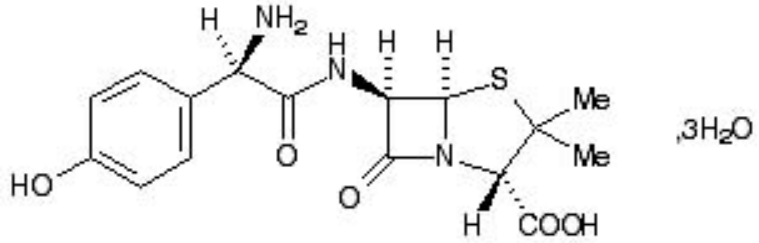
Clamoxyl 125/31.25

Amoxycillin Trihydrate and Potassium Clavulanate

PRODUCT INFORMATION

NAME OF THE MEDICINE

CLAMOXYL 125/31.25 (amoxycillin and clavulanic acid) is a combination product containing the semisynthetic antibiotic amoxycillin (as the trihydrate) and the β-lactamase inhibitor clavulanic acid (as the potassium salt). The chemical name of amoxycillin is D-(-)-α-amino-p-hydroxybenzyl-penicillin trihydrate. It is susceptible to hydrolysis by β-lactamases. Amoxycillin trihydrate is represented structurally as:



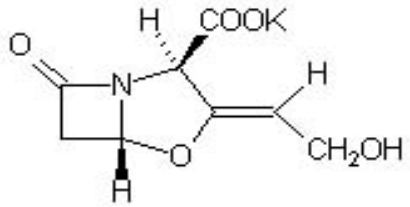
Molecular Formula: $C_{16}H_{19}N_3O_5S,3H_20$

Molecular Weight: 419.5

CAS Registry No.: 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.

The chemical name of potassium clavulanate is potassium Z-(2R,5R)-3-(B-hydroxyethylidene) clavam-2-carboxylate, and is represented structurally as:



Molecular Formula: $C_8H_8KNO_5$

Molecular Weight: 237.3

CAS Registry No.: 61177-45-5

DESCRIPTION

Each 5 mL of reconstituted oral syrup of CLAMOXYL 125/31.25 contains 125 mg amoxycillin (an aminopenicillin) as the trihydrate, and 31.25 mg clavulanic acid as the potassium salt. CLAMOXYL 125/31.25 (amoxycillin and clavulanic acid) also contains the following inactive ingredients: aspartame, hypromellose, colloidal anhydrous silica, silicon dioxide, succinic acid, xanthan gum, and mixed fruit flavour.

Each 125 mg of potassium clavulanate is equivalent to 0.63 mmol of potassium.

PHARMACOLOGY

Pharmacokinetics

Absorption: Amoxycillin and clavulanic acid are stable in the presence of gastric acid. These two components are rapidly absorbed if administered before or with a meal, but if given after meals, the serum levels of clavulanic acid are significantly reduced. In fasting subjects mean peak serum levels after 1 amoxycillin and clavulanic acid (250/125 mg) tablet were 2.98 mg/L (range 1.2 to 5.1) for clavulanic acid and 3.89 mg/L (range 2.4 to 6.0) for amoxycillin. These levels occurred at 30 to 120 minutes and 60 to 240 minutes respectively after dosing. Following 1 amoxycillin and clavulanic acid (500/125 mg) tablet peak serum levels in fasting subjects were 3.28 to 4.72 mg/L for clavulanic acid, and 10.28 to 12.06 mg/L for amoxycillin, and were achieved 60 to 120 minutes after dosing.

Following oral administration of amoxycillin and clavulanic acid (125/31.25 mg in 5 mL) syrup at a dose of 8.3 mg/kg (amoxycillin 6.6 mg/kg + clavulanic acid 1.7 mg/kg) to children with otitis media the means of peak concentrations were 2.76 mg/L for amoxycillin and 0.78 mg/L for clavulanic acid. In children given amoxycillin and clavulanic acid (250/62.5 mg in 5 mL) syrup 16.6 mg/kg (amoxycillin 13.3 mg/kg + clavulanic acid 3.3 mg/kg), the means of peak values were 4.94 mg/L for amoxycillin and 1.53 mg/L for clavulanic acid. Peak concentrations were reached at approximately 60 minutes (range 40 to 120 minutes).

The half life of the amoxycillin part of amoxycillin and clavulanic acid is approximately 1.2 hours and that of clavulanic acid approximately 1.0 hour.

Distribution: Following administration of amoxycillin and clavulanic acid, both amoxycillin and clavulanic acid have been shown to diffuse in significant concentrations into pus, pleural and peritoneal fluids. Both penetrate poorly into the CSF when the meninges are normal.

Amoxycillin penetrates into the CSF better through inflamed meninges but the maximum concentrations are still much lower than the peak serum levels. There are no data at present on the CSF penetration of clavulanic acid in patients with meningeal inflammation.

Clavulanic acid has been variously reported to be bound to human serum in the range of 9 - 30% and amoxycillin approximately 20% bound.

Metabolism and Excretion: Approximately seventy percent of the dose of amoxycillin is excreted as amoxycillin and approximately thirty to forty percent of a dose of clavulanic acid is excreted in the urine, as clavulanic acid, during the first six hours after administration. Following the administration of 125 mg of radiolabelled potassium clavulanate orally to normal volunteers 68% of the administered radioactivity was recovered in the 24 hour urine. Of this, 34% (i.e. 23% of the administered dose) represented unchanged clavulanic acid. 2,5-dihydro-4-(2-hydroxyethyl)-5-oxo-1H-pyrrole-3-carboxylic acid (the major metabolite) and 1-amino-4-hydroxy-butan-2-one accounted for a further 23% and 12% (i.e. 16% and 8% respectively of the administered dose). Small amounts of other yet unidentified metabolites were also present. These metabolites were also present in the urine of rat and dog. The extent of urinary excretion of clavulanic acid and its metabolites is lower in rat urine than in dog and human urine.

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

Microbiology

Like other penicillins, amoxycillin has a bactericidal effect on sensitive organisms during the stage of active multiplication. However, amoxycillin is susceptible to hydrolysis by β-lactamases and the addition of clavulanic acid in CLAMOXYL 125/31.25 (amoxycillin and 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:

Table 1 – Acquired resistance data for amoxycillin/clavulanic acid in Australia according to NCCLS guidelines (M100-S10) for amoxycillin/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/resistant *S. pneumoniae* Isolates

MIC ≤ 2 mcg/ml	MIC = 4 mcg/ml	MIC ≥ 8 mcg/ml
99.6%	0.3 %	0.1%

Table 3 – Acquired resistance data for amoxycillin/clavulanic acid from other countries

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

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

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

Table 4 – In Vitro Activity of amoxycillin/clavulanic acid

	N	MIC 90 (µg/mL)
GRAM POSITIVE AEROBES:		
Enterococcus faecalis	185	1
Staphylococcus aureus	229	1
Staphylococcus aureus (MSSA)	95	1
Staphylococcus aureus (MRSA)	20	16
Staphylococcus epidermidis	134	4
Staphylococcus saprophyticus	20	1
Coagulase negative staphylococci	83	2
Streptococcus agalactiae	20	0.06
Streptococcus pneumoniae	1,476	2
Streptococcus pyogenes	764	0.12
Streptococcus viridans	20	0.5
GRAM NEGATIVE AEROBES:		
Escherichia coli	325	8
Haemophilus influenzae	2,268	2
Haemophilus influenzae (BLN)	691	1
Haemophilus influenzae (BLP)	271	2
Klebsiella pneumoniae	200	4
Klebsiella oxytoca	34	8
Moraxella catarrhalis	35	0.25
Neisseria gonorrheae	35	1
Neisseria meningitidis	10	0.06
Proteus mirabilis	49	2
Proteus vulgaris	11	8
GRAM POSITIVE ANAEROBES:		
Clostridium species	13	0.5
Clostridium perfringens	16	0.06
Clostridium difficile	21	2
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 amoxycillin/clavulanic acid.
Proteus vulgaris and Klebsiella species may not be susceptible to amoxycillin/clavulanic acid at concentrations of amoxycillin and clavulanic acid achieved in the plasma. However at concentrations of amoxycillin and clavulanic acid achievable in the urine the majority of strains are susceptible.

Susceptibility Testing

Dilution or diffusion techniques - either quantitative (MIC) or breakpoint - should be used following a regularly updated, recognised and standardised method (eg. NCCLS). Standardised susceptibility test procedures require the use of laboratory control micro-organisms 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 micro-organism 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 situations where high dosage of drug can be used. This category also provides a buffer zone, which prevents small uncontrolled technical factors from causing major discrepancies in interpretation. A report of "Resistant" indicates that the pathogen is not likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations usually achievable; other therapy should be selected.

INDICATIONS

CLAMOXYL 125/31.25 (amoxycillin and clavulanic acid) is indicated in the treatment of the following infections when caused by CLAMOXYL sensitive, β-lactamase producing organisms:

Skin and Skin Structure Infections, including cases caused by β-lactamase producing *S. aureus*, *E. coli* and Klebsiella spp. (only some strains may be sensitive).

Urinary Tract Infections, including cases caused by β-lactamase producing *E. coli*, *P. mirabilis* and Klebsiella spp.

Upper Respiratory Tract Infections, such as sinusitis, including cases caused by β-lactamase producing *H.influenzae* and *M.catarrhalis*, and otitis media, especially cases caused by β-lactamase producing *H. influenzae*, *M. catarrhalis* and *S. aureus*.

Lower Respiratory Tract Infections, especially cases caused by β-lactamase producing *H.influenzae* and *M.catarrhalis.*

Appropriate culture and susceptibility studies should be performed to identify the causative organism(s) and determine its (their) susceptibility to CLAMOXYL 125/31.25 (amoxycillin and clavulanic acid). 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 amoxycillin susceptible organisms and β-lactamase producing organisms susceptible to CLAMOXYL 125/31.25 (amoxycillin and clavulanic acid) should not require the addition of another antibiotic due to the amoxycillin content of CLAMOXYL 125/31.25.

CONTRAINDICATIONS

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

CLAMOXYL 125/31.25 (amoxycillin and clavulanic acid) is contraindicated in patients with a previous history of amoxycillin/clavulanic acid-associated jaundice/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, CLAMOXYL 125/31.25 (AMOXYCILLIN AND CLAVULANIC ACID) SHOULD BE DISCONTINUED AND THE APPROPRIATE THERAPY INSTITUTED. SERIOUS ANAPHYLACTOID REACTIONS REQUIRE IMMEDIATE EMERGENCY TREATMENT WITH ADRENALINE. OXYGEN, INTRAVENOUS STEROIDS, AND AIRWAY MANAGEMENT, INCLUDING INTUBATION, SHOULD ALSO BE ADMINISTERED AS INDICATED.

Antibiotic associated pseudomembranous colitis has been reported with many antibiotics including amoxycillin. A toxin produced 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, eg. opiates and diphenoxylate with atropine (Lomotil) may prolong and/or worsen the condition and should not be used.

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

Since CLAMOXYL 125/31.25 (amoxycillin and clavulanic acid) contains amoxycillin, an aminopenicillin, it is not the treatment of choice in patients presenting with sore throat or pharyngitis because of the possibility that the underlying cause is infectious mononucleosis, in the presence of which there is a high incidence of rash if amoxycillin is used.

CLAMOXYL 125/31.25 (amoxycillin and clavulanic acid) should be given with caution to patients with lymphatic leukaemia since they are especially susceptible to amoxycillin induced skin rashes.

Amoxycillin-clavulanate should be avoided if infectious mononucleosis is suspected since the occurrence of a morbilliform rash has been associated with this condition following the use of 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 amoxycillin-clavulanate and oral anticoagulants. Appropriate monitoring should be undertaken when anticoagulants are prescribed concurrently. Adjustments in the dose of oral anticoagulants may be necessary to maintain the desired level of anticoagulation.

The possibility of superinfections with mycotic or bacterial pathogens should be kept in mind during therapy. If superinfections occur (usually involving Aerobacter, Pseudomonas or Candida), the drug should be discontinued and/or appropriate therapy instituted.

Cholestatic hepatitis, which may be severe but is usually reversible has been reported rarely. Signs and symptoms may not become apparent until several weeks after treatment has ceased. In most cases resolution has occurred with time. However, in extremely rare circumstances, deaths have been reported. These have almost always been cases associated with serious underlying disease or concomitant medications. Hepatic events subsequent to CLAMOXYL (amoxycillin and clavulanic acid) have occurred predominantly in adults and elderly patients. These events have been very rarely reported in children.

CLAMOXYL 125/31.25 (amoxycillin and 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**).

In patients with moderate or severe renal impairment CLAMOXYL 125/31.25 (amoxycillin and clavulanic acid) dosage should be adjusted as recommended in the **DOSAGE AND ADMINISTRATION** section.

Carcinogenecity

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

Genotoxicity

The genotoxic potential of amoxycillin and 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 and clavulanic acid at oral doses of up to 1200 mg/kg/day had no effect on fertility and reproductive performance in rats dosed with a 2:1 ratio formulation of amoxycillin and clavulanate.

Use in Pregnancy (Category B1)

Animal studies with orally and parenterally administered amoxycillin and clavulanic acid have shown no teratogenic effects. There is limited experience of the use of CLAMOXYL 125/31.25 (amoxycillin and clavulanic acid) in human pregnancy. In women with preterm, premature rupture of the foetal membrane (pPROM), prophylactic treatment with CLAMOXYL 125/31.25 (amoxycillin and clavulanic acid) may be associated with an increased risk of necrotising enterocolitis in neonates. As with all medicines, use should be avoided in pregnancy, especially during the first trimester, unless considered essential by the physician.

Use in Labour and Delivery

Oral ampicillin class antibiotics are generally poorly absorbed during labour. Studies in guinea pigs have shown that intravenous administration of ampicillin decreased the uterine tone, frequency of contractions,

height of contractions and duration of contractions. However, it is not known whether the use of CLAMOXYL 125/31.25 (amoxycillin and clavulanic acid) in humans during labour or delivery has immediate or delayed adverse effects on the foetus, prolongs the duration of labor or increases the likelihood that forceps delivery or other obstetrical intervention or resuscitation of the newborn will be necessary.

Use in Lactation

Amoxycillin is excreted in the milk; there are no data on the excretion of clavulanic acid in human milk. Therefore, caution should be exercised when CLAMOXYL 125/31.25 (amoxycillin and clavulanic acid) is 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 CLAMOXYL 125/31.25 (amoxycillin and clavulanic acid) will result in high urine concentrations of amoxycillin. Since high urine concentrations of ampicillin may result in false positive reactions when testing for the presence of glucose in urine using Clinitest, Benedict's Solution or Fehling's Solution, it is recommended that glucose tests based on enzymatic glucose oxidase reactions (such as Clinistix® or Testape®) be used.

Following administration of ampicillin to pregnant women a transient decrease in plasma concentration of total conjugated oestriol, oestriol-glucuronide, conjugated oestrone and oestradiol has been noted. This effect may also occur with amoxycillin, and therefore CLAMOXYL 125/31.25 (amoxycillin and clavulanic acid).

INTERACTIONS WITH OTHER MEDICINES

Concomitant use of probenecid is not recommended. Probenecid decreases the renal tubular secretion of amoxycillin but does not affect clavulanic acid excretion. Concurrent use with CLAMOXYL 125/31.25 (amoxycillin and clavulanic acid) may result in increased and prolonged blood levels of amoxycillin but not of clavulanic acid.

The concurrent administration of allopurinol and ampicillin increases substantially the incidence of rashes in patients receiving both drugs as compared to patients receiving ampicillin alone. It is not known whether this potentiation of ampicillin rashes is due to allopurinol or the hyperuricemia present in these patients. There are no data with CLAMOXYL 125/31.25 (amoxycillin and clavulanic acid) and allopurinol administered concurrently.

No information is available about the concurrent use of CLAMOXYL 125/31.25 (amoxycillin and clavulanic acid) 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 CLAMOXYL 125/31.25 (amoxycillin and clavulanic acid).

In common with other broad spectrum antibiotics, CLAMOXYL 125/31.25 (amoxycillin and clavulanic acid) 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 amoxycillin. If co-administration is necessary, the prothrombin time or international normalised ratio should be carefully monitored with the addition or withdrawal of amoxycillin.

In patients receiving mycophenolate mofetil, reduction in pre-dose concentration of the active metabolite mycophenolic acid of approximately 50% has been reported following commencement of oral amoxicillin plus clavulanic acid. The change in pre-dose level may not accurately represent changes in overall MPA exposure.

ADVERSE EFFECTS

CLAMOXYL 125/31.25 (amoxycillin and clavulanic acid) is generally well tolerated. In clinical trials, 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% cases at the low dose [one amoxycillin/clavulanic acid (250/125 mg) tablet T.D.S.] and 7% cases at the high dose [one amoxycillin/clavulanic acid (500/125 mg) tablet T.D.S.]. 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.

The following adverse reactions have been reported for ampicillin class antibiotics and may occur with CLAMOXYL 125/31.25 (amoxycillin and clavulanic acid):

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 pseudomembraneous colitis and haemorrhagic colitis) (see **PRECAUTIONS**).

Hypersensitivity and skin:

Common: skin rashes, pruritus, urticaria

Rare: angioneurotic oedema, anaphylaxis, erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis, serum sickness-like syndrome, hypersensitivity vasculitis, bullous exfoliative dermatitis and acute generalised exanthematous pustulosis (AGEP) have been reported rarely. Serious and occasional fatal hypersensitivity (anaphylactic) reactions and angioneurotic oedema can occur with oral penicillin (See **PRECAUTIONS**). Whenever such reactions occur, CLAMOXYL 125/31.25 (amoxycillin and clavulanic acid) should be discontinued, unless in the opinion of the physician no alternative treatment is available and continued use of CLAMOXYL 125/31.25 (amoxycillin and clavulanic acid) is considered essential.

Renal and urinary disorders:

Rare: interstitial nephritis

Very rare: crystalluria (see **OVERDOSAGE**)

Hepatobiliary:

Uncommon: a moderate rise in AST and/or ALT.

Rare: hepatitis and cholestatic jaundice which may be severe but is usually reversible (see **PRECAUTIONS**)

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.

Nervous system disorders:

Uncommon: dizziness, headache

Very rare: reversible hyperactivity, convulsions. Convulsions may occur with impaired renal function or in those receiving high doses.

Miscellaneous:

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

DOSAGE AND ADMINISTRATION

CLAMOXYL 125/31.25 (amoxycillin and clavulanic acid) should be taken immediately before or with the first mouthful of food.

Children: The usual dose is 20 mg/Kg/day, based on the amoxycillin component, in divided doses every eight hours. For otitis media, sinusitis, lower respiratory tract infections and other more severe infections, the dose should be 40 mg/kg/day, based on the amoxycillin component in divided doses every 8 hours.

The children's dosage is intended for individuals whose weight will not cause dosage to be calculated greater than that recommended for adults. Children weighing 40 kg and more should be dosed according to the adult recommendations for other CLAMOXYL preparations (for more information refer to the Product Information document for CLAMOXYL DUO 500/125 and CLAMOXYL DUO FORTE 875/125).

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 10 days, except for lower respiratory tract infection due to *H. influenzae* where treatment may be extended up to 14 days.

With Impaired Renal Function: Both amoxycillin 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 CLAMOXYL 125/31.25 (amoxycillin and clavulanic acid) dose is necessary, but the dosing interval should be extended according to the degree of renal impairment.

The following schedule is proposed:

Mild Impairment: (Creatinine clearance >30 mL/min)	No change in dosage.
Moderate Impairment: (Creatinine clearance 10 – 30 mL/min)	Dose every12 hours
Severe Impairment: (Creatinine clearance <10 mL/min)	Half dose every 12 hours

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

Direction for mixing syrup: Prepare a syrup at time of dispensing as follows: Tap bottle until all the powder flows freely. Add approximately 1/2 of the total amount of water for reconstitution (see table below) and shake vigorously to suspend powder. Add remainder of the water and again shake vigorously.

	Bottle Size	**Amount of water required for reconstitution**	**Final volume of reconstituted syrup**
CLAMOXYL 125/31.25 (amoxycillin and clavulanic acid) 125/31.25 mg in 5 mL oral suspension	145 mL	67 mL	75 mL

Each 5 mL will contain 125 mg amoxycillin (as the trihydrate) and 31.25 mg of clavulanic acid (as the potassium salt).

Reconstituted syrup must be stored under refrigeration (2 -8°C) and discarded after 7 days.

OVERDOSAGE

Serious and severe clinical symptoms are unlikely to occur after overdosage with CLAMOXYL 125/31.25 (amoxycillin and 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.

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

Amoxycillin may be removed from circulation by hemodialysis.

Contact the Poisons Information Centre (telephone 13 11 26) for further advice on overdose management.

PRESENTATION AND STORAGE CONDITIONS

CLAMOXYL 125/31.25 (amoxycillin and clavulanic acid) syrup (dry powder) should be stored below 25°C and protected from moisture. Under these conditions the shelf life for the powder is 18 months.

CLAMOXYL 125/31.25 (amoxycillin and clavulanic acid): Each 5 mL of reconstituted syrup contains 125 mg amoxycillin (as the trihydrate) and 31.25 mg clavulanic acid (as the potassium salt). Available in bottles of 145 mL.

NAME AND ADDRESS OF THE SPONSOR

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POISON SCHEDULE OF THE MEDICINE

S4 - Prescription Only Medicine

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

15/11/2007

DATE OF MOST RECENT AMENDMENT

23/01/2014