PRODUCT INFORMATION
CURAM® DUO 500/125 AND CURAM® DUO FORTE 875/125 TABLETS

NAME OF THE MEDICINE

Curam Duo 500/125 and Curam Duo Forte 875/125 tablet preparations are a combination products containing amoxycillin trihydrate and potassium clavulanate.

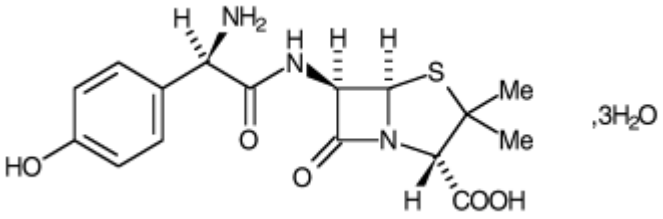
Chemical Name:

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

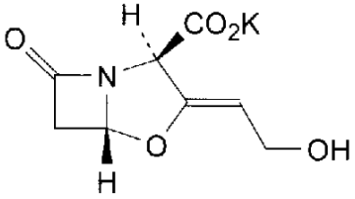
Potassium clavulanate
Potassium (*Z*)-(2*R*, 5*R*)-3-(2-hydroxyethylidene)-7-oxo-4-oxa-1-azabicyclo[3.2.0]heptane-2-carboxylate

Structural Formula:

Amoxycillin trihydrate



Potassium clavulanate



Molecular Formula:

Amoxycillin Trihydrate	$C_{16}H_{19}N_3O_5S, 3H_2O$
Potassium Clavulanate	$C_8H_8KNO_5$

Molecular Weight:

Amoxycillin Trihydrate	419.4
Potassium Clavulanate	237.3

CAS Number:

Amoxycillin Trihydrate	61336-70-7
Potassium Clavulanate	61177-45-5

DESCRIPTION

Amoxycillin trihydrate is white to almost white, crystalline powder, slightly soluble in water and in alcohol, practically insoluble in ether and in fatty oils. It dissolves in dilute acids and dilute solutions of alkali hydroxides.

Potassium clavulanate is white to almost white, crystalline powder, hygroscopic, freely soluble in water, slightly soluble in alcohol, and very slightly soluble in acetone.

Each tablet contains the following ingredients:

Active Ingredients:

	Amoxycillin (as trihydrate)	Clavulanic acid (as potassium clavulanate)
Curam Duo 500/125 Tablets	500mg	125mg
Curam Duo Forte 875/125 Tablets	875mg	125mg

Inactive Ingredients:

Magnesium stearate, purified talc, povidone, croscarmellose sodium, microcrystalline cellulose, triethyl citrate, ethylcellulose, sodium lauryl sulfate, cetyl alcohol, hypromellose and titanium dioxide.

Amoxycillin/clavulanic acid 875/125mg tablets also contain silicon dioxide.

PHARMACOLOGY

Pharmacological Actions

Amoxycillin/clavulanic acid preparations are a combination products containing the semi-synthetic antibiotic amoxycillin (as the trihydrate) and the beta-lactamase inhibitor potassium clavulanate (as the potassium salt of clavulanic acid).

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 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. (See Tables 1 to 4).

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 March to November 1997
[#]Data collected in 1999

Table 2

MIC distribution for sensitive/intermediate *S. pneumoniae* isolates

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

Table 3

Acquired resistance data for amoxycillin/clavulanic acid from other countries

Breakpoint	**Number of Pathogens (n)**	**Percentage acquired resistance (%)**
Sensitive aerobe gram positive		
Enterococcus faecalis	178	1.7
Staphylococcus aureus	955	2
Staphylococcus aureus (MSSA)	2,458	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	1,540	9.6
Moraxella catarrhalis	46	0
Proteus sp.	128	5
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 (mcg/mL) according to NCCLS guidelines (M100-S10) for amoxycillin and amoxycillin/clavulanic acid

Organisms	Antimicrobial Agents	MIC (mcg/mL) Interpretive Standards		
		S	I	R
Enterobacteriaceae	Amoxycillin/clavulanic acid	≤8/4	16/8	≥32/16
Non-Enterobacteriaceae*	NA	-	-	-
Staphylococcus sp.	Amoxycillin/clavulanic acid	≤4/2	-	≥8/4
Enterococcus sp.	NA	-	-	-
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**	NA	-	-	-

*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.

Susceptibility testing. *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 used of laboratory control microorganisms to control the technical aspects of the laboratory procedures.

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

CLINICAL TRIALS

Amoxycillin/clavulanic acid 875mg/125mg tablets twice daily versus amoxycillin/clavulanic acid 500mg/125mg tablets three times daily.
Three studies in 1,361 patients treated for 7 to 14 days for either lower respiratory tract infections, upper respiratory infections or complicated urinary tract infections compared a regimen of amoxycillin/clavulanic acid 875mg/125mg tablets every 12 hours to amoxycillin/clavulanic acid 500mg/125mg tablets dosed every eight hours (584, 170 and 607 patients respectively). Comparable efficacy was demonstrated between the 12 hourly and eight hourly dosing regimens. There was no significant difference in the percentage of adverse events in each group. The most frequently reported adverse event in two of the studies was diarrhoea; incidence rates were similar for the 875mg/125mg tablets every 12 hours and 500mg/125mg tablets every eight hours dosing regimens (14.9 and 14.3%, respectively). However, there was a statistically significant difference ($p < 0.05$) in rates of severe diarrhoea or withdrawals with diarrhoea between the regimens: 1.0% for 875mg/125mg 12 hourly dosing versus 2.5% for the 500mg/125mg eight hourly dosing. In the third study the most frequently reported adverse event was headache with an incidence of 5.7% (amoxycillin/clavulanic acid 500mg/125mg tablets every eight hours) versus 8.3% (amoxycillin/clavulanic 875mg/125mg tablets every 12 hours).

As noted previously, although there was no significant difference in the percentage of adverse events in each group there was a statistically significant difference in rates of severe diarrhoea or diarrhoea-related withdrawals between the regimens.

Amoxycillin/clavulanic acid 500mg/125mg tablets twice daily versus amoxycillin/clavulanic acid 250mg/125mg tablets three times daily.
Two studies in 908 patients treated for between five and ten days for either uncomplicated skin and skin structure infections (SSSI) or acute exacerbation of chronic bronchitis (AECB) compared a regimen of amoxycillin/clavulanic acid 500mg/125mg tablets every 12 hours with amoxycillin/clavulanic acid 250mg/125mg tablets every eight hours. Comparable efficacy was demonstrated between the 12 hourly and eight hourly dosing regimens.

There was no significant difference in the percentage of adverse events in each group, with the most frequently reported adverse event in the two studies being diarrhoea.

The clinical efficacy of amoxycillin/clavulanic acid 250mg/125mg tablets given in a twice daily versus three times daily regimen have been shown to be comparable in AECB and SSSI, despite the differences in some pharmacokinetic parameters.

Given the similar TMIC and the demonstration of equivalence between AECB and SSSI it would be reasonable to extrapolate to the remaining indications. Clinical safety and efficacy in other indications have been investigated, however these supportive studies were not sufficiently designed to demonstrate the relative efficacy of the twice daily versus three times daily dosage regimens, or compared the proposed regimen with other treatments.

Pharmacokinetics

Absorption. Amoxycillin/clavulanic acid tablet preparations are stable in the presence of gastric acid. Their 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/clavulanic acid tablet preparations should be administered at the start of a meal. The pharmacokinetics of amoxycillin are not affected by food.

Oral administration at the start of a light meal of amoxycillin/clavulanic acid 875mg/125mg tablets every 12 hours was compared with amoxycillin/clavulanic acid 500mg/125mg tablets every eight hours.

The following mean pharmacokinetic parameters (refer to Tables 5 & 6) were observed for amoxycillin and clavulanic acid following administration of amoxicillin/clavulanic acid 875mg/125mg tablets every 12 hours and amoxycillin/clavulanic acid 500mg/125mg tablets every eight hours:

Table 5

Amoxycillin Pharmacokinetics

Dose	**[1]C_{max} µg/mL**	**[2]$AUC_{(0\text{-}24hrs)}$ µg/hour/mL**	**[3]$t_{1/2}$ hours**	**[4]T_{max} hours**	**[5]$T_{(MIC\ 24\ hours)}$ hours**
875mg/125mg	11.64	53.52	1.19	1.50	10.46
500mg/125mg	7.19	53.35	1.15	1.50	13.30

Table 6

Clavulanic Acid Pharmacokinetics

Dose	**[1]C_{max} µg/mL**	**[2]$AUC_{(0\text{-}24hrs)}$ µg/hour/mL**	**[3]$t_{1/2}$ hours**	**[4]T_{max} hours**	**[5]$T_{(MIC\ 24\ hours)}$ hours**
875mg/125mg	2.18	10.16	0.96	1.25	6.08
500mg/125mg	2.40	15.72	0.98	1.50	9.43

The half-life and Cmax for clavulanate for amoxycillin/clavulanic acid 875mg/125mg tablets were not significantly different from amoxycillin/clavulanic acid 500mg/125mg tablets. However, the AUC(0-24 hours) was reduced, as would be expected with the lower daily dose of clavulanate, i.e twice daily dose (125 x 2mg of clavulanate) versus three times daily dose (125 x 3mg of clavulanate).

Oral administration of amoxycillin/clavulanic acid 500mg/125mg tablets every 12 hours was compared with amoxycillin/clavulanic acid 250mg/125mg tablets every eight hours at the start of a light meal. The following mean pharmacokinetic parameters were observed (refer to Tables 7 & 9):

Table 7

Amoxycillin Pharmacokinetics

Dose	**[1]C_{max} µg/mL**	**[2]$AUC_{(0\text{-}24hrs)}$ µg/hour/mL**	**[3]$t_{1/2}$ hours**	**[4]T_{max} hours**	**[5]$T_{(MIC\ 24\ hours)}$ hours**
500mg/125mg	6.51	33.43	1.26	1.50	8.54
250mg/125mg	3.32	26.66	1.36	1.50	9.49

Table 8

Clavulanic Acid Pharmacokinetics

Dose	**[1]C_{max} µg/mL**	**[2]$AUC_{(0\text{-}24hrs)}$ µg/hour/mL**	**[3]$t_{1/2}$ hours**	**[4]T_{max} hours**	**[5]$T_{(MIC\ 24\ hours)}$ hours**
500mg/125mg	1.75	8.60	1.01	1.50	5.69
250mg/125mg	1.47	12.60	1.01	1.50	8.24

[1]C_{max} = *peak plasma concentration*
[2]$AUC_{(0\text{-}24hrs)}$ = *area under the plasma concentration time curve between 0 and 24 hours after the first dose*
[3]$t_{1/2}$ = *half-life*
[4]T_{max} = *time to peak plasma concentration*
[5]$T_{(MIC\ 24\ hours)}$ = *time above the minimum inhibitory concentration*

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. 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%. 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 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) is present as 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.

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

INDICATIONS

Short-term treatment of bacterial infections at the following sites when caused by amoxycillin/clavulanic acid sensitive, beta-lactamase producing organisms:

- Skin and skin structure infections.
- Urinary tract infections (complicated and uncomplicated).
- Upper respiratory tract infections, such as sinusitis, otitis media and recurrent tonsillitis.
- Lower respiratory tract infections, including community acquired pneumonia and acute exacerbations of chronic bronchitis.

Appropriate culture and susceptibility studies should be performed to identify the causative organism(s) and determine its (their) susceptibility to amoxycillin/clavulanic acid tablet preparations. However, when there is reason to believe an infection may involve any of the beta-lactamase producing organisms listed in the microbiological section, 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/clavulanic acid tablet preparations should not require the addition of another antibiotic due to the amoxycillin content of these products.

CONTRAINDICATIONS

History of allergic reactions to beta-lactams, e.g. penicillins, cephalosporins, carbapenems or monobactams.

Previous history of amoxycillin/clavulanic acid associated jaundice/hepatic dysfunction.

PRECAUTIONS

Hypersensitivity Reactions.
Before initiating therapy with amoxicillin/clavulanic acid, 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/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.

Pseudomembranous Colitis. 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 *Cl. difficile* should be considered. Fluids, electrolytes and protein replacement therapy 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/clavulanic acid tablet preparations contain 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.

Amoxycillin/clavulanic acid should be given with caution to patients with lymphatic leukaemia since they are especially susceptible to amoxycillin induced skin rashes.

Amoxycillin/clavulanic acid should be avoided if infectious mononucleosis is suspected since the occurrence of a morbilliform rash has been associated with this condition following the use of 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 amoxicillin/clavulanic acid 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. 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 occurred in patients with serious underlying disease or taking concomitant medications.

Hepatic events subsequent to amoxycillin/clavulanic acid therapy have been reported predominantly in males and elderly patients and may be associated with prolonged treatment. These events have been very rarely reported in children.
Hepatitis and cholestatic jaundice have also been reported rarely. These events have been noted with other penicillins and cephalosporins.

Impaired hepatic function. Amoxycillin/clavulanic acid 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).

Impaired renal function. Curam Duo Forte 875/125 tablets should not be used in patients with moderate to severe renal impairment (creatinine clearance less than or equal to 30mL/minute). Curam Duo 500/125 should be used with care in patients with moderate or severe renal impairment. The dosage of Curam Duo 500/125 should be adjusted as recommended in the Dosage and Administration section.

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

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.

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).
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 fetus having been observed. Studies in animals have not shown evidence of an increased occurrence of foetal damage.

Animal studies with orally and parenterally administered amoxycillin/clavulanic acid have shown no teratogenic effects. There is limited experience of the use of amoxycillin/clavulanic acid in human pregnancy. In women with preterm, premature rupture of the foetal membrane (pPROM), prophylactic treatment with amoxycillin/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 amoxycillin/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.

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/clavulanic acid is given to a breastfeeding woman.

Effects on laboratory tests. Oral administration of amoxycillin/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 amoxycillin/clavulanic acid tablet preparations.

INTERACTIONS WITH OTHER MEDICINES

Probenecid decreases the renal tubular secretion of amoxycillin but does not affect clavulanic acid excretion. Concurrent use with amoxycillin/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 amoxycillin/clavulanic acid and allopurinol administered concurrently.

No information is available about the concurrent use of amoxycillin/clavulanic acid and alcohol. However, the ingestion of alcohol whilst being treated with some other beta-lactam antibiotics has precipitated a disulfiram like reaction in some patients. Therefore the ingestion of alcohol should be avoided during and for several days after treatment with amoxycillin/clavulanic acid tablet

In common with other broad spectrum antibiotics, amoxycillin/clavulanic acid may affect the gut flora, leading to lower oestrogen re-absorption and reduced efficacy of oral contraceptives. Patients should be warned accordingly.

In the 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.

Penicillins may reduce the excretion of methotrexate causing a potential increase in toxicity.

ADVERSE EFFECTS

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

Clinical trials

Amoxycillin/clavulanic acid 875mg/125mg tablets. The most frequently reported adverse events related or possibly related to amoxycillin/clavulanic acid 875mg/125mg tablets 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 the amoxycillin/clavulanic acid 875mg/125mg tablets twice daily regimen, 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

	875/125mg 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

**Denominator is number of females*

Amoxycillin/clavulanic acid 500mg/125mg and amoxycillin/clavulanic acid 250mg/125mg tablets. In clinical trials with the 250mg/125mg and 500mg/125mg strengths, 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 (amoxycillin/clavulanic acid 250mg/125mg tablets three times daily) and 7% of cases at the high dose (amoxycillin/clavulanic acid 500mg/125mg tablets 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.

In recent trials with amoxycillin/clavulanic acid 500mg/125mg tablets, the most frequently reported adverse events related or possibly related to treatment were diarrhoea (12.8%), nausea (5.2%), headache (4.8%), abdominal pain (4.5%).

The following adverse events have been observed during clinical trials with the amoxycillin/clavulanic acid 500mg/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

	500/125mg q 12hr
Total number of patients	**462**
Adverse Event	**Frequency (%)**
Diarrhoea	12.8
Nausea	5.2
Headache	4.8
Upper Respiratory Infection	1.9
Genital moniliasis	1.9
Vomiting	1.5
Dyspepsia	1.1
Injury	1.1

Postmarketing. The following adverse reactions have been reported for ampicillin class antibiotics and may occur with amoxycillin/clavulanic acid tablet preparations.

very common: ≥1/10
common: ≥1/100 and < 1/10
uncommon: ≥ 1/1,000 and < 1/100
rare: ≥1/10,000 and < 1/1,000
very rare: < 1/10,000
Not known: cannot be estimated from the available data

Infections and Infestations
Common: mucocutaneous candidiasis
Not known: overgrowth of non-susceptible organism

Gastrointestinal disorders
Very common: diarrhea
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
Uncommon: moderate rise in AST and/or ALT
Rare:; hepatitis, cholestatic jaundice, which may be severe but is usually reversible.

Central nervous system
Uncommon: dizziness, headache
Very rare: reversible hyperactivity, and convulsions. Convulsions may occur in patients with impaired renal function or in those receiving high doses.
Not known: aseptic meningitis

Haemopoietic and lymphatic systems
Uncommon: thrombocytosis
Rare: anaemia, thrombocytopenia, thrombocytopenic purpura, eosinophilia, reversible leucopenia (including neutropenia and 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
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 putulosis (AGEP) have been reported rarely. Whenever such reactions occur, amoxycillin/clavulanic acid tablets should be discontinued, unless in the opinion of the doctor no alternative treatment is available and continued therapy is considered essential. Serious and occasionally 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/clavulanic acid tablet preparations should be taken immediately before or with the first mouthful of food, to minimise potential gastrointestinal intolerance and to optimise absorption.

Adults. The usual adult dose is one Curam Duo 500/125 tablet every 12 hours.

For more severe infections, the dose should be one Curam Duo Forte 875/125 tablet every 12 hours.

Note. Although the proportion of amoxycillin increases with increasing strength of amoxycillin/clavulanic acid tablet preparations, the amount of clavulanic acid remains the same. Therefore, the tablets are not directly substitutable.

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.

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

Impaired renal function. Curam Duo Forte 875/125 tablets should not be used in patients with moderate to severe renal impairment (creatinine clearance less than or equal to 30mL/minute).

Both amoxycillin and clavulanic acid are excreted by the kidneys and the serum half-life increases in patients with renal failure. No adjustment to the initial dose is necessary, but the dosing interval should be extended according to the degree of renal impairment. The following schedule is proposed for amoxycillin/clavulanic acid tablets preparations:

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

Moderate impairment (creatinine clearance 10 to 30mL/minute).
Curam Duo 500/125 – one tablet, 12-hourly only.

Severe impairment (creatinine clearance < 10mL/minute).
Curam Duo 500/125 - one tablet every 24 hours.

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

Children. Children weighing 40kg and more should be dosed according to the adult recommendations. Treatment should usually be continued for 48 to 72 hours beyond the time that the child 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.

Children weighing less than 40kg should not use amoxycillin/clavulanic acid tablet preparations.

OVERDOSAGE

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

Serious and severe clinical symptoms are unlikely to occur after overdosage with amoxycillin/clavulanic acid. If encountered, gastrointestinal symptoms and disturbance of the fluid and electrolyte balances may be evident. They may be treated symptomatically, with attention to the water/ electrolyte balance.

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

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

Amoxycillin may be removed from the circulation by haemodialysis.

PRESENTATION AND STORAGE CONDITIONS

CURAM DUO 500/125 tablets contain amoxicillin (as trihydrate) 500mg and clavulanic acid (as potassium clavulanate) 125mg. Off-white, oval, biconvex, film-coated and scored on both sides. Aluminium/aluminium strip packs or aluminium/aluminium blister packs x 10 tablets.

CURAM DUO FORTE 875/125 tablets contain amoxicillin (as trihydrate) 875mg and clavulanic acid (as potassium clavulanate) 125mg. White to pale yellow, oblong, biconvex, film-coated and scored on both sides. Aluminium/aluminium strip packs or aluminium/aluminium blister packs x 10 tablets.

Not all presentations maybe marketed in Australia.

Store below 25 °C.
Protect from moisture.

NAME AND ADDRESS OF THE SPONSOR

Sandoz Pty Ltd
ABN 60 075 499 553
54 Waterloo Road
Macquarie Park, NSW 2113
Australia

POISON SCHEDULE OF THE MEDICINE

Schedule 4 – Prescription Only Medicine

DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (THE ARTG): 28/03/2003

DATE OF THE MOST RECENT AMENDMENT: 16/03/2016