

**APO-AMOXYCILLIN / CLAVULANIC ACID 500/125 TABLETS**

**NAME OF THE MEDICINE**

Amoxicillin trihydrate and potassium clavulanate.

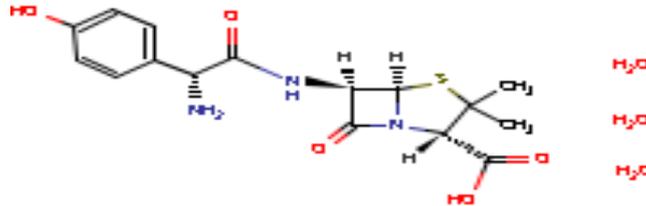
**Chemical Names:**

Amoxicillin trihydrate: (2S,5R,6R)-6-[(R)-2-amino-2-(4-hydroxyphenyl)acetamido]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid trihydrate.

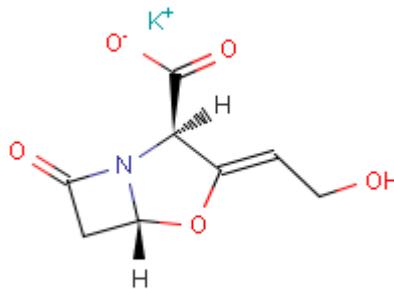
Potassium Clavulanate: potassium (Z)-(2R,5R)-3-(2-hydroxyethylidene)-7-oxo-4-oxa-1-azabicyclo[3.2.0]heptane-2-carboxylate.

**Structural Formulae:**

Amoxicillin trihydrate:



Potassium clavulanate:

**Molecular Formulae:**

Amoxicillin trihydrate:  $C_{16}H_{19}N_3O_5S \cdot 3H_2O$   
 Potassium clavulanate:  $C_8H_8KNO_5$

**Molecular Weights:**

Amoxicillin trihydrate: 419.5  
 Potassium clavulanate: 237.3

**CAS Registry Numbers:**

Amoxicillin trihydrate: 61336-70-7  
 Potassium clavulanate: 61177-45-5

## DESCRIPTION

Amoxicillin and Clavulanic Acid 500 mg / 125 mg is a combination product containing the semi-synthetic antibiotic, amoxicillin (as the trihydrate) and the  $\beta$ -lactamase inhibitor, potassium clavulanate (the potassium salt of clavulanic acid).

Amoxicillin is susceptible to hydrolysis by  $\beta$ -lactamases. Clavulanic acid is produced by the fermentation of *Streptomyces clavuligerus*. It is an irreversible inhibitor of many  $\beta$ -lactamase enzymes except type 1 (Richmond). It is a  $\beta$ -lactam compound with only weak antibacterial activity.

## PHARMACOLOGY

**Actions:** Semisynthetic penicillin antibiotic (amoxicillin) and beta-lactamase inhibitor (clavulanic acid).

### Pharmacokinetics

Pharmacokinetic parameters obtained for 875 mg/125 mg and 500 mg/125 mg amoxicillin/clavulanic acid tablets show a linear relationship for both strengths.

**Absorption:** Amoxicillin and Clavulanic Acid tablets are stable in the presence of gastric acid. The two components are rapidly absorbed if administered before or with a meal, but if given after meals, the serum levels of clavulanic acid are significantly reduced. To optimise absorption of clavulanic acid, Amoxicillin and Clavulanic Acid 500/125 tablets should be administered at the start of a meal. The pharmacokinetics of amoxicillin are not affected by food.

The mean pharmacokinetic parameters are shown in the following table for the oral administration of 875 mg/125 mg and 500 mg/125 mg amoxicillin/clavulanic acid tablets.

Dose**and regimen	AUC <sub>0-24</sub> ( $\mu\text{g} \cdot \text{hr/mL}$ )*		C <sub>max</sub> ( $\mu\text{g/mL}$ )*	
	amoxicillin ( $\pm$ S.D.)	clavulanate (S.D.) ( $\pm$ )	amoxicillin ( $\pm$ S.D.)	clavulanate ( $\pm$ S.D.)
500 mg/125 mg q12h	33.4 $\pm$ 6.76	8.6 $\pm$ 1.95	6.5 $\pm$ 1.41	1.75 $\pm$ 0.61
500 mg/125 mg q8h	53.35 $\pm$ 8.87	15.7 $\pm$ 3.86	7.19 $\pm$ 2.26	2.4 $\pm$ 0.83
875 mg/125 mg q12h	53.52 $\pm$ 12.31	10.2 $\pm$ 3.04	11.64 $\pm$ 2.78	2.2 $\pm$ 0.99
* Mean values of 14 volunteers (n= 15 for clavulanate potassium in the low-dose regimens). Peak concentrations occurred approximately 1.5 hours after the dose.				
** Administered at the start of a light meal.				

**Distribution:** Following oral administration, both amoxicillin and clavulanic acid have been shown to diffuse in significant concentrations into pus, bile and pleural, synovial and peritoneal fluids. Both penetrate poorly into the cerebrospinal fluid (CSF) when the meninges are normal. Amoxicillin penetrates into the CSF better through inflamed meninges but the maximum concentrations are still much lower than the peak serum levels. There are no data at present on the CSF penetration of clavulanic acid in patients with meningeal inflammation.

Neither amoxicillin nor clavulanic acid is highly protein bound. Clavulanic acid has been variously reported to be bound to human serum in the range of 9 to 30% and amoxicillin approximately 20%. From animal studies, there is no evidence to suggest either component accumulates in any organ.

**Excretion:** As with other penicillins, renal excretion is the major route of amoxicillin clearance, while clavulanate elimination is via both renal and non-renal mechanisms. Approximately 70% of the dose of amoxicillin is excreted in urine as amoxicillin. For clavulanic acid, following the administration of 125 mg of radiolabelled potassium clavulanate orally to normal volunteers, 68% of the administered radioactivity was recovered in the urine in 24 hours. Of this, 34% (i.e. 23% of the administered dose) represented unchanged clavulanic acid. 2,5-dihydro-4- (2-hydroxyethyl)-5-oxo-1H-pyrrole-3-carboxylic acid (the major metabolite) and 1-amino-4- hydroxy-butan-2-one accounted for a further 23 and 12% (i.e. 16 and 8% respectively of the administered dose). Small amounts of other yet

unidentified metabolites were also present. These metabolites were also present in the urine of rat and dog. The extent of urinary excretion of clavulanic acid and its metabolites is lower in rat urine than in dog and human urine.

Concurrent administration of probenecid delays amoxicillin excretion but does not delay renal excretion of clavulanic acid.

### Pharmacodynamics

#### Microbiology:

Like other penicillins, amoxicillin has a bactericidal effect on sensitive organisms during the stage of active multiplication. However, amoxicillin is susceptible to hydrolysis by beta-lactamases and the addition of clavulanic acid in Amoxicillin and Clavulanic Acid tablets 500/125 tablets extends the antimicrobial spectrum of amoxicillin to include organisms normally resistant to amoxicillin due to beta-lactamase production.

*In vitro* studies have demonstrated the susceptibility of most strains of the following organisms.

#### Penicillin non-susceptibility:

***The degree of resistance to treatment is classified according to minimum inhibitory concentrations (MICs), defined as the minimum concentration of a particular antibiotic needed to stop pneumococcal growth in vitro***

### Definition of penicillin resistance

<i>Level of resistance*</i>	<b>Minimum inhibitory concentration</b>
Susceptible	≤0.06 µg/mL
Intermediate susceptibility	0.1-1 µg/mL
Resistant	≥2 µg/mL

\*As defined by the United States of America National Committee for Clinical and Laboratory Standards (NCCLS)

### Resistance in *Streptococcus pneumoniae*

The following antimicrobial resistance in clinically significant isolates of *Streptococcus pneumoniae* was reported by the Australian Group for Antimicrobial Resistance (AGAR) in 2003:

<b>Streptococcus pneumoniae</b>	<b>invasive isolates</b>	<b>non-invasive isolates</b>
penicillin susceptible (MIC < 0.064 µg/L)	86%	75%
High-level penicillin resistance	2.6%	6.9%
Multi-drug resistant	6.8%	16.7%

Further evidence of the increase in antibiotic resistance is provided by a 1997 Australian-wide surveillance study showing that approximately 25 percent of the 1,020 isolated strains were non-susceptible to penicillin (16.8% were of intermediate resistant and 8.6% were resistant).

Rate of resistance to amoxicillin-clavulanate was found to be 3.1%.

### Resistance in *Haemophilus influenzae*

Minimal Inhibitory Concentrations (MICs) to 16 different antibiotics were determined for collection of 970 isolates of *H. influenzae* within Australia. The overall rate of beta-lactamase production was 16% but there was wide variation between the isolates. In invasive strains beta-lactamase production was

22.3% but in respiratory tract isolates it was 35.3%. In non-invasive strains the resistance to amoxicillin-clavulanate was 2.1%.

It should be noted that resistance can vary from region to region and that information on local resistance should be taken into account.

#### Acquired resistance data for amoxicillin/clavulanic acid from other countries

Breakpoint	Number of pathogens	Percent acquired resistance
<b>Sensitive aerobe gram positive</b>		
<i>Enterococcus faecalis</i>	178	1.7
<i>Staphylococcus aureus</i>	955	2
<i>Staphylococcus aureus</i> (MSSA)	2458	2
Coagulase negative staphylococci	158	7
<i>Streptococcus agalactiae</i>	96	1
<i>Streptococcus pneumoniae</i>	196	8.5
<i>Streptococcus pneumoniae</i> (Pen-S)	154	0
<i>Streptococcus pyogenes</i>	76	0
Streptococcus species	28	0
<b>Sensitive aerobe gram negative</b>		
<i>Escherichia coli</i>	946	5
<i>Haemophilus influenzae</i>	180	1.1
<i>Haemophilus influenzae</i> (BLN)	150	1.3
<i>Haemophilus influenzae</i> (BLP)	30	0
<i>Klebsiella pneumoniae</i>	355	1
<i>Klebsiella oxytoca</i>	1540	9.6
<i>Moraxella catarrhalis</i>	46	0
Proteus species	128	5
<b>Sensitive anaerobe</b>		
Clostridium species	42	0
<i>Clostridium difficile</i>	27	0
Peptostreptococcus species	17	0
<i>Bacteroides fragilis</i>	98	5
<i>Bacteroides fragilis</i> group	163	7
Fusobacterium species	16	0
<b>Intermediate aerobe gram negative</b>		
Acinetobacter species	49	12
<b>Resistant aerobe gram positive</b>		
<i>Staphylococcus aureus</i> (MRSA)	147	59.2
<b>Resistant aerobe gram negative</b>		
Citrobacter species	84	56
Enterobacter species	181	86
Morganella species	39	97
Providencia species	14	79
Serratia species	61	89
<i>S. maltophilia</i>	57	96

The percent acquired resistance data provided in the above table have been collected from the following countries during the time period specified: USA 1996; Canada 93-94; USA/Canada 96-97; France 94-95; USA/Arabia 94-95; USA 96-97; USA 91-93; Belgium 93-94; UK, Netherlands 89-95.

It should be noted that methicillin resistant strains are resistant to amoxicillin/clavulanic acid tablets. *Proteus vulgaris* and *Klebsiella* species may not be susceptible to amoxicillin/clavulanic acid tablets at concentrations of amoxicillin and clavulanic acid achieved in the plasma. However, at concentrations of amoxicillin and clavulanic acid achievable in the urine, the majority of strains are

susceptible.

**Susceptibility tests:**

Dilution or diffusion techniques - either quantitative (MIC) or breakpoint should be used following a regularly updated, recognized and standardized method (e.g. NCCLS). Standardised susceptibility test procedures require the use of laboratory control microorganisms to control the technical aspects of the laboratory procedures.

A report of “Susceptible” indicates that the pathogen is likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations usually achievable. A report of “Intermediate” indicates that the result should be considered equivocal, and if the microorganism is not fully susceptible to alternative, clinically feasible drugs, the test should be repeated. This category implies possible clinical applicability in body sites where the drug is physiologically concentrated or in situations where high dosage of drug can be used. This category also provides a buffer zone, which prevents small uncontrolled technical factors from causing major discrepancies in interpretation. A report of “Resistant” indicates that the pathogen is not likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations usually achievable: other therapy should be selected.

Note: The prevalence of resistance may vary geographically for selected species and local information on resistance is desirable, particularly when treating severe infections.

**INDICATIONS**

Short term treatment of bacterial infections at the following sites when caused by sensitive organisms (refer to **Microbiology**):

- Urinary Tract Infections (uncomplicated and complicated)
- Lower Respiratory Tract Infections, including community acquired pneumonia and acute exacerbations of chronic bronchitis
- Upper Respiratory Tract Infections, such as sinusitis, otitis media and recurrent tonsillitis
- Skin and Skin Structure Infection

Appropriate culture and susceptibility studies should be performed to identify the causative organism(s) and determine its (their) susceptibility to Amoxicillin and Clavulanic Acid tablets. However, when there is reason to believe an infection may involve any of the beta-lactamase producing organisms listed above, therapy may be instituted prior to obtaining the results from bacteriological and susceptibility studies. Once these results are known, therapy should be adjusted if appropriate.

The treatment of mixed infections caused by amoxicillin susceptible organisms and beta-lactamase producing organisms susceptible to Amoxicillin and Clavulanic Acid tablets should not require the addition of another antibiotic due to the amoxicillin content of this product.

**CONTRAINDICATIONS**

- A history of allergic reaction to beta-lactams e.g. penicillins or cephalosporins
- A previous history of amoxicillin/clavulanic acid-associated jaundice or hepatic dysfunction.

## PRECAUTIONS

### Anaphylactic Reactions

**SERIOUS AND OCCASIONALLY FATAL HYPERSENSITIVITY (ANAPHYLACTOID) REACTIONS HAVE BEEN REPORTED IN PATIENTS ON PENICILLIN THERAPY. ALTHOUGH ANAPHYLAXIS IS MORE FREQUENT FOLLOWING PARENTERAL THERAPY, IT HAS OCCURRED IN PATIENTS ON ORAL PENICILLINS. THESE REACTIONS ARE MORE LIKELY TO OCCUR IN INDIVIDUALS WITH A HISTORY OF PENICILLIN HYPERSENSITIVITY AND/OR A HISTORY OF SENSITIVITY TO MULTIPLE ALLERGENS.**

**THERE HAVE BEEN REPORTS OF INDIVIDUALS WITH A HISTORY OF PENICILLIN HYPERSENSITIVITY WHO HAVE EXPERIENCED SEVERE REACTIONS WHEN TREATED WITH CEPHALOSPORINS. BEFORE INITIATING THERAPY WITH ANY PENICILLIN, CAREFUL INQUIRY SHOULD BE MADE CONCERNING PREVIOUS HYPERSENSITIVITY REACTIONS TO PENICILLINS, CEPHALOSPORINS, OR OTHER ALLERGENS.**

**IF AN ALLERGIC REACTION OCCURS, AMOXYCILLIN AND CLAVULANIC ACID TABLETS SHOULD BE DISCONTINUED AND THE APPROPRIATE THERAPY INSTITUTED. SERIOUS ANAPHYLACTOID REACTIONS REQUIRE IMMEDIATE EMERGENCY TREATMENT WITH ADRENALINE. OXYGEN, INTRAVENOUS STEROIDS, AND AIRWAY MANAGEMENT, INCLUDING INTUBATION, SHOULD ALSO BE ADMINISTERED AS INDICATED.**

Antibiotic associated pseudomembranous colitis has been reported with many antibiotics including amoxicillin. A toxin produced with *Clostridium difficile* appears to be the primary cause. The severity of the colitis may range from mild to life threatening. It is important to consider this diagnosis in patients who develop diarrhoea or colitis in association with antibiotic use (this may occur up to several weeks after cessation of antibiotic therapy). Mild cases usually respond to drug discontinuation alone. However in moderate to severe cases appropriate therapy with a suitable oral antibiotic agent effective against *Clostridium difficile* should be considered. Fluids, electrolytes and protein replacement should be provided when indicated. Drugs which delay peristalsis, e.g. opiates and diphenoxylate with atropine (Lomotil®) may prolong and/or worsen the condition and should not be used.

### Other

As with any potent drug, periodic assessment of organ system functions, including renal, hepatic and haemopoietic function, is advisable during prolonged therapy.

Since Amoxicillin and Clavulanic Acid tablets contain amoxicillin, an aminopenicillin, these are not the treatment of choice in patients presenting with sore throat or pharyngitis because of the possibility that the underlying cause is infectious mononucleosis, in the presence of which there is a high incidence of rash if amoxicillin is used.

Amoxicillin and Clavulanic Acid tablets should be given with caution to patients with lymphatic leukaemia since they are especially susceptible to amoxicillin induced skin rashes.

The possibility of superinfections with mycotic or bacterial pathogens should be kept in mind during therapy. If superinfections occur (usually involving *Aerobacter*, *Pseudomonas* or *Candida*), the drug should be discontinued and/or appropriate therapy instituted.

Hepatitis and cholestatic jaundice have been reported rarely. These events have been noted with other penicillins and cephalosporins.

Cholestatic hepatitis, which may be severe but is usually reversible, has been reported. Signs and symptoms may not become apparent until several weeks after treatment has ceased. In most cases resolution has occurred with time. However, in extremely rare circumstances, deaths have been reported. These have almost always been cases associated with serious underlying disease or taking concomitant medications.

Hepatic events subsequent to amoxicillin/clavulanic acid have occurred predominantly in males and elderly patients and may be associated with prolonged treatment.

**Impaired renal function:**

Amoxicillin and Clavulanic Acid 500 /125 tablets should be used with care in patients with moderate or severe renal impairment. The dosage of Amoxicillin and Clavulanic Acid 500/125 tablets should be adjusted as recommended in the Dosage and Administration section.

**Impaired hepatic function:**

Amoxicillin and Clavulanic Acid tablets should be used with care in patients with evidence of hepatic dysfunction.

**Carcinogenesis, mutagenesis, impairment of fertility**

Long-term studies in animals have not been performed to evaluate carcinogenic or mutagenic potential.

**Use in Pregnancy (Category B1)**

Animal studies with orally and parenterally administered amoxicillin and clavulanic acid have shown no teratogenic effects. There is limited experience of the use of Amoxicillin and Clavulanic Acid tablets in human pregnancy. In women with preterm, premature rupture of the foetal membrane (pPROM), prophylactic treatment with amoxicillin and clavulanic acid may be associated with an increased risk of necrotising enterocolitis in neonates. As with all medicines, use should be avoided in pregnancy, especially during the first trimester, unless considered essential by the doctor.

*Category B1:*

*Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human foetus having been observed. Studies in animals have not shown evidence of an increased occurrence of foetal damage.*

**Use in Labour and Delivery**

Oral ampicillin class antibiotics are generally poorly absorbed during labour. Studies in guinea pigs have shown that intravenous administration of ampicillin decreased the uterine tone, frequency of contractions, height of contractions and duration of contractions. However, it is not known whether the use of Amoxicillin and Clavulanic Acid tablets in humans during labour or delivery has immediate or delayed adverse effects on the foetus, prolongs the duration of labour or increases the likelihood that forceps delivery or other obstetrical intervention or resuscitation of the newborn will be necessary.

**Use in Lactation**

Amoxicillin is excreted in the milk; there are no data on the excretion of clavulanic acid in human milk. Therefore, caution should be exercised when Amoxicillin and Clavulanic Acid tablets are administered to a breastfeeding woman.

**Interactions with Other Medicines**

Probenecid decreases the renal tubular secretion of amoxicillin but does not affect clavulanic acid excretion. Concurrent use with Amoxicillin and Clavulanic Acid tablets may result in increased and prolonged blood levels of amoxicillin but not of clavulanic acid.

The concurrent administration of allopurinol and ampicillin increases substantially the incidence of rashes in patients receiving both drugs as compared to patients receiving ampicillin alone. It is not known whether this potentiation of ampicillin rashes is due to allopurinol or the hyperuricaemia present in these patients. There are no data with Amoxicillin and Clavulanic Acid tablets and allopurinol administered concurrently.

No information is available about the concurrent use of Amoxicillin and Clavulanic Acid tablets and alcohol. However, the ingestion of alcohol whilst being treated with some other beta-lactam antibiotics has precipitated a disulfiram (Antabuse<sup>®</sup>) like reaction in some patients. Therefore the ingestion of alcohol should be avoided during and for several days after treatment with Amoxicillin and Clavulanic Acid tablets.

In common with other broad spectrum antibiotics, Amoxicillin and Clavulanic Acid tablets may reduce the efficacy of oral contraceptives and patients should be warned accordingly.

### Effect on Laboratory Tests

Oral administration of Amoxicillin and Clavulanic Acid tablets will result in high urine concentrations of amoxicillin. Since high urine concentrations of ampicillin may result in false positive reactions when testing for the presence of glucose in urine using Clinitest, Benedict's Solution or Fehling's Solution, it is recommended that glucose tests based on enzymatic glucose oxidase reactions (such as Clinistix or Testape) be used.

Following administration of ampicillin to pregnant women a transient decrease in plasma concentration of total conjugated oestriol, oestriol-glucuronide, conjugated oestrone and oestradiol has been noted. This effect may also occur with amoxicillin and therefore Amoxicillin and Clavulanic Acid tablets.

### ADVERSE EFFECTS

Amoxicillin and clavulanic acid tablets are generally well tolerated. The majority of events were of a mild and transient nature.

### Clinical Trials

During clinical trials, the most frequently reported adverse events related or possibly related to amoxicillin and clavulanic acid therapy were diarrhoea (14.9%), nausea (7.9%), headache (6.8%), abdominal pain (4.5%), vomiting (3.8%), genital moniliasis (3.6%) and vaginitis (3.4%).

The following adverse events have been observed during clinical trials with amoxicillin and clavulanic acid 875mg/125mg tablets, however it should be noted that causality has not necessarily been established for these events:

*The most frequently (greater than or equal to 1%) reported adverse experiences in decreasing order for the twice daily regimen (n = 584) - Diarrhoea (14.9%), nausea (7.9%), headache (6.8%), abdominal pain (4.5%), vomiting (3.8%), genital moniliasis (3.6%), vaginitis (3.4%- denominator is number of females), back pain (1.9%), dizziness (1.7%), fungal infection (1.7%), rash (1.5%), sinusitis (1.4%), fatigue (1.2%), genital pruritus (1.2%), injury (1.0%), pain (1.0%), urinary tract infection (1.0%), insomnia (1.0%), myalgia (1.0%).*

During clinical trials, the most frequently reported adverse events related or possibly related to Amoxicillin and Clavulanic Acid 500 mg/125 mg therapy were diarrhoea (12.8%), nausea (5.2%), headache (4.8%), abdominal pain (4.5%).

The following adverse events have been observed during clinical trials with Amoxicillin and Clavulanic acid 500 mg/125 mg, however it should be noted that causality has not necessarily been established for these events.

*The most frequently (greater than or equal to 1%) reported adverse experiences in decreasing order for the twice daily regimen (n = 462):*

Diarrhoea (12.8%), nausea (5.2%), headache (4.8%), upper respiratory infection (1.9%), genital moniliasis (1.9%), vomiting (1.5%), dyspepsia (1.1%), injury (1.1%).

### Post-Marketing

In addition, the following adverse reactions have been reported for ampicillin class antibiotics and may occur with Amoxicillin and Clavulanic Acid 500 mg/ 125 mg tablets:

very common  $\geq 1/10$

common  $\geq 1/100$  and  $< 1/10$

uncommon  $\geq 1/1000$  and  $< 1/100$

rare  $\geq 1/10000$  and  $< 1/1000$

very rare  $< 1/10000$

*Gastrointestinal*

Rare: Nausea, indigestion, gastritis, stomatitis, glossitis, black "hairy" tongue, enterocolitis. Mucocutaneous candidiasis and antibiotic associated colitis (including pseudomembranous colitis and haemorrhagic colitis), see PRECAUTIONS.

*Hepatobiliary*

Rare: Moderate rise in AST and/or ALT. Hepatitis, cholestatic jaundice which may be severe but is usually reversible.

*CNS*

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

*Haematopoietic and Lymphatic*

Rare: Anaemia, thrombocytopenia, thrombocytopenic purpura, eosinophilia, reversible leukopenia (including neutropenia or agranulocytosis); these are usually reversible on discontinuation of therapy and are believed to be hypersensitivity phenomena; Prolongation of bleeding time and prothrombin time.

Uncommon: Thrombocytosis.

*Hypersensitivity and Skin*

Common: Skin rashes, pruritis, urticaria.

Rare: Angioneurotic oedema, anaphylaxis, serum-sickness-like syndrome, erythema multiforme, Stevens-Johnson syndrome, hypersensitivity, vasculitis, toxic epidermal necrolysis, bullous exfoliative dermatitis and acute generalised exanthematous pustulosis (AGEP).

Whenever such reactions occur, Amoxicillin and Clavulanic Acid tablets should be discontinued, unless in the opinion of the physician no alternative treatment is available and continued use is considered essential. Serious and occasional fatal hypersensitivity (anaphylactic) reactions and angioneurotic oedema can occur with oral penicillins (see **PRECAUTIONS**).

*Miscellaneous*

Rare: Interstitial nephritis, superficial tooth discolouration which can usually be removed by brushing.

**DOSAGE AND ADMINISTRATION**

*APO-Amoxicillin and Clavulanic Acid 500/125 tablets should be taken immediately before or with the first mouthful of food, to minimise potential gastrointestinal intolerance and to optimise absorption.*

**Adults**

The usual adult dose is one APO-Amoxicillin and Clavulanic Acid 500/125 tablet every 12 hours.

Treatment should usually be continued for 48 to 72 hours beyond the time that the patient becomes asymptomatic or evidence of bacterial eradication has been obtained. Treatment should not exceed 14 days without review.

**Adults with Impaired Renal Function**

Both amoxicillin and clavulanic acid are excreted by the kidneys and the serum half-life of each increases in patients with renal failure. No adjustment to the initial Amoxicillin and Clavulanic Acid 500/125 dose is necessary, but the dosing interval should be extended according to the degree of renal impairment.

The following schedule is proposed for APO-Amoxicillin and Clavulanic Acid 500/125.

Mild impairment (creatinine clearance > 30 mL/minute): No change in dosage.

Moderate impairment (creatinine clearance 10 to 30 mL/minute): One tablet 12 hourly.

Severe impairment (creatinine clearance < 10 mL/minute): One tablet every 24 hours.

Haemodialysis decreases serum concentrations of both amoxicillin and clavulanic acid and an additional dose should be administered at the end of dialysis.

**Adults with Impaired Hepatic Function**

Data are currently insufficient for a dosage recommendation. Dose with caution, and monitor hepatic function at regular intervals.

**Children**

Children weighing 40 kg and more should be dosed according to the adult recommendations.

**OVERDOSAGE**

**Symptoms**

Serious and severe clinical symptoms are unlikely to occur after overdosage with Amoxicillin and Clavulanic Acid tablets. If encountered, gastrointestinal symptoms and disturbance of the fluid and electrolyte balances may be evident.

**Treatment**

Symptoms may be treated symptomatically, with attention to the water/electrolyte balance. Amoxicillin may be removed from the circulation by haemodialysis.

**Contact the Poisons Information Centre on 13 11 26 (Australia) for advice on the management of overdosage.**

## **PRESENTATION AND STORAGE CONDITIONS**

### **APO-Amoxicillin and Clavulanic Acid Amoxicillin 500 mg / 125 mg tablets:**

White, convex capsule shaped film coated tablet

Blister packs of 10 tablets

AUST R number 153775

**APO-Amoxicillin and Clavulanic Acid 500 mg / 125 mg tablets** are intended for oral administration. Each tablet contains amoxicillin trihydrate equivalent to amoxicillin 500 mg and potassium clavulanate equivalent to clavulanic acid 125mg.

In addition, each tablet contains the following inactive ingredients: microcrystalline cellulose, sodium starch glycollate, colloidal anhydrous silica, magnesium stearate, purified talc, titanium dioxide, methyl cellulose, diethyl phthalate and dimethicone 100.

Store below 25°C.

Protect from moisture.

## **NAME AND ADDRESS OF THE SPONSOR**

Southern Cross Pharma Pty Ltd

56 Illabunda Drive

Malua Bay, NSW, 2536

## **NAME AND ADDRESS OF THE DISTRIBUTOR**

Apotex Pty Ltd

66 Waterloo Road

North Ryde NSW 2113

Australia

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## **POISONS SCHEDULE OF THE MEDICINE**

S4 - Prescription Only Medicine.

**Date of TGA approval:** 3 April 2009

**Date of most recent amendment:** 15 August 2009