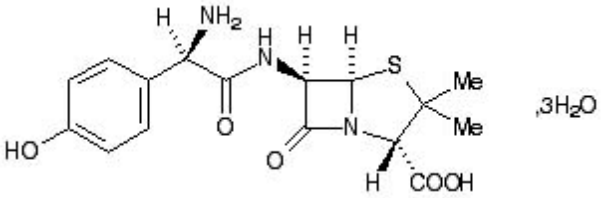
AMCLAVOX DUO 500/125 & AMCLAVOX DUO FORTE 875/125 TABLETS
Amoxicillin and clavulanic acid tablets

PRODUCT INFORMATION

NAME OF THE MEDICINE

AMCLAVOX DUO tablets are combination products containing the semisynthetic antibiotic, amoxicillin (as trihydrate), and the β-lactamase inhibitor, potassium clavulanate (as the potassium salt of clavulanic acid).

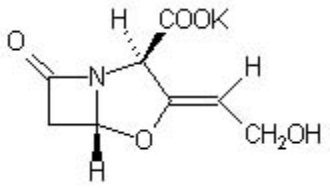
Chemically, amoxicillin trihydrate is (2S,5R,6R)-6-[[(2R)-2-Amino-2-(4–hydroxyphenyl)acetyl]amino]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid trihydrate. It is susceptible to hydrolysis by β-lactamases. Amoxicillin trihydrate may be represented structurally as:



CAS – 61336-70-7.

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.

Chemically potassium clavulanate is potassium (2R,3Z,5R)-3-(2-hydroxyethylidene)-7-oxo-4-oxa-1-azabicyclo[3.2.0]-heptane-2- carboxylate , and may be represented structurally as:



CAS – 61177-45-5.

Molecular Formula:
Amoxicillin trihydrate: $C_{16}H_{19}N_3O_5S.3H_20$
Potassium clavulanate: $C_8H_8KNO_5$

Molecular Weight:
Amoxicillin trihydrate: 419.4
Potassium clavulanate: 237.3

DESCRIPTION

Amoxicillin trihydrate is a white to almost white, crystalline powder, slightly soluble in water, very slightly soluble in ethanol (96%), practically insoluble in fatty oils. It dissolves in dilute acids and dilute solutions of alkali hydroxides. It having pKa 9.48 & log P is 0.76.

Potassium clavulanate is white to almost white, crystalline powder, hygroscopic, freely soluble in water, slightly soluble in alcohol, and very slightly soluble in acetone. It having pKa 2.7 & log P is -1.16.

AMCLAVOX DUO FORTE 875/125 & AMCLAVOX DUO 500/125 tablets also contain the inactive ingredients: Microcrystalline cellulose, magnesium stearate, sodium starch glycollate Type A and colloidal anhydrous silica. The tablet coating contains hypromellose, titanium dioxide, propylene glycol, purified talc, ethylcellulose.

PHARMACOLOGY

Pharmacokinetics

Absorption

Amoxicillin and clavulanic acid tablets 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 AMCLAVOX DUO tablets should be administered at the start of a meal. The pharmacokinetics of amoxicillin are not affected by food.

Oral administration of amoxicillin and clavulanic acid (875mg/125mg) tablets every 12 hours was compared with amoxicillin and clavulanic acid (500mg/125mg) tablets every 8 hours at the start of a light meal. The following mean pharmacokinetic parameters were observed for amoxicillin for amoxicillin and clavulanic acid (875/125mg) tablets taken every 12 hours and amoxicillin and clavulanic acid (500mg/125mg) tablets taken every 8 hours respectively: peak plasma concentration (C_{max}) of 11.64 and 7.19 μg/mL, area under the plasma concentration-time curve between 0 and 24 hours after the first dose ($AUC_{(0\text{-}24\ hours)}$) of 53.52 and 53.35 μg.h/mL, half life (t½) of 1.19 and 1.15 hours, time to peak plasma concentration (T_{max}) of 1.50 and 1.50 hours and the time above the minimum inhibitory concentration (T_{MIC} 24 hours) of 10.46 hours and 13.30 hours.

The following pharmacokinetic parameters were observed for clavulanic acid for amoxicillin and clavulanic acid (875/125mg) tablets taken every 12 hours and amoxicillin and clavulanic acid (500mg/125mg) tablets taken every 8 hours respectively: C_{max} of 2.18 and 2.40 μg /mL,

$AUC_{(0\text{-}24\ hours)}$ of 10.16 and 15.72 μg.h/mL, t½ of 0.96 and 0.98 hours and T_{max} of 1.25 and 1.50 hours, and (T_{MIC} 24 hours) of 6.08 hours and 9.43 hours.

The t½ and C_{max} for clavulanate for amoxicillin and clavulanic acid (875/125mg) tablets were not significantly different from amoxicillin and clavulanic acid (500/125mg) tablets. However, the $AUC_{(0\text{-}24\ hours)}$ was reduced, as would be expected with the lower daily dose of clavulanate, i.e. 250mg in amoxicillin and clavulanic acid (875/125mg) tablets vs 375mg in amoxicillin and clavulanic acid (500/125mg) tablets.

Oral administration of amoxicillin and clavulanic acid (500mg/125mg) tablets every 12 hours was compared with amoxicillin and clavulanic acid (250mg/125mg) tablets every 8 hours at the start of a light meal.

The following mean pharmacokinetic parameters were observed for amoxicillin for amoxicillin and clavulanic acid (500/125mg) tablets taken every 12 hours and amoxicillin and clavulanic acid (250mg/125mg) tablets taken every 8 hours respectively: peak plasma concentration (C_{max}) of 6.51 and 3.32 μg/mL, area under the plasma concentration-time curve between 0 and 24 hours after the first dose ($AUC_{(0\text{-}24\ hours)}$) of 33.43 and 26.66 μg.h/mL, half life (t½) of 1.26 and 1.36 hours, time to peak plasma concentration (T_{max}) of 1.50 and 1.50 hours and the time above the minimum inhibitory concentration (T_{MIC} 24 hours) of 8.54 hours and 9.49 hours.

The following pharmacokinetic parameters were observed for clavulanic acid for amoxicillin and clavulanic acid (500/125mg) tablets taken every 12 hours and amoxicillin and clavulanic acid (250mg/125mg) tablets taken every 8 hours respectively: C_{max} of 1.75 and 1.47 μg/mL, $AUC_{(0\text{-}24\ hours)}$ of 8.6 and 12.6 μg.h/mL, t½ of 1.01 and 1.01 hours and T_{max} of 1.50 and 1.50 hours, and (T_{MIC} 24 hours) of 5.69 hours and 8.24 hours.

Distribution

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

Neither amoxicillin nor clavulanic acid is highly protein bound. Clavulanic acid has been variously reported to be bound to human serum in the range of 9 - 30% and amoxicillin 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 amoxicillin clearance, while clavulanate elimination is via both renal and non-renal mechanisms. Approximately 70% of the dose of amoxicillin is excreted in urine as amoxicillin. For clavulanic acid, following the administration of 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 amoxicillin excretion but does not delay renal excretion of clavulanic acid.

CLINICAL TRIALS

Amoxicillin and clavulanic acid (875/125mg) tablets versus amoxicillin and clavulanic acid (500/125mg) tablets:
Three pivotal studies in 1,361 patients treated for between 7 and 14 days for either lower respiratory tract infections, upper respiratory infections or complicated urinary tract infections compared a regimen of amoxicillin and clavulanic acid (875/125mg) tablets every 12 hours (q12h) to amoxicillin and clavulanic acid (500/125mg) tablets dosed every 8 hours (q8h) (584, 170 and 607 patients respectively). Comparable efficacy was demonstrated between the q12h and q8h 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 875/125mg q12h and 500/125mg q8h 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 875/125mg q12h dosing versus 2.5% for the 500/125mg q8h dosing. In the third study the most frequently reported adverse event was headache with an incidence of 5.7% (amoxicillin and clavulanic acid (500/125mg) tablets q8h) versus 8.3% (amoxicillin and clavulanic acid (875/125mg) tablets q12h).

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 withdrawals with diarrhoea between the regimens.

Amoxicillin and clavulanic acid (500/125mg) tablets versus amoxicillin and clavulanic acid (250/125mg) tablets:
Two pivotal studies in 908 patients treated for between 5 and 10 days for either uncomplicated Skin and Skin Structure infections (SSSI) or Acute Exacerbation of Chronic Bronchitis (AECB) compared a regimen of amoxicillin and clavulanic acid (500/125 mg) tablets every 12 hours with amoxicillin and clavulanic acid (250/125 mg) tablets every 8 hours. Comparable efficacy was demonstrated between the 12 hourly and 8 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 amoxicillin and clavulanic acid (250/125 mg) 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 were investigated, however these supportive studies were not sufficiently designed to demonstrate the relative efficacy of the two amoxicillin and clavulanate acid dosing regimens, or compared the proposed regimen with other treatments.

Microbiology:
Like other penicillins, amoxicillin has a bactericidal effect on sensitive organisms during the stage of active multiplication. However, amoxicillin is susceptible to hydrolysis by β-lactamases and the addition of clavulanic acid in amoxicillin and clavulanic acid tablets extends the antimicrobial spectrum of amoxicillin to include organisms normally resistant to amoxicillin due to β-lactamase production. *In vitro* studies have demonstrated the susceptibility of most strains of the following organisms.

Table 1: Acquired resistance data for amoxicillin/clavulanic acid in Australia according to NCCLS guidelines (M100-S10) for amoxicillin/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 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 amoxicillin/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 amoxicillin and amoxicillin/clavulanic acid

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

*No interpretive standards for amoxicillin or amoxicillin/clavulanic acid.
**A streptococcal isolate that is susceptible to penicillin can be considered susceptible to ampicillin, amoxicillin and amoxicillin/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 amoxicillin/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
Peptostreptococcus species	19	0.5
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
Peptostreptococcus sp.	19	0.5

GRAM NEGATIVE ANAEROBES:		
Bacteroides fragilis	98	2
Bacteroides fragilis group	163	4
Fusobacterium species	23	0.125
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 amoxicillin and clavulanic acid tablets. *Proteus vulgaris* and *Klebsiella* species may not be susceptible to amoxicillin and clavulanic acid tablets at concentrations of amoxicillin and clavulanic acid achieved in the plasma. However at concentrations of amoxicillin and clavulanic acid achievable in the urine the majority of strains are susceptible.

Susceptibility testing:

Diffusion Technique:
For Kirby-Bauer method of susceptibility testing, a 30 µg amoxicillin and clavulanic acid (20 µg amoxicillin + 10 µg clavulanic acid) diffusion disc should be used. With this procedure, a report from the laboratory of "Susceptible" indicates that the infecting organism is likely to respond to amoxicillin and clavulanic acid therapy and a report of "Resistant" indicates that the infecting organism is not likely to respond to therapy. An "Intermediate Susceptibility" report suggests that the infecting organism would be susceptible to amoxicillin and clavulanic acid if the infection is confined to tissues or fluids (e.g. urine) in which high antibiotic levels are attained.

Dilution Techniques:
Broth or agar dilution methods may be used to determine the minimal inhibitory concentration (MIC) value susceptibility of bacterial isolates to amoxicillin and clavulanic acid. Tubes should be inoculated to contain 104 to 105 organisms/mL or plates "spotted" with 103 to 104 organisms.

The recommended dilution method employs a constant amoxicillin/ clavulanic acid ratio of 2 to 1 in all tubes with increasing concentrations of amoxicillin. MICs are reported in terms of amoxicillin concentration in the presence of clavulanic acid at constant 2 parts amoxicillin to 1 part clavulanic acid.

Recommended amoxicillin 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-β-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 amoxicillin and clavulanic acid tablets:

	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 amoxicillin/clavulanic acid.

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

INDICATIONS

AMCLAVOX DUO 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 (complicated and uncomplicated)
- 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 infections.

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

The treatment of mixed infections caused by amoxicillin susceptible organisms and β-lactamase producing organisms susceptible to amoxicillin and clavulanic acid tablets preparations should not require the addition of another antibiotic due to the amoxicillin content of these products.

CONTRAINDICATIONS

A history of allergic reaction to β-lactams e.g. penicillins or cephalosporins is a contraindication.

AMCLAVOX DUO tablets are contraindicated in patients with a previous history of amoxicillin/clavulanic acid-associated jaundice or hepatic dysfunction.

PRECAUTIONS

Before initiating therapy with amoxicillin-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, AMCLAVOX DUO TABLETS SHOULD BE DISCONTINUED AND THE APPROPRIATE THERAPY INSTITUTED. SERIOUS ANAPHYLACTOID REACTIONS REQUIRE IMMEDIATE EMERGENCY TREATMENT WITH ADRENALINE. OXYGEN, INTRAVENOUS STEROIDS, AND AIRWAY MANAGEMENT, INCLUDING INTUBATION, SHOULD ALSO BE ADMINISTERED AS INDICATED.

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

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

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

AMCLAVOX DUO tablets should be given with caution to patients with lymphatic leukaemia since they are especially susceptible to amoxicillin induced skin rashes.

Amoxicillin-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 amoxicillin.

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

AMCLAVOX DUO 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 amoxicillin, it is advisable to maintain adequate fluid intake and urinary output in order to reduce the possibility of amoxicillin crystalluria (see OVERDOSAGE).

AMCLAVOX DUO FORTE 875/125 tablets should not be used in patients with moderate to severe renal impairment (creatinine clearance $\leq$ 30mL/min).

AMCLAVOX DUO 500/125 tablets should be used with care in patients with moderate or severe renal impairment. The dosage of amoxicillin and clavulanic acid should be adjusted as recommended in the “DOSAGE AND ADMINISTRATION” section.

Carcinogenicity

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

Genotoxicity

The genotoxic potential of amoxicillin/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

Amoxicillin/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 amoxicillin and clavulanate.

Use in Pregnancy: (Category B1).

Animal studies with orally and parenterally administered amoxicillin and clavulanic acid have shown no teratogenic effects. There is limited experience of the use of amoxicillin and clavulanic acid tablets in human pregnancy. In women with preterm, premature rupture of the foetal membrane (pPROM), prophylactic treatment with amoxicillin and clavulanic acid may be associated with an increased risk of necrotising enterocolitis in neonates. As with all medicines, use should be avoided in pregnancy, especially during the first trimester, unless considered essential by the 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 amoxicillin and clavulanic acid tablets in humans during labour or delivery has immediate or delayed adverse effects on the foetus, prolongs the duration of labour or increases the likelihood that forceps delivery or other obstetrical intervention or resuscitation of the newborn will be necessary.

Use in Lactation:

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

Effects on ability to drive and use machines:

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

Effects on laboratory tests:

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

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

INTERACTIONS WITH OTHER MEDICINES

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

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

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

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

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

ADVERSE EFFECTS

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

Clinical Trials:

During clinical trials, the most frequently reported adverse events related or possibly related to amoxicillin and clavulanic acid (875/125mg) 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 amoxicillin and clavulanic acid (875/125mg) therapy, 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

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

The following adverse events have been observed during clinical trials with amoxicillin and clavulanic acid (500/125mg) therapy, 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

Post Marketing:

In addition, the following adverse reactions have been reported for ampicillin class antibiotics and may occur with amoxicillin and clavulanic acid 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
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 systems
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
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 putulosis (AGEP) have been reported rarely. Whenever such reactions occur, AMCLAVOX DUO tablets should be discontinued, unless in the opinion of the physician no alternative treatment is available and continued use of AMCLAVOX DUO 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

AMCLAVOX DUO tablets should be taken immediately before or with the first mouthful of food, to minimise potential gastrointestinal intolerance and to optimise absorption.

Adults:
The usual adult dose is one AMCLAVOX DUO 500/125 tablet every 12 hours.
For more severe infections, the dose should be one AMCLAVOX DUO FORTE 875/125 tablet every 12 hours.

Note: Since both AMCLAVOX DUO FORTE 875/125 tablets and AMCLAVOX DUO 500/125 tablets contain the same amount of clavulanic acid (125mg, as the potassium salt), two AMCLAVOX DUO 500/125 tablets are not equivalent to one AMCLAVOX DUO FORTE 875/125 tablet. Therefore, two AMCLAVOX DUO 500/125 tablets should not be substituted for one AMCLAVOX DUO FORTE 875/125 tablet for treatment of more severe infections.

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:
AMCLAVOX DUO FORTE 875/125 tablets should not be used in patients with moderate to severe renal impairment (creatinine clearance $\leq$ 30mL/min).

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

The following schedule is proposed for AMCLAVOX DUO 500/125 tablets:

Mild Impairment: (Creatinine clearance > 30mL/min)	No change in dosage.
Moderate Impairment: (Creatinine clearance 10 - 30mL/min)	One AMCLAVOX DUO 500/125 tablet 12 hourly
Severe Impairment: (Creatinine clearance < 10mL/min)	One AMCLAVOX DUO 500/125 tablet every 24 hours

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

Adults with Impaired Hepatic Function:
Data 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.

It is recommended that amoxicillin and clavulanic acid suspensions* should be used for children weighing less than 40 kg.

*Amoxicillin and clavulanic acid as a suspension formulation is not available in this brand, however is available in other brands.

OVERDOSAGE

Serious and severe clinical symptoms are unlikely to occur after overdosage with AMCLAVOX DUO tablets. 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.

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

Amoxicillin may be removed from the circulation by haemodialysis.

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

PRESENTATION AND STORAGE CONDITIONS

AMCLAVOX DUO 500 /125 tablets contain amoxicillin (as trihydrate) 500 mg and clavulanic acid (as potassium clavulanate) 125 mg. White colored capsule shaped film coated tablet debossed with ‘l 06’ on one side and plain on other side. Aluminium/aluminium strip or PA/Aluminium/PVC/Aluminium blister packs x 10 tablets.

AMCLAVOX DUO FORTE 875 /125 tablets contain amoxicillin (as trihydrate) 875 mg and clavulanic acid (as potassium clavulanate) 125 mg. White colored capsule shaped film coated tablet debossed with 'l 07' on one side and plain on other side. Aluminium/aluminium strip or PA/Aluminium/PVC/Aluminium blister packs x 10 tablets.

Store below 25°C.
Protect from moisture.

NAME AND ADDRESS OF THE SPONSOR

Micro Labs Pty Ltd
15 Melliodora Crescent,
Greensborough, VIC-3088
Australia

POISON SCHEDULE OF THE MEDICINE

Schedule 4 – Prescription Only Medicine

DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (THE ARTG):

07/04/2016

DATE OF THE MOST RECENT AMENDMENT:

07/08/2017