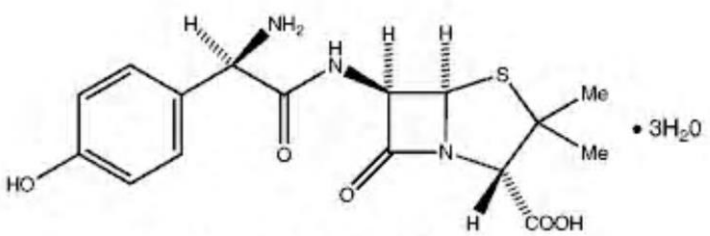
PRODUCT INFORMATION
APO-AMOXYCILLIN AND CLAVULANIC ACID 400/57 POWDER FOR ORAL SUSPENSION

NAME OF THE MEDICINE

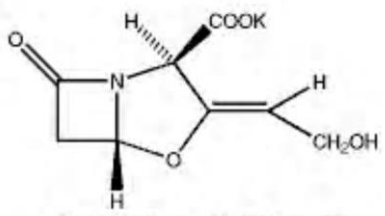
Chemical name: (2*S*,5*R*,6*R*)-6-[[(2*R*)-2-Amino-2-(4-hydroxyphenyl)acetyl]amino]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid trihydrate.
Generic name: Amoxycillin trihydrate
Chemical structure:



Amoxycillin trihydrate

CAS [61336-70-7]
Empirical formula: $C_{16}H_{19}N_3O_5S.3H_2O$ MW: 419.5

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



Potassium clavulanate

CAS [61177-45-5]
Empirical formula: $C_8H_8KNO_5$ MW: 237.3

DESCRIPTION

APO-AMOXYCILLIN AND CLAVULANIC ACID 400/57 is a combination product containing the semisynthetic antibiotic, amoxycillin (as the trihydrate) and the beta-lactamase inhibitor, clavulanic acid (as the potassium salt).

Amoxycillin 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 15.12.0598, 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 400/57 contains aspartame 8.5mg/5mL.

Each 5 mL of suspension contains 0.29 mmol of potassium.

PHARMACOLOGY

Microbiology

Like other penicillins, amoxycillin has a bactericidal effect on sensitive organisms during the stage of active multiplication. However, amoxycillin is susceptible to hydrolysis by beta-lactamases and the addition of clavulanic acid in Apo-Amoxycillin And Clavulanic Acid 400/57 extends the antimicrobial spectrum of amoxycillin to include organisms normally resistant to amoxycillin 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 (µg/mL)[#]**
[#] Expressed as concentration of amoxycillin in the presence of clavulanic acid at a constant 2 parts amoxycillin to 1 part clavulanic acid.	
E. coli ATCC 25922	2 to 8
E. coli ATCC 35218	4 to 16
E. faecalis ATCC 29212	0.25 to 1.0
H. influenzae ATCC 49247	2 to 16
S. aureus ATCC 29213	0.12 to 0.5
S. pneumoniae 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) ≤ 0.06µg/mL or less is considered to be susceptible. Non-susceptible isolates are defined as intermediate non-susceptible (0.12-1µg/mL) or resistant (≥ 2µg/mL). Until 2000, the MIC interpretive standards for penicillin and amoxycillin 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

Streptococcus pneumoniae	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. Amoxycillin 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. To optimise absorption of clavulanic acid, amoxycillin and clavulanic acid oral suspension should be administered at the start of a meal. The pharmacokinetics of amoxycillin are not affected by food.

In children aged 2 to 12 years, oral administration of amoxycillin and clavulanic acid oral suspension (7:1 ratio) every 12 hours at a dose of amoxycillin 45mg/kg/day (clavulanic acid 6.4mg/kg/day) was compared to amoxycillin and clavulanic acid oral suspension (4:1 ratio) every eight hours at a dose of amoxycillin 40mg/kg/day (clavulanic acid 10mg/kg/day), either immediately prior to the start of a meal or at least three hours after a meal.

In this study, the following mean pharmacokinetic parameters were observed for amoxycillin for amoxycillin and clavulanic acid oral suspension (45mg/kg/day) taken every 12 hours and amoxycillin and clavulanic acid oral suspension (40mg/kg/day) taken every 8 hours respectively: peak plasma concentration (C_{max}) of 12.0 and 7.33 microgram/mL, area under the plasma concentration time curve between 0 and 24 hours after the first dose (AUC(0 to 24 hours)) of 35.2 and 18.6 microgram.hour/mL, half-life ($t_{1/2}$) of 1.22 and 1.02 hours, median time to peak plasma concentration (T_{max}) of 1.0 and 2.1 hours and the mean predicted time above the minimum inhibitory concentration (T_{MIC}24 hours) of 12.3 and 14.0 hours.

The following pharmacokinetic parameters were observed for clavulanic acid for amoxycillin and clavulanic acid oral suspension (45mg/kg/day) taken every 12 hours and amoxycillin and clavulanic acid oral suspension (40mg/kg/day) taken every 8 hours respectively: C_{max} of 5.49 and 2.66 microgram/mL, AUC(0 to 24 hours) of 13.3 and 5.51 microgram.hour/mL, $t_{1/2}$ of 0.99 and 0.94 hours and median T_{max} of 1.0 and 1.6 hours, and mean predicted T_{MIC}24 hours of 9.80 and 9.81 hours.

The clinical efficacy of amoxycillin and clavulanic acid oral suspension (7:1 ratio) and amoxycillin and clavulanic acid oral suspension (4:1 ratio) have been shown to be comparable in the approved indications, despite the differences in some pharmacokinetic parameters.

Oral administration of single doses of APO-AMOXYCILLIN AND CLAVULANIC ACID 400/57 amoxycillin 400mg/5mL & clavulanic acid 57mg/5mL oral suspension to fasting adult volunteers yielded comparable pharmacokinetic data to reference amoxycillin 400mg/5mL & clavulanic acid 57mg/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 400mg/57mg amoxycillin 400mg/5mL & clavulanic acid 57mg/5mL oral suspension to fasting adult volunteers

Dose	AUC_{0-t} (µg.hr/mL)		C_{max} (µg/mL)	
amoxicillin 400mg/5mL & clavulanic acid 57mg/5mL	amoxycillin (±S.D.)	clavulanic acid (±S.D.)	amoxycillin (±S.D.)	clavulanic acid (±S.D.)
APO-AMOXYCILLIN AND CLAVULANIC ACID 400/57 amoxycillin 400mg/5mL & clavulanic acid 57 mg/5mL suspension	28.15 ± 9.51	4.879 ± 1.648	10.57 ± 3.27	2.442 ± 0.735
Amoxycillin 400mg/5mL & clavulanic acid 57mg/5mL reference suspension	28.40 ± 10.52	4.926 ± 1.788	11.08 ± 3.25	2.506 ± 0.813

Distribution. Following oral administration, both amoxycillin and clavulanic acid have been shown to diffuse in significant concentrations into pus, bile, pleural, synovial and peritoneal fluids. Therapeutic concentrations of both compounds have been detected in gall bladder, abdominal tissue, skin fat and muscle tissues. Both penetrate poorly into the cerebrospinal fluid (CSF) when the meninges are normal. Amoxycillin 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 amoxycillin 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 amoxycillin approximately 20% bound. From animal studies, there is no evidence to suggest either component accumulates in any organ.

Metabolism and excretion. As with other penicillins, renal excretion is the major route of amoxycillin clearance, while clavulanate clearance is via both renal and nonrenal mechanisms. Approximately 70% of the dose of amoxycillin is excreted in urine as amoxycillin. For clavulanic acid, following the administration of 125mg 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 amoxycillin excretion but does not notably delay renal excretion of clavulanic acid.

Similar elimination pharmacokinetics occur in adults, children and infants with mature renal function.

CLINICAL TRIALS

A randomised, single blind study in 868 children aged 2 months to 12 years with acute otitis media compared the efficacy of amoxycillin and clavulanic acid oral suspension (7:1 ratio) amoxycillin 45mg/kg/day (clavulanic acid 6.4mg/kg/day) administered every 12 hours for five days (n = 293) or ten days (n = 287) with amoxycillin and clavulanic acid oral suspension (4:1 ratio) amoxycillin 40mg/kg/day (clavulanic acid 10mg/kg/day) given every eight hours for ten days (n = 288). At the end of therapy (days 12 to 14) equivalent per protocol clinical success rates of 78.8% (n = 189) and 86.5% (n = 178), respectively, were demonstrated for the 8 and 12 hourly ten day treatment groups, compared with a 71.1% (n = 197) success rate for the 12 hourly five day treatment group. At 32 to 38 days follow-up, equivalent success rates were demonstrated for 8 and 12 hourly ten day regimens of 64.2 and 63.1%, respectively, compared with a 57.8% success rate for the 12 hourly five day treatment group.

INDICATIONS

APO-AMOXYCILLIN AND CLAVULANIC ACID 400/57 (amoxycillin and clavulanic acid) is indicated for the short-term treatment of the following bacterial infections when caused by sensitive organisms (see MICROBIOLOGY): skin and skin structure infections; urinary tract infections (complicated and uncomplicated); upper respiratory tract infections including sinusitis and otitis media; lower respiratory tract infections including acute exacerbations of chronic bronchitis and community acquired pneumonia.

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 400/57 (amoxycillin 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 amoxycillin susceptible organisms and beta-lactamase producing organisms susceptible to APO-AMOXYCILLIN AND CLAVULANIC ACID 400/57 (amoxycillin and clavulanic acid) should not require the addition of another antibiotic due to the amoxycillin content of APO-AMOXYCILLIN AND CLAVULANIC ACID 400/57.

CONTRAINDICATIONS

APO-AMOXYCILLIN AND CLAVULANIC ACID 400/57 (amoxycillin 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 400/57 (amoxycillin and clavulanic acid) is also contraindicated in patients with a previous history of cholestatic jaundice/ hepatic dysfunction associated with Amoxycillin and Clavulanic acid.

PRECAUTIONS

Use with caution in the following circumstances:

APO-AMOXYCILLIN AND CLAVULANIC ACID 400/57 (amoxycillin 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 400/57 (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 amoxycillin. 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 400/57 (amoxycillin and clavulanic acid) contains amoxycillin, 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 amoxycillin is used.

APO-AMOXYCILLIN AND CLAVULANIC ACID 400/57 (amoxycillin and clavulanic acid) should be given with caution to patients with lymphatic leukaemia since they are especially susceptible to amoxycillin 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 amoxycillin 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 children with renal impairment, dosage should be adjusted according to degree of impairment using the Curam 125/31.25 formulation. APO-AMOXYCILLIN AND CLAVULANIC ACID 400/57 suspension is not recommended for use in children with renal impairment.

Impaired hepatic function. APO-AMOXYCILLIN AND CLAVULANIC ACID 400/57 (amoxycillin and clavulanic acid) should be used with care in patients with evidence of hepatic dysfunction.

Effects on fertility
Amoxycillin 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 amoxycillin and clavulanate.

Use in pregnancy [Category B1]
Animal studies with orally and parenterally administered amoxycillin and clavulanic acid have shown no teratogenic effects. There is limited experience of the use of amoxycillin and clavulanic acid in human pregnancy. In women with preterm, premature rupture of the foetal membrane (pPROM), prophylactic treatment with amoxycillin 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 APO-AMOXYCILLIN AND CLAVULANIC ACID 400/57 (amoxycillin 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
Amoxycillin 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 400/57 (amoxycillin 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 APO-AMOXYCILLIN AND CLAVULANIC ACID 400/57 (amoxycillin and clavulanic acid).

Genotoxicity
The genotoxic potential of amoxycillin 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 400/57 (amoxycillin and clavulanic acid) will result in high urine concentrations of amoxycillin. 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 amoxycillin

and therefore APO-AMOXYCILLIN AND CLAVULANIC ACID 400/57 (amoxycillin 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 amoxycillin but does not notably affect clavulanic acid excretion. Concurrent use with APO-AMOXYCILLIN AND CLAVULANIC ACID 400/57 (amoxycillin and clavulanic acid) may result in increased and prolonged blood levels of amoxycillin 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 400/57 (amoxycillin and clavulanic acid) and allopurinol administered concurrently.

In common with other antibiotics, APO-AMOXYCILLIN AND CLAVULANIC ACID 400/57 (amoxycillin and clavulanic acid) may affect the gut flora, leading to lower oestrogen reabsorption and reduced efficacy of oral contraceptives.

ADVERSE EFFECTS

Amoxycillin and clavulanic acid is generally well tolerated. The majority of events were of a mild and transient nature.

Clinical trials. The following adverse events reported in a pivotal clinical trial with amoxycillin and clavulanic acid 400mg/57mg/5mL oral suspension (45/6.4mg/kg/day every 12 hours for ten days) and are compared to amoxycillin and clavulanic acid 125mg/31.25mg/5mL oral suspension (40/10mg/kg/day every 8 hours for ten days) in Table 5.

Table 6:
The most frequently (≥ 1%) reported adverse experiences in decreasing order for the BD 10 days regimen.

Adverse experience	**TDS 10 days % (n = 288)**	**BD 10 days % (n = 287)**
Coughing	12.5	11.5
Vomiting	10.8	10.1
Rhinitis	9.0	9.1
URI	8.3	8.0
Fever	5.2	7.0

Pharyngitis	6.9	5.6
Diarrhoea	9.7	5.2
Dermatitis, contact (diaper rash)	9.0	4.5
Rash	3.8	3.5
Therapeutic response increased (accidental/intentional overdose)	1.0	3.5
Conjunctivitis	3.5	2.8
Infection, fungal	1.0	2.4
Abdominal pain	3.8	2.1
Respiratory disorder (Not specified)	1.0	2.1
Asthma	2.1	1.7
Tooth Ache	3.5	1.7
Insomnia	2.4	1.7
Moniliasis	1.0	1.7
Infection, viral	1.7	1.7
Hyperkinesia	0.3	1.7
Injury	0.7	1.4
Otitis Media	0.7	1.4
Headache	1.4	1.4
Constipation	0.0	1.4
Somnolence	1.0	1.0
Earache	2.4	1.0
Sinusitis	1.7	1.0
Allergy	0.7	1.0
Gastroenteritis	0.7	1.0
Ear disorder (not specified)	1.0	0.7
Lymphadenopathy, cervical	1.0	0.7
Herpes zoster	2.8	0.7
Nausea	1.7	0.3

Postmarketing. In addition, the following adverse reactions have been reported for ampicillin class antibiotics and may occur with APO-AMOXYCILLIN AND CLAVULANIC ACID 400/57 (amoxycillin and clavulanic acid). Very common: greater than or equal to 1/10; common: greater than or equal to 1/100 and < 1/10; uncommon: greater than or equal to 1/1,000 and < 1/100; rare: greater than or equal to 1/10,000 and < 1/1,000; very rare: < 1/10,000.

Infections and infestations. Common: mucocutaneous candidiasis.

Gastrointestinal. Rare. Nausea, indigestion, gastritis, stomatitis, glossitis, black 'hairy' tongue, enterocolitis. 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.

Central nervous system. Very rare. Reversible hyperactivity, dizziness, headache, convulsions. Convulsions may occur in patients with impaired renal function or those receiving high doses.

Haemopoietic and lymphatic. Rare. Anaemia, thrombocytopenia, thrombocytopenic purpura, eosinophilia, reversible leucopenia (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, pruritus, 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) have been reported rarely. Whenever such reactions occur, APO-AMOXYCILLIN AND CLAVULANIC ACID 400/57 (amoxycillin 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 400/57 (amoxycillin and clavulanic acid) 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

Adults

APO-AMOXYCILLIN AND CLAVULANIC ACID 400/57 (amoxycillin 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

Children aged 2 months up to 12 years. For moderate to severe infections the dose should be 45mg/kg/day, based on the amoxycillin component, (or clavulanic acid 6.4mg/kg/day) in two divided doses every 12 hours.

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

There are no clinical data available for APO-AMOXYCILLIN AND CLAVULANIC ACID 400/57 (amoxycillin and clavulanic acid) in infants with immature renal function. The use of APO-AMOXYCILLIN AND CLAVULANIC ACID 400/57 (amoxycillin and clavulanic acid) in this group cannot be recommended.

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

APO-AMOXYCILLIN AND CLAVULANIC ACID 400/57 (amoxycillin and clavulanic acid) is not recommended for use in children with renal impairment or in haemodialysis. In children with renal impairment, dosage should be adjusted according to degree of impairment using the alternative APO-AMOXYCILLIN AND CLAVULANIC ACID 125/31.25 formulation.

Directions for reconstituting the oral suspension

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

Add 55mL of water to 10.1g of the powder for reconstitution of 60mL ready-for-use suspension. Each 5mL will contain amoxycillin (as the trihydrate) 400mg and clavulanic acid (as the potassium salt) 57mg.

Shake oral suspension well before using. 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 overdosage with APO-AMOXYCILLIN AND CLAVULANIC ACID 400/57 (amoxycillin 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.

Amoxycillin may be removed from the circulation by haemodialysis.

PRESENTATION AND STORAGE CONDITIONS

APO-AMOXYCILLIN AND CLAVULANIC ACID 400/57 Powder for Oral Suspension (off white powder) is packaged in amber glass bottle with screw closure. The off-white reconstituted oral suspension (60 mL) contains amoxycillin 400 mg/5 mL (as trihydrate) & clavulanic acid 57 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