

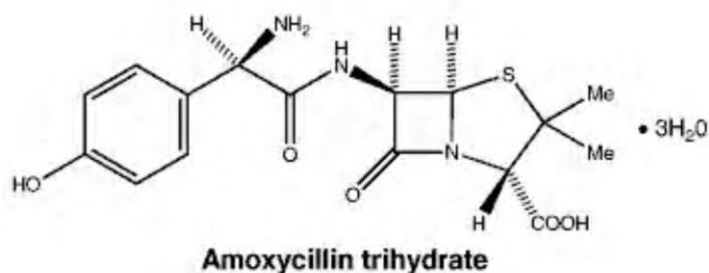
**PRODUCT INFORMATION**  
**APO-AMOXYCILLIN AND CLAVULANIC ACID 125/31.25 POWDER FOR**  
**ORAL SUSPENSION**

**NAME OF THE MEDICINE**

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

*Generic name:* Amoxicillin trihydrate

*Chemical structure:*



CAS [61336-70-7]

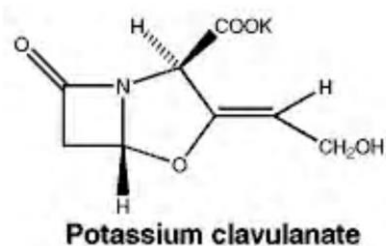
*Empirical formula:* C<sub>16</sub>H<sub>19</sub>N<sub>3</sub>O<sub>5</sub>S.3H<sub>2</sub>O

MW: 419.5

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

*Generic name:* potassium clavulanate

*Chemical structure:*



CAS [61177-45-5]

*Empirical formula:* C<sub>8</sub>H<sub>8</sub>KNO<sub>5</sub>

MW: 237.3

**DESCRIPTION**

APO-AMOXYCILLIN AND CLAVULANIC ACID 125/31.25 is a combination product containing the semisynthetic antibiotic, amoxicillin (as the trihydrate) and the beta-lactamase inhibitor, clavulanic acid (as the potassium salt).

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.

*Excipients:* Lemon Flavouring 15.02.0598, Peach-Apricot Flavouring 26F22, Citric acid anhydrous, Sodium citrate anhydrous, Aspartame, Talc-purified, Orange Flavouring 55301 AP0551, Guar gum and Silicon dioxide. Contains sulfites.

When reconstituted as directed, APO-AMOXYCILLIN AND CLAVULANIC ACID 125/31.25 contains aspartame 8.5mg/5mL.

Each 5 mL of suspension contains 0.16 mmol of potassium.

## PHARMACOLOGY

### 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 APO-AMOXYCILLIN AND CLAVULANIC ACID 125/31.25 extends the antimicrobial spectrum of amoxicillin to include organisms normally resistant to amoxicillin due to beta-lactamase production.

### In-vitro studies

*In-vitro* studies do not always reflect the target patient population, in which the host's immune system usually plays an important role in the clinical and microbiological outcome of infection. For example, they are essentially simulations of infection in immunocompromised persons in that the total antibacterial activity observed is solely dependent on the medicine. Also methodological differences between laboratories and the difficulties of dilution and diffusion techniques can make the data unreliable.

### *Susceptibility tests:*

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

Current Standards for amoxicillin/clavulanic acid powder should provide the following MIC values. See Table 1.

Microorganism	MIC Range ( $\mu\text{g/mL}$ ) <sup>#</sup>
<sup>#</sup> Expressed as concentration of amoxicillin in the presence of clavulanic acid at a constant 2 parts amoxicillin to 1 part clavulanic acid.	
<i>E. coli</i> ATCC 25922	2 to 8
<i>E. coli</i> ATCC 35218	4 to 16
<i>E. faecalis</i> ATCC 29212	0.25 to 1.0
<i>H. influenzae</i> ATCC 49247	2 to 16
<i>S. aureus</i> ATCC 29213	0.12 to 0.5
<i>S. pneumoniae</i> ATCC 49619	0.03 to 0.12

Recommended interpretive criteria based on usual dosage regimens and routes of administration (Interpretive breakpoints) as defined by the Clinical and Laboratory Standard Institute (CLSI) guidelines are listed below.

#### Susceptible (S)

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.

#### Intermediate (I)

A report of "Intermediate" Category includes isolates with antimicrobial agent MICs that approach usually attainable blood and tissue levels and for which response rates may be lower than for susceptible isolates. 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

#### Resistant (R)

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.

#### *Streptococcus pneumoniae*

Antimicrobial susceptibility and resistance by *S. pneumoniae* is usually defined and discussed in the context of activity by penicillin. By definition, a *S. pneumoniae* isolate with a minimum inhibitory concentration (MIC)  $\leq 0.06\mu\text{g/mL}$  or less is considered to be susceptible. Non-susceptible isolates are defined as intermediate non-susceptible ( $0.12\text{--}1\mu\text{g/mL}$ ) or resistant ( $\geq 2\mu\text{g/mL}$ ). Until 2000, the MIC interpretive standards for penicillin and amoxicillin were similar for *S. pneumoniae*.

For *S. pneumoniae* from non-meningitis sources: Isolates should be tested using amoxicillin/clavulanic acid and the following criteria should be used (see Table 2):

**Table 2: Minimum Inhibitory Concentrations (MIC) breakpoints for *Streptococcus pneumoniae***

Level of resistance*	MIC µg/mL
Susceptible (S)	≤ 2µg/mL
Intermediate susceptibility (I)	4µg/mL
Resistant (R)	≥ 8µg/mL

\* interpretive breakpoints as defined by the clinical and laboratory standard institute (CLSI) guideline.  
 Note: These interpretive criteria are based on the recommended doses for respiratory tract infections.

**Table 3: Resistance in *Streptococcus pneumoniae***

Following antimicrobial resistance in clinically significant isolates of *Streptococcus pneumoniae* was reported by the Australian Group for Antimicrobial Resistance (AGAR).

**Table 3**

<i>Streptococcus pneumoniae</i>	Invasive isolates	Non-invasive isolates
Penicillin susceptible (MIC < 0.064mg/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% of the 1,020 isolated strains were non-susceptible to penicillin (16.8% were intermediately resistant and 8.6% were resistant). Rates of resistance to amoxicillin-clavulanate was found to be 3.1%

**Resistance in *Haemophilus influenzae***

**Table 4: Minimum Inhibitory Concentrations (MIC) breakpoints for *Haemophilus influenzae***

Level of resistance	MIC µg/mL
Susceptible (S)	≤ 1µg/mL
Intermediate susceptibility (I)	2µg/mL
Resistant (R)	≥ 4µg/mL

These interpretive standards are applicable only to broth micro dilution test with *Haemophilus influenzae* using Haemophilus test medium (HTM).

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 states.

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%.

### Pharmacokinetics

**Absorption.** Amoxicillin and clavulanic acid are stable in the presence of gastric acid. These 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. In fasting subjects mean peak serum levels after one amoxicillin and clavulanic acid (250/125mg) tablet were 2.98mg/L (range 1.2 to 5.1) for clavulanic acid and 3.89mg/L (range 2.4 to 6.0) for amoxicillin. These levels occurred at 30 to 120 minutes and 60 to 240 minutes respectively after dosing. Following one amoxicillin and clavulanic acid (500/125mg) tablet, peak serum levels in fasting subjects were 3.28 to 4.72mg/L for clavulanic acid and 10.28 to 12.06mg/L for amoxicillin, and were achieved 60 to 120 minutes after dosing.

Following oral administration of amoxicillin and clavulanic acid (125/31.25mg in 5mL) suspension at a dose of 8.3mg/kg (amoxicillin 6.6mg/kg and clavulanic acid 1.7mg/kg) to children with otitis media, the means of peak concentrations were 2.76mg/L for amoxicillin and 0.78mg/L for clavulanic acid. In children given amoxicillin and clavulanic acid (400/57mg in 5mL) suspension 16.6mg/kg (amoxicillin 13.3mg/kg and clavulanic acid 3.3mg/kg), the means of peak values were 4.94mg/L for amoxicillin and 1.53mg/L for clavulanic acid. Peak concentrations were reached at approximately 60 minutes (range 40 to 120 minutes). The half-life of the amoxicillin is approximately 1.2 hours and that of clavulanic acid approximately 1.0 hour.

Oral administration of single doses of APO-AMOXYCILLIN AND CLAVULANIC ACID 125/31.25 amoxicillin 125mg/5mL & clavulanic acid 31.25mg/5mL oral suspension to fasting adult volunteers yielded comparable pharmacokinetic data to reference amoxicillin 125mg/5mL & clavulanic acid 31.25mg/5mL oral suspension and these data are tabulated in Table 5 below.

**Table 5: Pharmacokinetic data following oral administration of single doses of APO-AMOXYCILLIN AND CLAVULANIC ACID 125/31.25 amoxicillin 125mg/5mL & clavulanic acid 31.25mg/5mL oral suspension to fasting adult volunteers**

Dose	AUC <sub>0-t</sub> (µg.hr/mL)		C <sub>max</sub> (µg/mL)	
	amoxicillin (±S.D.)	clavulanic acid (±S.D.)	amoxicillin (±S.D.)	clavulanic acid (±S.D.)
APO-AMOXYCILLIN AND CLAVULANIC ACID 125/31.25 amoxicillin 125mg/5mL & clavulanic acid 31.25mg/5mL suspension	18.00 ± 5.19	4.276 ± 1.123	7.23 ± 1.52	2.490 ± 0.790
amoxicillin 125mg/5mL & clavulanic acid 31.25mg/5mL reference suspension	17.33 ± 5.26	4.264 ± 1.053	6.93 ± 1.36	2.413 ± 0.641

The following mean amoxicillin and clavulanic acid pharmacokinetic parameters in children have been reported for reference amoxicillin/clavulanic acid suspension products. See Table 6 below.

**Table 6: Pharmacokinetic data following oral administration of single doses of reference amoxicillin 125mg/85mL & clavulanic acid 31.25mg/5mL oral suspension to children**

Dose	C <sub>max</sub> (µg/mL)	
	amoxicillin	clavulanic acid
amoxicillin 125mg/5mL & clavulanic acid 31.25mg/5mL suspension		
8.3mg/Kg (8h)	2.76	0.78
16.6mg/Kg (12h)	4.94	1.53

*Distribution.* Following administration of amoxicillin and clavulanic acid, both amoxicillin and clavulanic acid have been shown to diffuse in significant concentrations into pus, pleural 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.

*Metabolism and excretion.* Approximately 70% of the dose of amoxicillin is excreted as amoxicillin and approximately 30 to 40% of a dose of clavulanic acid is excreted in the urine, as clavulanic acid, during the first six hours after administration.

Following the administration of radiolabelled potassium clavulanate 125mg orally to normal volunteers, 68% of the administered radioactivity was recovered in the 24 hour urine. 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.

Clavulanic acid has been variously reported to be bound to human serum in the range of 9 to 30% and amoxicillin approximately 20% bound.

## INDICATIONS

APO-AMOXYCILLIN AND CLAVULANIC ACID 125/31.25 (amoxicillin and clavulanic acid) is indicated for the treatment of the following infections when caused by APO-AMOXYCILLIN AND CLAVULANIC ACID 125/31.25 sensitive, beta-lactamase producing organisms:

Skin and skin structure infections, including cases caused by beta-lactamase producing *Staph. aureus*, *E. coli* and *Klebsiella* sp. (only some strains may be sensitive).

Urinary tract infections, including cases caused by beta-lactamase producing *E. coli*, *P. mirabilis* and *Klebsiella* sp.

Upper respiratory tract infections, such as sinusitis, including cases caused by beta-lactamase producing *H. influenzae* and *M. catarrhalis*, and otitis media, especially cases caused by beta-lactamase producing *H. influenzae*, *M. catarrhalis* and *Staph. aureus*.

Lower respiratory tract infections, especially cases caused by beta-lactamase producing *H. influenzae* and *M. catarrhalis*.

Appropriate culture and susceptibility studies should be performed to identify the causative organism(s) and determine its (their) susceptibility to APO-AMOXYCILLIN AND CLAVULANIC ACID 125/31.25 (amoxicillin and clavulanic acid). However, when there is reason to believe an infection may involve any of the beta-lactamase producing organisms listed in Microbiology, 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 APO-AMOXYCILLIN AND CLAVULANIC ACID 125/31.25 (amoxicillin and clavulanic acid) should not require the addition of another antibiotic due to the amoxicillin content of APO-AMOXYCILLIN AND CLAVULANIC ACID 125/31.25.

## **CONTRAINDICATIONS**

APO-AMOXYCILLIN AND CLAVULANIC ACID 125/31.25 (amoxicillin and clavulanic acid) is contraindicated in patients with a history of allergic reaction to beta-lactams, e.g. penicillins or cephalosporins.

APO-AMOXYCILLIN AND CLAVULANIC ACID 125/31.25 (amoxicillin and clavulanic acid) is also contraindicated in patients with a previous history of cholestatic jaundice/ hepatic dysfunction associated with Amoxicillin and Clavulanic acid.

## **PRECAUTIONS**

Use with caution in the following circumstances:

APO-AMOXYCILLIN AND CLAVULANIC ACID 125/31.25 (amoxicillin and clavulanic acid) contains aspartame, and should be used with caution in patients with phenylketonuria.

**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, APO-AMOXYCILLIN AND CLAVULANIC ACID 125/31.25 (AMOXYCILLIN AND CLAVULANIC ACID) 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 by *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 *Cl. 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.

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

Since APO-AMOXYCILLIN AND CLAVULANIC ACID 125/31.25 (amoxicillin and clavulanic acid) contains amoxicillin, an aminopenicillin, it is 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.

APO-AMOXYCILLIN AND CLAVULANIC ACID 125/31.25 (amoxicillin and clavulanic acid) should be given with caution to patients with lymphatic leukaemia since they are especially susceptible to amoxicillin induced skin rashes.

Prolonged use may also occasionally result in overgrowth of nonsusceptible organisms.

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.

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 concomitant medications. Hepatic events subsequent to amoxicillin and clavulanic acid have occurred predominantly in males and elderly patients and may be associated with prolonged treatment. These events have been very rarely reported in children.

*Impaired renal function.* In patients with moderate or severe renal impairment, APO-AMOXYCILLIN AND CLAVULANIC ACID 125/31.25 (amoxicillin and clavulanic acid) dosage should be adjusted (see DOSAGE AND ADMINISTRATION).

*Impaired hepatic function.* APO-AMOXYCILLIN AND CLAVULANIC ACID 125/31.25 (amoxicillin and clavulanic acid) should be used with care in patients with evidence of hepatic dysfunction.

#### Effects on fertility

Amoxicillin and clavulanic acid at oral doses of up to 1,200mg/kg/day had no effect on fertility and reproductive performance in rats dosed with a 2:1 ratio formulation of amoxicillin and clavulanate.

#### 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 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.

*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 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 obstetric intervention or resuscitation of the newborn infant will be necessary.

Australian categorisation definition of:

#### 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 lactation

Amoxicillin is excreted in milk. There are no data on the excretion of clavulanic acid in human or animal milk. Therefore, caution should be exercised when APO-AMOXYCILLIN AND CLAVULANIC ACID 125/31.25 (amoxicillin and clavulanic acid) is administered to a breastfeeding woman.

#### Carcinogenicity/mutagenicity

Long-term studies in animals have not been performed to evaluate the carcinogenic potential of amoxicillin and clavulanic acid.

#### Genotoxicity

The genotoxic potential of amoxicillin and clavulanic acid was investigated in assays for chromosomal damage (mouse micronucleus test and a dominant lethal test) and gene conversion. All were negative.

#### Effects on laboratory tests

Oral administration of APO-AMOXYCILLIN AND CLAVULANIC ACID 125/31.25 (amoxicillin and clavulanic acid) 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 Tes-Tape) 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 APO-AMOXYCILLIN AND CLAVULANIC ACID 125/31.25 (amoxicillin and clavulanic acid).

#### Effect on ability to drive or operate machinery

Adverse effects on the ability to drive or operate machinery have not been observed.

### **INTERACTIONS WITH OTHER MEDICINES**

Concomitant use of probenecid is not recommended. Probenecid decreases the renal tubular secretion of amoxicillin but does not notably affect clavulanic acid excretion. Concurrent use with APO-AMOXYCILLIN AND CLAVULANIC ACID 125/31.25 (amoxicillin and clavulanic acid) 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 APO-AMOXYCILLIN AND CLAVULANIC ACID 125/31.25 (amoxicillin and clavulanic acid) and allopurinol administered concurrently.

No information is available about the concurrent use of APO-AMOXYCILLIN AND CLAVULANIC ACID 125/31.25 (amoxicillin and clavulanic acid) and alcohol. However, the ingestion of alcohol while being treated with some other beta-lactam antibiotics has precipitated a disulfiram (Antabuse)-like reaction in some patients. Therefore, the ingestion of alcohol should be avoided during and for several days after treatment with APO-AMOXYCILLIN AND CLAVULANIC ACID 125/31.25 (amoxicillin and clavulanic acid).

In common with other antibiotics, APO-AMOXYCILLIN AND CLAVULANIC ACID 125/31.25 (amoxicillin and clavulanic acid) may affect the gut flora, leading to lower oestrogen reabsorption and reduced efficacy of oral contraceptives.

## ADVERSE EFFECTS

Amoxicillin and clavulanic acid is generally well tolerated. In clinical trials, the overall incidence of adverse effects, of suspected or unknown relationship to the drug, varied between 16 and 23.3%, depending on the dose. The majority of side effects observed were of a mild and transient nature, but therapy was discontinued because of drug related side effects in 4.2% of cases at the low dose (one amoxicillin and clavulanic acid (250/125mg) tablet three times daily) and 7% of cases at the high dose (one amoxicillin and clavulanic acid (500/125mg) tablet three times daily). The most frequently reported adverse effects were diarrhoea (6%), nausea (2%), vomiting (1%), abdominal pain, skin rashes, urticaria and erythema multiforme, vaginitis, abnormal taste, headache, dizziness, tiredness and hot flushes. The incidence and severity of adverse effects, particularly nausea and diarrhoea, increased with the higher recommended dose.

The following adverse reactions which follow have been reported for ampicillin class antibiotics and may occur with APO-AMOXYCILLIN AND CLAVULANIC ACID 125/31.25 (amoxicillin and clavulanic acid).

*Infections and infestations.* Mucocutaneous candidiasis.

*Gastrointestinal.* Gastritis, stomatitis, glossitis, black 'hairy' tongue, enterocolitis. Antibiotic associated colitis (including pseudomembranous colitis and haemorrhagic colitis) have been reported rarely (see PRECAUTIONS).

*Hypersensitivity reactions.* Skin rashes, pruritus, urticaria, erythema multiforme, rare cases of Stevens-Johnson syndrome, toxic epidermal necrolysis, serum sickness-like syndrome, hypersensitivity vasculitis and an occasional case of bullous exfoliative dermatitis and acute generalised exanthematous pustulosis (AGEP) have been reported rarely. Serious and occasional fatal hypersensitivity (anaphylactic) reactions and angioneurotic oedema can occur with oral penicillin (see PRECAUTIONS). Whenever such reactions occur, APO-AMOXYCILLIN AND CLAVULANIC ACID 125/31.25 (amoxicillin and clavulanic acid) should be discontinued, unless in the opinion of the doctor no alternative treatment is available and continued use of APO-AMOXYCILLIN AND CLAVULANIC ACID 125/31.25 (amoxicillin and clavulanic acid) is considered essential.

*Renal.* Interstitial nephritis can occur rarely.

*Liver.* A moderate rise in AST and/or ALT has been noted in patients treated with amoxicillin and clavulanic acid. Hepatitis and cholestatic jaundice, which may be severe but is usually reversible, have been reported (see PRECAUTIONS).

*Haemopoietic and lymphatic systems.* Anaemia, thrombocytopenia, thrombocytopenic purpura, eosinophilia, leucopenia (including neutropenia or agranulocytosis) have been reported during therapy with penicillins. These reactions are usually reversible on discontinuation of therapy and are believed to be hypersensitivity phenomena. A slight thrombocytosis was noted in less than 1% of the patients treated with amoxicillin and clavulanic acid.

Prolongation of bleeding time and prothrombin time have also been reported.

*Central nervous system.* Central nervous system effects have been seen very rarely. These include reversible hyperactivity, dizziness, headache and convulsions. Convulsions may occur with impaired renal function or in those receiving high doses.

*Miscellaneous.* Superficial tooth discolouration has been reported rarely, and mostly with the suspension. It can usually be removed by brushing.

## **DOSAGE AND ADMINISTRATION**

### Adults

APO-AMOXYCILLIN AND CLAVULANIC ACID 125/31.25 (amoxicillin and clavulanic acid) should be taken immediately before or with the first mouthful of food, to minimise potential gastrointestinal intolerance and to optimise absorption.

### Infants and children

The usual dose is 20mg/kg/day, based on the amoxicillin component, in divided doses every eight hours. For otitis media, sinusitis, lower respiratory tract infections and other more severe infections, the dose should be 40mg/kg/day, based on the amoxicillin component in divided doses every eight hours.

The children's dosage is intended for individuals whose weight will not cause dosage to be calculated greater than that recommended for adults.

Children weighing 40 kg and more should be dosed according to the adult recommendations for other APO-AMOXYCILLIN AND CLAVULANIC ACID preparations (for more information refer to the product information for APO-AMOXYCILLIN AND CLAVULANIC ACID 400/57).

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 ten days except for lower respiratory tract infection due to *H. influenzae* where treatment may be extended up to 14 days.

### Use in hepatic impairment

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

### Use in renal impairment

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 APO-AMOXYCILLIN AND CLAVULANIC ACID 125/31.25 (amoxicillin and clavulanic acid) dose is necessary, but the dosing interval should be extended according to the degree of renal impairment. The following schedule is proposed.

*Mild impairment.* Creatinine clearance > 30mL/minute: no change in dosage.

*Moderate impairment.* Creatinine clearance 10 to 30mL/minute: one dose every 12 hours.

*Severe impairment.* Creatinine clearance < 10mL/minute: half a dose every 12 hours. Haemodialysis decreases serum concentrations of both amoxicillin and clavulanic acid and an additional dose should be administered at the end of dialysis.

### Directions for reconstituting the oral suspension.

Prepare a suspension at time of dispensing as follows. Tap bottle until all the powder flows freely. Add approximately half of the total amount of water for reconstitution (see below) and shake vigorously to suspend powder. Add remainder of the water and again shake vigorously.

Add 71mL of water to 6.75g of the powder for reconstitution of 75mL ready-for-use suspension.

Each 5mL will contain amoxicillin (as the trihydrate) 125mg and clavulanic acid (as the potassium salt) 31.25mg.

Reconstituted suspension must be stored under refrigeration (2°C to 8°C) and discarded after seven days.

## **OVERDOSAGE**

Contact the Poisons Information Centre on 13 11 26 for advice on management of overdose.

Problems of overdose with APO-AMOXYCILLIN AND CLAVULANIC ACID 125/31.25 (amoxicillin and clavulanic acid) are unlikely to occur. If encountered, gastrointestinal symptoms and disturbance of the fluid and electrolyte balance may be evident. They may be treated symptomatically, with attention to the water/ electrolyte balance.

Amoxicillin may be removed from the circulation by haemodialysis.

## **PRESENTATION AND STORAGE CONDITIONS**

APO-AMOXICILLIN AND CLAVULANIC ACID 125/31.25 Powder for Oral Suspension (off-white powder) is packaged in amber glass bottle with screw closure. The off-white reconstituted oral suspension (75 mL) contains amoxicillin 125 mg/5 mL (as trihydrate) & clavulanic acid 31.25 mg/5 mL (as potassium clavulanate).

Also contains a 5-mL measuring spoon.

Store dry powder below 25°C. Under these conditions the shelf life is 3 years.  
Store reconstituted suspension at 2°C to 8°C in a refrigerator. Under these conditions the shelf life is 7 days.

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

Sandoz Pty Ltd  
ABN 60 075 449 553  
Level 2, 19 Harris Street  
Pyrmont NSW 2009  
Tel: 1800 634 500

## **POISON SCHEDULE OF THE MEDICINE**

Schedule 4 – Prescription Medicine

**DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (THE ARTG):** 15/12/2011

**DATE OF THE MOST RECENT AMENDMENT:** 24/02/2014