AUSTRALIAN PRODUCT INFORMATION

ALPHACLAV® DUO VIATRIS 500/125 and ALPHACLAV® DUO FORTE VIATRIS 875/125

(amoxicillin and clavulanic acid) film coated tablets

1 NAME OF THE MEDICINE

Amoxicillin trihydrate and potassium clavulanate

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

ALPHACLAV DUO VIATRIS 500/125 and ALPHACLAV DUO FORTE VIATRIS 875/125 tablets (amoxicillin and clavulanic acid tablets) are combination products containing the semisynthetic antibiotic, amoxicillin (as the trihydrate) and the β-lactamase inhibitor, potassium clavulanate (as the potassium salt of clavulanic acid).

ALPHACLAV DUO VIATRIS 500/125 Tablets: each film coated tablet contains 500mg amoxicillin as the trihydrate and 125mg clavulanic acid as the potassium salt.

ALPHACLAV DUO FORTE VIATRIS 875/125 Tablets: each film coated tablet contains 875mg amoxicillin as the trihydrate and 125mg clavulanic acid as the potassium salt.

Excipients with known effect: contains 25 mg of elemental potassium per tablet

For the full list of excipients, see Section 6.1 LIST OF EXCIPIENTS.

3 PHARMACEUTICAL FORM

ALPHACLAV DUO FORTE VIATRIS 875/125 Tablets: A white elongated capsule shaped film coated tablet.

ALPHACLAV DUO VIATRIS 500/125 Tablets: A white, oval shaped, film coated tablet with marking "CA625" on one side.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

ALPHACLAV DUO VIATRIS 500/125 and ALPHACLAV DUO FORTE VIATRIS 875/125 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 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 should not require the addition of another antibiotic due to the amoxicillin content of these products.

4.2 DOSE AND METHOD OF ADMINISTRATION

ALPHACLAV DUO VIATRIS 500/125 and ALPHACLAV DUO FORTE VIATRIS 875/125 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 ALPHACLAV DUO VIATRIS 500/125 tablet every 12 hours. For more severe infections, the dose should be one ALPHACLAV DUO FORTE VIATRIS 875/125 tablet every 12 hours.

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

Renal Impairment

ALPHACLAV DUO FORTE VIATRIS 875/125 tablets should not be used in patients with moderate to severe renal impairment (creatinine clearance ≤ 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 amoxicillin and clavulanic acid tablet dose is necessary, but the dosing interval should be extended according to the degree of renal impairment.

The following schedule is proposed for ALPHACLAV DUO VIATRIS 500/125:

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

Hepatic Impairment

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 be used for children weighing less than 40 kg.

4.3 CONTRAINDICATIONS

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

Previous history of amoxicillin/clavulanic acid-associated jaundice or hepatic dysfunction.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Identified 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. HYPERSENSITIVITY REACTIONS CAN ALSO PROGRESS TO KOUNIS SYNDROME, A SERIOUS ALLERGIC REACTION THAT CAN RESULT IN MYOCARDIAL INFARCTION. PRESENTING SYMPTOMS OF SUCH REACTIONS CAN INCLUDE CHEST PAIN OCCURRING IN ASSOCIATION WITH AN ALLERGIC REACTION TO AMOXICILLIN AND CLAVULANIC ACID TABLETS (see Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)). IF AN ALLERGIC REACTION OCCURS, ALPHACLAV DUO VIATRIS 500/125 OR ALPHACLAV DUO FORTE VIATRIS 875/125 THERAPY 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.

Drug-induced enterocolitis syndrome (DIES) has been reported mainly in children receiving amoxicillin/clavulanate (see Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)). DIES is an allergic reaction with the leading symptom of protracted vomiting (1-4 hours after administration of amoxicillin/clavulanate) in the absence of allergic skin or respiratory symptoms. Further symptoms could comprise abdominal pain, diarrhoea, hypotension or leucocytosis with neutrophilia. There have been severe cases including progression to shock.

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 amoxicillin and clavulanic acid 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.

Amoxicillin and clavulanic acid 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 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.

Use in Hepatic Impairment

Amoxicillin and clavulanic acid tablets should be used with care in patients with evidence of hepatic dysfunction.

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

Use in Renal Impairment

In patients with reduced urine output, crystalluria (including acute renal injury) 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 Sections 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS) and 4.9 OVERDOSE).

ALPHACLAV DUO FORTE VIATRIS 875/125 tablets should not be used in patients with moderate to severe renal impairment (creatinine clearance ≤ 30mL/min).

ALPHACLAV DUO VIATRIS 500/125 tablets should be used with care in patients with moderate or severe renal impairment. The dosage of ALPHACLAV DUO VIATRIS 500/125 should be adjusted as recommended in section 4.2 DOSE AND METHOD OF ADMINISTRATION.

Use in the Elderly

No data available

Paediatric Use

See Section 4.2 DOSE AND METHOD OF ADMINISTRATION

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.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

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. 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 amoxicillin. If co-administration is necessary, the prothrombin time or international normalised ratio should be carefully monitored with the addition or withdrawal of amoxicillin.

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

4.6 FERTILITY, PREGNANCY AND LACTATION

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 – Pregnancy Category B1

Animal studies with orally and parenterally administered amoxicillin and clavulanic acid tablets 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.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

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

4.8 ADVERSE EFFECTS (UNDESIRABLE 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 tablet 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 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

	875/125mg 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

During clinical trials, the most frequently reported adverse events related or possibly related to amoxicillin and clavulanic acid 500/125mg tablet 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 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

Post Marketing

In addition, the following adverse reactions have been reported for ampicillin class antibiotics and may occur with amoxicillin and clavulanic acid 500/125mg tablets and amoxicillin and clavulanic acid 875/125mg 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

Cardiac disorders

not known: Kounis syndrome (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

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 Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).
not known: Drug-induced enterocolitis syndrome, pancreatitis acute

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.
not known: aseptic meningitis

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) and drug reaction with eosinophilia and systemic symptoms (DRESS), and symmetrical drug-related intertriginous and flexural exanthema (SDRIFE) (baboon syndrome) have been reported rarely. Whenever such reactions occur, ALPHACLAV DUO VIATRIS 500/125 or ALPHACLAV DUO FORTE VIATRIS 875/125 should be discontinued, unless in the opinion of the physician no alternative treatment is available and continued use of ALPHACLAV DUO VIATRIS 500/125 or ALPHACLAV DUO FORTE VIATRIS 875/125 is considered essential. Serious and occasional fatal hypersensitivity (anaphylactic) reactions and angioneurotic oedema can occur with oral penicillins (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).
not known: Linear IgA disease

Renal and urinary disorders:

rare: interstitial nephritis
not known: crystalluria (including acute renal injury) (see Section 4.9 OVERDOSE)

Miscellaneous

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

Reporting Suspected Adverse Effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

Serious and severe clinical symptoms are unlikely to occur after overdosage with amoxicillin and clavulanic acid 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 Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Amoxicillin 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).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of Action

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

		Percentage of Strains	
	Number of Pathogens (n)	**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

Breakpoints	Number of Pathogens (n)	Percentage acquired resistance (%)
Sensitive aerobe gram positive		
Enterococcus faecalis	178	1.7
Staphylococcus aureus	955	2

Breakpoints	Number of Pathogens (n)	Percentage acquired resistance (%)
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 (µg/mL) according to NCCLS guidelines (M100-S10) for amoxicillin and amoxicillin/clavulanic acid

Organisms	Antimicrobial Agents	MIC (µg/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 MIC_{90} 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	1.0
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 mcg amoxicillin and clavulanic acid (20 mcg amoxicillin + 10 mcg 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]

ORGANSIMS	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:

	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.

Clinical Trials

Amoxicillin and clavulanic acid (875/125mg) tablets 12 hourly vs Amoxicillin and clavulanic acid (500/125mg) tablets 8 hourly

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 (875/125 mg) tablets every 12 hours (q12h) to amoxicillin and clavulanic acid (500/125 mg) 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 875/125 mg q12h and 500/125 mg 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 875/125 mg q12h dosing versus 2.5% for the 500/125 mg q8h dosing. In the third study the most frequently reported adverse event was

headache with an incidence of 5.7% (amoxicillin and clavulanic acid (500/125 mg) tablets q8h) vs 8.3% (amoxicillin and clavulanic acid (875/125 mg) 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 12 hourly vs Amoxicillin and clavulanic acid (250/125 mg) tablets 8 hourly

Two pivotal studies in 908 patients treated for between 5 and 10 days for either uncomplicated Skin and Skin Structure Infections or Acute Exacerbation of Chronic Bronchitis compared a regimen of amoxicillin and clavulanic acid (500/125mg) tablets every 12 hours with amoxicillin and clavulanic acid (250/125mg) 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 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 clavulanic acid tablets regimens, or compared the proposed regimen with other treatments.

5.2 PHARMACOKINETIC PROPERTIES

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 amoxicillin and clavulanic acid 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 (Table 6 and 7) 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:

Table 6: Amoxicillin 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 7: 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 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(0-24 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) every 8 hours at the start of a light meal (Table 8 and 9).

Table 8: Amoxicillin Pharmacokinetics

Dose	[1]Cmax µg/mL	[2]AUC(0-24hrs) µg/hour/mL	[3]t1/2 hours	[4]Tmax 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 9: Clavulanic Acid Pharmacokinetics

Dose	[1]Cmax µg/mL	[2]AUC(0-24hrs) µg/hour/mL	[3]t1/2 hours	[4]Tmax 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 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 cerebrospinal fluid (CSF) when the meninges are normal. Amoxicillin penetrates into the CSF better through inflamed meninges, but the maximum concentrations are still much lower than the peak serum levels. There are no data at present on the CSF penetration of clavulanic acid in patients with meningeal inflammation.

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% (ie. 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.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

The genotoxic potential of amoxicillin/clavulanic acid was investigated in assays for chromosomal damage (mouse micronucleus 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 or mutagenic potential.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

ALPHACLAV DUO FORTE VIATRIS 875/125 tablets also contain the inactive ingredients: magnesium stearate, croscarmellose sodium, purified talc and microcrystalline cellulose. The tablet coating contains titanium dioxide, hypromellose, ethyl cellulose, hyprolose and propylene glycol.

ALPHACLAV DUO VIATRIS 500/125 tablets also contain the inactive ingredients: magnesium stearate, croscarmellose sodium, purified talc and microcrystalline cellulose. The tablet coating contains titanium dioxide, hypromellose, ethyl cellulose, hyprolose and propylene glycol.

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECUATIONS FOR STORAGE

Store below 25°C. Protect from moisture.

6.5 NATURE AND CONTENTS OF CONTAINER

Both ALPHACLAV DUO FORTE VIATRIS 875/125 Tablets and ALPHACLAV DUO VIATRIS 500/125 Tablets are presented in PVC/Al blister packs of 2, 10 and 60.

Some strengths, pack sizes and/or pack types may not be marketed.

Australian Register of Therapeutic Goods (ARTG)

AUST R 255078 - ALPHACLAV DUO VIATRIS 500/125 amoxicillin 500 mg and clavulanic acid 125 mg tablets blister pack

AUST R 255073 - ALPHACLAV DUO FORTE VIATRIS 875/125 amoxicillin 875 mg and clavulanic acid 125 mg tablets blister pack

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

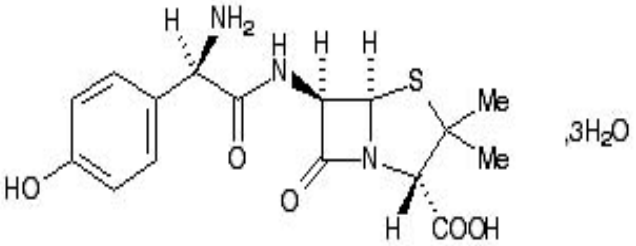
In Australia, any unused medicine or waste material should be disposed of in accordance with local requirements.

PHYSICOCHEMICAL PROPERTIES

Chemical Structure

Amoxicillin trihydrate

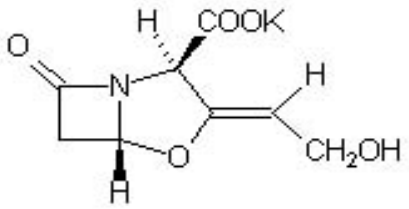
Chemically, amoxicillin trihydrate is (2S,5R,6R)-6-[[(2R)-2-Amino-2-(4-hydroxyphenyl)acetyl] amino]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid trihydrate. It is susceptible to hydrolysis by β- lactamases. Amoxicillin trihydrate may be represented structurally as:



Molecular formula: $C_{16}H_{19}N_3O_5S.3H_2O$
Molecular weight: 419.4

Clavulanic acid

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:



Molecular formula: $C_8H_8KNO_5$
Molecular weight: 237.3

Amoxicillin 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. It has a pKa of 2.8 and 7.2, with a partition coefficient of -2.69.

Potassium clavulanate is white to almost white, crystalline powder, hygroscopic, freely soluble in water, slightly soluble in alcohol, and very slightly soluble in acetone. The pKa is 2.7, with a partition coefficient of - 1.38.

CAS Number

Amoxicillin Trihydrate 61336-70-7

Potassium Clavulanate 61177-45-5

7 MEDICINE SCHEDULE (POISONS STANDARD)

S4 (Prescription Only Medicine)

8 SPONSOR

Alphapharm Pty Ltd trading as Viatris

Level 1, 30 The Bond

30-34 Hickson Road

Millers Point NSW 2000

www.viatris.com.au

Phone: 1800 274 276

9 DATE OF FIRST APPROVAL

17/01/2017

10 DATE OF REVISION

20/05/2024

Summary Table of Changes

Section Changed	Summary of New Information
All	Minor editorial changes
4.8	Symmetrical drug-related intertriginous and flexural exanthema (SDRIFE) (baboon syndrome) added to Hypersensitivity and Skin.

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