APO-AMOXYCILLIN AND CLAVULANIC ACID 875MG/125MG TABLETS

NAME OF THE MEDICINE

Amoxycillin trihydrate and potassium clavulanate.

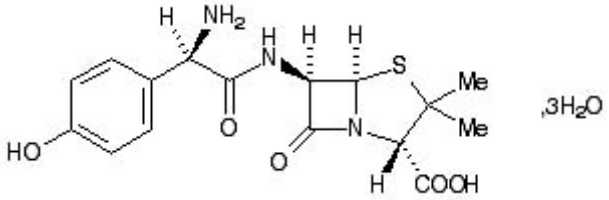
Chemical Names:

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

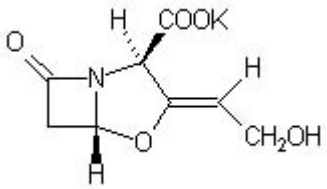
Potassium clavulanate: potassium (Z)-(2R,5R)-3-(2-hydroxyethylidene)-7-oxo-4-oxa-1-azabicyclo[3.2.0]heptane-2-carboxylate.

Structural Formulae:

Amoxycillin trihydrate:



Potassium clavulanate:



Molecular Formulae:

Amoxycillin trihydrate: $C_{16}H_{19}N_3O_5S.3H_20$

Potassium clavulanate: $C_8H_8KNO_5$

Molecular Weights:

Amoxycillin trihydrate: 419.5

Potassium clavulanate: 237.3

CAS Registry Numbers:

Amoxycillin trihydrate: 61336-70-7

Potassium clavulanate: 61177-45-5

DESCRIPTION

Amoxycillin and Clavulanic Acid 875 mg /125 mg is a combination product containing the semi-synthetic antibiotic, amoxycillin (as the trihydrate) and the β-lactamase inhibitor, potassium clavulanate (the potassium salt of clavulanic acid).

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

Amoxycillin and Clavulanic Acid 875 mg/125mg tablets are intended for oral administration. Each tablet contains amoxycillin trihydrate equivalent to amoxycillin 875 mg and potassium clavulanate equivalent to clavulanic acid 125mg.

In addition, each tablet contains the following inactive ingredients: microcrystalline cellulose, crospovidone, carmellose sodium, hydroxypropylcellulose, magnesium stearate, titanium dioxide, colloidal anhydrous silica, purified talc, triethyl citrate, polysorbate 80, ethylcellulose.

PHARMACOLOGY

Pharmacological Actions

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 β-lactamases and the addition of clavulanic acid in Amoxycillin and Clavulanic Acid tablets extends the antimicrobial spectrum of amoxycillin to include organisms normally resistant to amoxycillin due to beta-lactamase production. *In vitro* studies have demonstrated the susceptibility of most strains of the following organisms:

Table 1 - Acquired Resistance Data for Amoxycillin / Clavulanic Acid in Australia According to NCCLS Guidelines (M100-S10) for Amoxycillin / Clavulanic Acid

	Number of Pathogens (n)	Percentage of Strains (%)	
		Intermediate	Resistant
Streptococcus pneumoniae *	1020	0.3	0.1
Haemophilus influenzae #	303	0.0	0.3

* Data collected between March to November 1997.
\# Data collected in 1999

Table 2 - MIC (Minimum Inhibitory Concentration) Distribution for Sensitive / Intermediate *S. pneumoniae* Isolates

MIC ≤ 1	1 > MIC < 2	MIC ≥ 2
96.8%	2.3%	0.9%

Table 3 - Acquired Resistance Data for Amoxycillin / Clavulanic Acid from Other Countries

Breakpoints	Number of Pathogens (n)	Percentage acquired resistance (%)
Sensitive Aerobe Gram-Positive		
Enterococcus faecalis	178	1.7
Staphylococcus aureus	955	2
Staphylococcus aureus (MSSA)	2458	2
Coagulase negative staphylococci	158	7
Streptococcus agalactiae	96	1
Streptococcus pneumoniae	196	8.5
Streptococcus pneumoniae (Pen-S)	154	0
Streptococcus pyogenes	76	0
Streptococcus species	28	0
Sensitive Aerobe Gram-Negative		
Escherichia coli	946	5
Haemophilus influenzae	180	1.1
Haemophilus influenzae (BLN)	150	1.3
Haemophilus influenzae (BLP)	30	0
Klebsiella pneumoniae	355	1
Klebsiella oxytoca	1540	9.6
Moraxella catarrhalis	46	0
Proteus sp.	128	5

Breakpoints	Number of Pathogens (n)	Percentage acquired resistance (%)
Sensitive Anaerobe		
Clostridium species	42	0
Clostridium difficile	27	0
Peptostreptococcus species	17	0
Bacteroides fragilis	98	5
Bacteroides fragilis group	163	7
Fusobacterium species	16	0
Intermediate Aerobe Gram-Negative		
Acinetobacter sp.	49	12
Resistant Aerobe Gram-Positive		
Staphylococcus aureus (MRSA)	147	59.2
Resistant Aerobe Gram-Negative		
Citrobacter sp.	84	56
Enterobacter sp.	181	86
Morganella sp.	39	97
Providencia sp.	14	79
Serratia sp.	61	89
S. maltophilia	57	96

The percent acquired resistance data provided in the above table has been collected from the following countries during the time period specified: US, 1996; Canada, 1993-1994; US/Canada, 1996-1997; France, 1994-1995; US, Arabia, 1994-1995; US, 1996-1997; US, 1991-1993; Belgium, 1993-1994; UK, Netherlands, 1989-1995.

Note: Resistance can vary from region to region and information on local resistance should be taken into account.

Table 4 - MIC Interpretive Standards (µg/mL) according to NCCLS Guidelines (M100-S10) for Amoxycillin and Amoxycillin / Clavulanic Acid

		MIC (µg/mL) Interpretive Standards		
Organisms	**Antimicrobial Agents**	**S**	**I**	**R**
Enterobacteriaceae	amoxycillin/clavulanic acid	≤ 8/4	16/8	≥ 32/16
Non-Enterobacteriaceae*	N/A	–	–	–
Staphylococcus sp.	amoxycillin/clavulanic acid	≤ 4/2	–	≥ 8/4
Enterococcus sp.*	N/A	–	–	–
Haemophilus sp.	amoxycillin/clavulanic acid	≤ 4/2	-	≥ 8/4
Streptococcus pneumoniae	amoxycillin	≤ 2	4	≥ 8
	amoxycillin/clavulanic acid	≤ 2/1	4/2	≥ 8/4
Streptococcus sp. other than *S. pneumoniae***	N/A	–	–	–

* No interpretive standards for amoxycillin or amoxycillin/clavulanic acid.

** A streptococcal isolate that is susceptible to penicillin can be considered susceptible to ampicillin, amoxycillin and amoxycillin/clavulanic acid.

The MIC90 data provided in the above table has been collected from the following countries during the time period specified: US: 91-97; UK: Not Stated; France: 94-95; Belgium: 93-94.

It should be noted that NCCLS breakpoints are reviewed on a regular basis and may be amended according to the data available.

The following *in vitro* data are available but their clinical significance is unknown.

Table 5 - In vitro activity of Amoxycillin / Clavulanic Acid

	n	MIC 90 (µg/mL)
GRAM POSITIVE AEROBES		
Enterococcus faecalis	185	1
Staphylococcus aureus	229	1
Staphylococcus aureus (MSSA)	95	1
Staphylococcus aureus (MRSA)	20	16
Staphylococcus epidermidis	134	4
Staphylococcus saprophyticus	20	1
Coagulase negative *staphylococci*	83	2
Streptococcus agalactiae	20	0.06
Streptococcus pneumoniae	1,476	2
Streptococcus pyogenes	764	0.12
Streptococcus viridans	20	0.5
GRAM NEGATIVE AEROBES		
Escherichia coli	325	8
Haemophilus influenzae	2,268	2
Haemophilus influenzae (BLN)	691	1
Haemophilus influenzae (BLP)	271	2
Klebsiella pneumoniae	200	4
Klebsiella oxytoca	34	8
Moraxella catarrhalis	35	0.25
Neisseria gonorrheae	35	1
Neisseria meningitidis	10	0.06
Proteus mirabilis	49	2
Proteus vulgaris	11	8
GRAM POSITIVE ANAEROBES		
Clostridium species	13	0.5
Clostridium perfringens	16	0.06
Clostridium difficile	21	2
Clostridium perfringens	16	0.06
Clostridium perfringens	10	0.12
Clostridium perfringens	10	0.25
Clostridium difficile	21	2
Clostridium difficile	10	1
Clostridium difficile	10	1
Propionibacterium sp.	11	0.06
Peptostreptococcus and Ruminococcus sp.	23	0.25
Peptostreptococci	19	0.25
Peptostreptococcus sp.	14	1.0
Peptostreptococcus sp.	19	0.5
GRAM NEGATIVE ANAEROBES		
Bacteroides fragilis	98	2
Bacteroides fragilis group	163	4
Fusobacterium species	23	0.125

	n	MIC 90 (µg/mL)
GRAM NEGATIVE ANAEROBES		
Bacteroides fragilis	20	4
Bacteroides fragilis	19	2
Bacteroides fragilis	24	2
Bacteroides fragilis	176	1
Bacteroides thetaiotamicron	14	32
Bacteroides vulgatus	21	4
Other Bacteroides sp. of B. fragilis group	17	16
Bacteroides fragilis group	80	8
Non-B. fragilis	163	2
Prevotella sp.	15	8
Prevotella, Porphyromonas and Bacteroides sp.	27	0.25
Fusobacterium sp.	23	0.125
Fusobacterium sp.	14	0.125
B. capillosus	10	1
P. bivia	15	2
P. disiens	13	0.25

Note: Methicillin resistant strains are resistant to Amoxycillin and Clavulanic Acid tablets.

Proteus vulgaris and *Klebsiella* species may not be susceptible to Amoxycillin and Clavulanic Acid tablets at concentrations of amoxycillin and clavulanic acid achieved in the plasma. However at concentrations of amoxycillin and clavulanic acid achievable in the urine the majority of strains are susceptible.

Susceptibility Testing

Dilution or Diffusion Techniques

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

"Susceptible" indicates that the infecting organism is likely to respond to Amoxycillin and Clavulanic acid therapy and a report of "Resistant". An "Intermediate Susceptibility" 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. The category suggests that the infecting organism would be susceptible to Amoxycillin and Clavulanic acid if the infection is confined to tissues or fluids (e.g. urine) in which high antibiotic levels are attained. 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 infecting organism is not likely respond to therapy; 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.

Recommended Amoxycillin and Clavulanic Acid Susceptibility Ranges[1,2]

Organisms	Resistant	Intermediate	Susceptible
Gram Negative Enteric Bacteria	≤13mm	14-17mm	≥18mm
Staphylococcus[3] and Haemophilus spp	≤19mm	------	≥20mm

1. The non-beta-lactamase-producing organisms which are normally susceptible to ampicillin, such as *Streptococci*, will have similar zone sizes as for ampicillin discs.
2. The quality control cultures should have the following assigned daily ranges for amoxycillin and clavulanic acid:

	Discs	Mode MIC (mg/L)
E. coli (ATCC25922)	19-25mm	4/2 - 8/4

S. aureus (ATCC25923)	28-36mm	0.25/0.12 - 0.5/0.25
E. coli (ATCC35218)	18-22mm	4/2 - 8/4

The Mode MIC is expressed as the concentration of amoxycillin/clavulanic acid.

3. Organisms which show susceptibility to amoxycillin and clavulanic acid but are resistant to methicillin/oxacillin should be considered resistant.

Pharmacokinetics

Absorption

Amoxycillin and Clavulanic Acid tablets are stable in the presence of gastric acid. Both 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 tablets should be administered at the start of a meal. The pharmacokinetics of amoxycillin are not affected by food.

The following mean pharmacokinetic parameters were observed after administration of a single dose of Amoxycillin and Clavulanic acid 875mg/125mg tablets under fasting conditions. For amoxycillin, peak plasma concentration (C_{max}) was 9.89 µg/mL, area ($AUC_{(0\text{-inf hours})}$) was 29.301 µg.h/mL, half-life ($t_{1/2}$) was 1.06 hours and time to peak plasma concentration (T_{max}) was 1.92 hours. For clavulanic acid, peak plasma concentration (C_{max}) was 2.63 µg/mL, area ($AUC_{(0\text{-inf hours})}$) was 5.89 µg.h/mL, half-life ($t_{1/2}$) was 0.98 hours and time to peak plasma concentration (T_{max}) was 1.47 hours.

Distribution

Following oral administration, both amoxycillin 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 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 are highly protein bound. Clavulanic acid has been variously reported to be bound to human serum in the range of 9 - 30% and amoxycillin approximately 20% bound. 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 amoxycillin clearance, while clavulanate elimination is via both renal and non-renal mechanisms. Approximately 70% of the dose of amoxycillin is excreted in urine as amoxycillin. 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 amoxycillin excretion but does not delay renal excretion of clavulanic acid.

INDICATIONS

Amoxycillin and Clavulanic Acid tablets are indicated for 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 Amoxycillin 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 amoxycillin susceptible organisms and beta-lactamase producing organisms susceptible to Amoxycillin and Clavulanic Acid tablets should not require the addition of another antibiotic due to the amoxycillin content of this product.

CONTRAINDICATIONS

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

PRECAUTIONS

Before initiating therapy with amoxycillin-clavulanate, careful enquiry should be made concerning previous hypersensitivity reactions to penicillins, cephalosporins or other allergens.

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 amoxycillin. 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.

General

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

Since Amoxycillin and Clavulanic Acid tablets contain amoxycillin, 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 amoxycillin is used.

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

Amoxycillin-clavulanate should be avoided if infectious mononucleosis is suspected since the occurrence of a morbilliform rash has been associated with this condition following the use of amoxycillin.

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

Abnormal prolongation of prothrombin time (increased INR) has been reported rarely in patients receiving amoxycillin-clavulanate and oral anticoagulants. Appropriate monitoring should be undertaken when anticoagulants are prescribed concurrently. Adjustments in the dose of oral anticoagulants may be necessary to maintain the desired level of anticoagulation.

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 rarely. 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 tablets have occurred predominantly in males and elderly patients and may be associated with prolonged treatment. These events have been very rarely reported in children.

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

In patients with reduced urine output, crystalluria has been observed very rarely, predominantly with parenteral therapy. During the administration of high doses of amoxycillin, it is advisable to maintain adequate fluid intake and urinary output in order to reduce the possibility of amoxycillin crystalluria (see **OVERDOSAGE)**.

Amoxycillin and Clavulanic Acid 875mg/125mg tablets should not be used in patients with moderate to severe renal impairment (creatinine clearance $\leq$ 30mL/min).

Effects on fertility

Amoxycillin/clavulanic acid at oral doses of up to 1200 mg/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 tablets 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 physician.

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 Amoxycillin 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

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

Paediatric Use

The tablets are not recommended for children weighing less than 40 kg.

Genotoxicity

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

Carcinogenicity

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

Effect on Laboratory Tests

Oral administration of Amoxycillin and Clavulanic Acid tablets 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 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 amoxycillin and therefore Amoxycillin and Clavulanic Acid tablets.

INTERACTIONS WITH OTHER MEDICINES

Probenecid decreases the renal tubular secretion of amoxycillin but does not affect clavulanic acid excretion. Concurrent use with Amoxycillin and Clavulanic Acid tablets 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 hyperuricemia present in these patients. There are no data with Amoxycillin and Clavulanic Acid tablets and allopurinol administered concurrently.

No information is available about the concurrent use of Amoxycillin 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®) like reaction in some patients. Therefore the ingestion of alcohol should be avoided during and for several days after treatment with Amoxycillin and Clavulanic Acid tablets.

In common with other antibiotics, Amoxycillin and Clavulanic Acid tablets may affect the gut flora, leading to lower oestrogen reabsorption and reduced efficacy of combined oral contraceptives.

In literature there are rare cases of increased international normalised ratio in patients maintained on acenocoumarol or warfarin and prescribed a course of amoxycillin. If co-administration is necessary, the prothrombin time or international normalised ratio should be carefully monitored with the addition or withdrawal of amoxycillin.

ADVERSE EFFECTS

Amoxycillin and clavulanic acid is 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 amoxycillin and clavulanic acid 875mg/125mg 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 amoxycillin and clavulanic acid 875mg/125mg tablets, however it should be noted that causality has not necessarily been established for these events:

The most frequently (≥1%) reported adverse experiences in decreasing order for the BD regimen:

	875/125 mg q 12hr
TOTAL NUMBER OF PATIENTS	584
Adverse Event	**Frequency (%)**
Diarrhoea	14.9
Nausea	7.9
Headache	6.8
Abdominal pain	4.5
Vomiting	3.8
Genital moniliasis	3.6
Vaginitis	3.4
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

Post-Marketing

In addition, the following adverse reactions have been reported for ampicillin class antibiotics and may occur with Amoxycillin and Clavulanic Acid 875mg/125mg tablets:

Very common	≥1/10
Common	≥1/100 and <1/10
Uncommon	≥1/1000 and <1/100
Rare	≥1/10000 and <1/1000
Very rare	<1/10000

Infections and Infestations:

Common:	Mucocutaneous candidiasis.

Gastrointestinal disorders

Very common:	diarrhoea
Common:	nausea, vomiting
Uncommon:	indigestion
Rare:	gastritis, stomatitis, glossitis, black "hairy" tongue, enterocolitis. Antibiotic-associated colitis (including pseudomembranous colitis and haemorrhagic colitis), see **PRECAUTIONS**.

Hepatobiliary Disorders

Uncommon:	Moderate rise in AST and/or ALT.

Rare:	Hepatitis, cholestatic jaundice which may be severe but is usually reversible.

Nervous System Disorders

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

Haematopoietic and Lymphatic System Disorders

Uncommon:	Thrombocytosis.
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.

Hypersensitivity and Skin Disorders

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

Renal and urinary disorders:

Rare:	interstitial nephritis
Very rare:	crystalluria (see **OVERDOSAGE**)

Miscellaneous

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

DOSAGE AND ADMINISTRATION

Amoxycillin and Clavulanic Acid 875mg/125mg tablets should be taken immediately before or with the first mouthful of food, to minimise potential gastrointestinal intolerance and to optimise absorption.

Adults

For more severe infections, the dose is one Amoxycillin and Clavulanic Acid 875mg/125mg Tablet every 12 hours. Note that lower doses of amoxycillin are used for milder infections in adults (Amoxycillin and Clavulanic Acid 500mg/125mg).

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

Amoxycillin and Clavulanic Acid 875mg/125mg tablets should not be used in patients with moderate to severe renal impairment (creatinine clearance $\leq$ 30mL/min).

Both amoxycillin and clavulanic acid are excreted by the kidneys and the serum half-life of each increases in patients with renal failure.

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

Adults with Impaired Hepatic Function

Data is 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.

Amoxycillin and Clavulanic Acid 875mg/125mg tablets are not recommended for children weighing less than 40 kg.

OVERDOSAGE

Symptoms

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

Amoxycillin crystalluria, in some cases leading to renal failure, has been observed (*see* **PRECAUTIONS**).

Treatment

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

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

PRESENTATION AND STORAGE CONDITIONS

APO-Amoxycillin and Clavulanic Acid Amoxycillin 875 mg/125mg tablets:
White to off-white oblong film-coated tablets with bevelled edges, scored and debossed, with 875/125 on one side and debossed with AMC on the other side.

Blister packs of 10 tablets
AUST R number 163696

Store below 25°C. Protect from moisture.

NAME AND ADDRESS OF THE SPONSOR

Apotex Pty Ltd
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Macquarie Park NSW 2113

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POISONS SCHEDULE OF THE MEDICINE

S4 - Prescription Only Medicine.

Date of first inclusion on the Australian Register of Therapeutic Goods (The ARTG) : 3 September 2009

Date of most recent amendment: 09 March 2017