillin and clavulanic acid serum concentrations achieved with amoxicillin/clavulanic acid are similar to those produced by the oral administration of equivalent doses of amoxicillin or clavulanic acid alone.

Distribution

About 25% of total plasma clavulanic acid and 18% of total plasma amoxicillin is bound to protein. The apparent volume of distribution is around 0.3-0.4 l/kg for amoxicillin and around 0.2 l/kg for clavulanic acid.

Following intravenous administration, both amoxicillin and clavulanic acid have 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 for either component.

Amoxicillin, like most penicillins, can be detected in breast milk. Trace quantities of clavulanic acid can also be detected in breast milk (see section 4.6).

Both amoxicillin and clavulanic acid have 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. Clavulanic acid is extensively metabolized in man and eliminated in urine and faeces and as carbon dioxide in expired air.

Elimination

The major route of elimination for amoxicillin is via the kidney, whereas for clavulanic acid it is by both renal and non-renal mechanisms.

Amoxicillin/clavulanic acid has a mean elimination half-life of approximately one hour and a mean total clearance of approximately 25 l/h in healthy subjects. Approximately 60 to 70% of the amoxicillin and approximately 40 to 65% of the clavulanic acid are excreted unchanged in urine during the first 6 h after administration of single amoxicillin/clavulanic acid 250 mg/125 mg or 500 mg/125 mg tablets. Various studies have found the urinary excretion to be 50-85% for amoxicillin and between 27-60% for clavulanic acid over a 24 hour period. In the case of clavulanic acid, the largest amount of drug is excreted during the first 2 hours after administration.

Concomitant use of probenecid delays amoxicillin excretion but does not delay renal excretion of clavulanic acid (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/clavulanic acid to healthy males and female subjects, gender has no significant impact on the pharmacokinetics of either amoxicillin or clavulanic acid.

Renal impairment

The total serum clearance of amoxicillin/clavulanic acid decreases proportionately with decreasing renal function. The reduction in drug clearance is more pronounced for amoxicillin than for clavulanic acid, as a higher proportion of amoxicillin is excreted *via* the renal route. Doses in renal impairment must therefore prevent undue accumulation of amoxicillin while maintaining adequate levels of clavulanic acid (see section 4.2).

Hepatic impairment

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

5.3 Preclinical safety data

Nonclinical data reveal no special hazard for humans based on studies of safety pharmacology, genotoxicity and toxicity to reproduction.

Repeat dose toxicity studies performed in dogs with amoxicillin/clavulanic acid demonstrate gastric irritancy and vomiting, and discoloured tongue.

Carcinogenicity studies have not been conducted with amoxicillin/clavulanic acid or its components.

6. PHARMACEUTICAL PARTICULARS

6.1 Incompatibilities

Not applicable.

6.2 Shelf-life

If properly stored, Curam retains its full potency up to the date of expiration shown on the pack.

6.3 Storage Conditions

Store below 25°C, protect from light and moisture.

Store in the original container.

6.4 Presentation

Oblong, biconvex, white to slightly yellowish film coated tablets, embossed on one side (GG N6), size approx. 10 x 21 mm.

Blister packs of 10, 12, 14, 16, 20, 30 tablets, 72 and 100 tablets.

Not all pack sizes will be marketed.

7. PRODUCT REGISTRATION HOLDER

Sandoz Products Malaysia Sdn. Bhd.

Unit 1202, Level 12, Uptown 1,

No. 1, Jalan SS21/ 58, Damansara Uptown,

47400 Petaling Jaya Selangor, Malaysia

8. DATE OF REVISION OF THE TEXT

April 2025