NEW ZEALAND DATA SHEET

1. PRODUCT NAME

Curam Powder for oral suspension

Curam Film coated tablet

Curam Duo 500/125 Film coated tablet

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Curam tablet

250 + 125 mg

Each tablet contains Amoxicillin Trihydrate Ph. Eur. equivalent to amoxicillin 250 mg and Potassium Clavulanate Ph. Eur. equivalent to clavulanic acid 125 mg.

Curam Duo 500/125 tablet

500 + 125 mg

Each tablet contains Amoxicillin Trihydrate Ph. Eur. equivalent to amoxicillin 500 mg and Potassium Clavulanate Ph. Eur. equivalent to clavulanic acid 125 mg.

Curam powder for oral suspension

125 + 31.25 mg/5 mL

Reconstituted suspension contains in 5 mL, Amoxicillin Trihydrate Ph. Eur. equivalent to amoxicillin 125 mg and Potassium Clavulanate Ph. Eur. equivalent to clavulanic acid 31.25 mg.

250 + 62.5 mg/5 mL

Reconstituted suspension contains in 5 mL, Amoxicillin Trihydrate Ph. Eur. equivalent to amoxicillin 250 mg and Potassium Clavulanate Ph. Eur. equivalent to clavulanic acid 62.5 mg.

List of excipients with known effect: Aspartame.

For the full list of excipients, see Section 6.1 List of excipients.

3. PHARMACEUTICAL FORM

Curam tablet

Tablet, film-coated, oblong biconvex formed, off-white colour, scored on both sides.

Curam Duo 500/125 tablet

Tablet, film-coated, oval biconvex formed, off-white colour, scored on both sides.

Curam powder for oral suspension

Suspension, oral, powder for, white to yellowish colour.

4. CLINICAL PARTICULARS

4.1. THERAPEUTIC INDICATIONS

Short-term treatment of common bacterial infections such as:

Upper respiratory tract infections (including ENT): e.g. tonsillitis, sinusitis, otitis media

Lower respiratory tract infections: e.g. acute exacerbations of chronic bronchitis, lobar and broncho-pneumonia

Genito-urinary tract infections: e.g. cystitis, urethritis, pyelonephritis, female genital infections

Skin and soft tissue infections

Bone and joint infections: e.g. osteomyelitis

Other infections: e.g. septic abortion, puerperal sepsis, intra-abdominal sepsis, septicaemia, peritonitis and post-surgical infections.

Prophylaxis against infection which may be associated with major surgical procedures such as gastro-intestinal, pelvic, head and neck, cardiac, renal, joint replacement and biliary tract surgery.

Infections caused by amoxicillin susceptible organisms are amenable to amoxicillin/clavulanic acid treatment due to its amoxicillin content. Mixed infections caused by amoxicillin susceptible organisms in conjunction with amoxicillin/clavulanic acid susceptible beta-lactamase-producing organisms may therefore be treated by amoxicillin/clavulanic acid.

4.2. DOSE AND METHOD OF ADMINISTRATION

Dosage

Adults and children 40 kg and over

One Curam Duo 500/125 tablet twice daily for mild to moderate infections. For lower respiratory tract infections, complicated urinary tract infections or severe infections at other sites, one to two Curam Duo 500/125 tablets three times daily.

Weight based dosage recommendations for children up to 12 years and <40 kg

Lower dose (recommended for infections such as skin and soft tissue and recurrent tonsillitis): 20/5 to 40/10 mg/kg/day given as 3 divided doses.

Higher dose (recommended for infections such as otitis media, sinusitis, lower respiratory tract infections and urinary tract infections): 40/10 to 60/15 mg/kg/day given as 3 divided doses.

The usual maximum dose of Curam powder for oral suspension is 625mg (i.e. 500mg amoxicillin + 125mg clavulanic acid) three times a day.

There is no clinical data available on doses of Curam powder for oral suspension higher than 40/10 mg/kg/day in children under 2 years.

Other considerations

Dose recommendations in this data sheet may be different to those in local clinical guidelines. If a high dose of Curam or Curam Duo 500/125 is required (for the amoxicillin component),

consider combining Curam or Curam Duo 500/125 with amoxicillin to keep the clavulanic levels within the normal therapeutic range.

Dosage for surgical prophylaxis

Surgical prophylaxis with amoxicillin/clavulanic acid should aim to protect the patient for the period of risk of infection. Accordingly, procedures in adults lasting for less than 1 hour are successfully covered by 1.2 g amoxicillin/clavulanic acid intravenous given at induction of anaesthesia. Longer operations require subsequent doses of 1.2 g amoxicillin/clavulanic acid IV (up to 4 doses in 24 hours), and this regime can be continued for several days if the procedure has significantly increased the risk of infection. Clear clinical signs of infection at operation will require a normal course of IV or oral amoxicillin/clavulanic acid therapy post-operatively.

Method of administration

Therapy can be started parenterally and continued with an oral preparation.

Curam oral suspensions

To minimise potential gastrointestinal intolerance, administer at the start of a meal. The absorption of amoxicillin/clavulanic acid is optimised when taken at the start of a meal.

Treatment should not be extended beyond 14 days without review.

For administration of suspensions to children below 3 months, a syringe graduated to permit accurate and reproducible volumes to be dispensed, should be used.

Dosage adjustment in:

- renal impairment

Dosing adjustments are based on the maximum recommended level of amoxicillin.

Adults

Mild impairment (creatinine clearance > 30 mL/min): no change in dosage. Moderate impairment (creatinine clearance 10 to 30 mL/min): 1 tablet 12 hourly. For severe impairment (creatinine clearance < 10 mL/min): 1 tablet once daily. Dialysis decreases serum concentrations of amoxicillin/clavulanic acid. An additional dose may need to be supplemented at the end of dialysis.

Children

Oral suspension (in the majority of cases, parenteral therapy, where available, may be preferred). Mild impairment (creatinine clearance > 30 mL/min): no change in dosage. Moderate impairment (creatinine clearance 10 to 30 mL/min) 15 + 3.75 mg/kg given 12 hourly (maximum 500 + 125 mg twice daily). Severe impairment (creatinine clearance < 10 mL/min) 15/3.75 mg/kg given as a single daily dose (maximum 500 + 125 mg). Dialysis decreases serum concentrations of amoxicillin/clavulanic acid. Prior to haemodialysis one additional dose of 15 + 3.75 mg/kg should be administered. In order to restore circulating drug levels, another dose of 15 + 3.75 mg/kg should be administered after haemodialysis.

- hepatic impairment

Administer with caution; monitor hepatic function at regular intervals for both adults and children. There are as yet insufficient data on which to base a dosage recommendation.

- elderly

No adjustment needed dose as for adults. If there is evidence of renal impairment, dose should be adjusted as for renally impaired adults (see above).

4.3. CONTRAINDICATIONS

Hypersensitivity to one of the constituents of the medicine.

In patients with a history of hypersensitivity to other beta-lactams such as penicillins, cephalosporins, carbapenems or monobactams.

Curam and Curam Duo are contraindicated in patients with a previous history of amoxicillin/clavulanic acid – associated jaundice or hepatic dysfunction.

4.4. SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Before initiating therapy with amoxicillin/clavulanic acid, careful enquiry should be made concerning previous hypersensitivity reactions to penicillins, cephalosporins, or other allergens.

Serious and occasionally fatal hypersensitivity reactions (anaphylactoid and severe cutaneous adverse reactions) have been reported in patients on penicillin therapy. These reactions are more likely to occur in individuals with a history of penicillin hypersensitivity. 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/clavulanic acid (see section 4.8 Undesirable effects). Drug-induced enterocolitis syndrome has been reported mainly in children receiving amoxicillin-clavulanate (see section 4.8 Undesirable effects). Drug-induced enterocolitis syndrome is an allergic reaction with the leading symptom of protracted vomiting (1-4 hours after medicinal product administration) in the absence of allergic skin or respiratory symptoms. Further symptoms could comprise abdominal pain, lethargy, diarrhoea, hypotension or leucocytosis with neutrophilia. In severe cases, drug-induced enterocolitis syndrome can progress to shock. If an allergic reaction occurs, amoxicillin/clavulanic acid therapy should be discontinued and appropriate alternative therapy instituted. Serious anaphylactoid reactions require immediate emergency treatment with adrenaline or epinephrine. Oxygen, intravenous steroids and airway management, including intubation may also be required.

Amoxicillin/clavulanic acid should be avoided if infectious mononucleosis is suspected since the occurrence of a morbilliform rash has been associated with this condition following the use of amoxicillin.

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

Pseudomembranous colitis has been reported with the use of antibiotics and may range in severity from mild to life-threatening. Therefore, it is important to consider its diagnosis in patients who develop diarrhoea during or after antibiotic use. If prolonged or significant diarrhoea occurs or the patient experiences abdominal cramps, treatment should be discontinued immediately and the patient investigated further.

In general, amoxicillin/clavulanic acid is well tolerated and possesses the characteristic low toxicity of the penicillin group of antibiotics. Periodic assessment of organ system functions; including renal, hepatic and haematopoietic function is advisable during prolonged therapy.

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

Amoxicillin/clavulanic acid should be used with caution in patients with evidence of hepatic dysfunction.

Hepatic effects have been reported predominantly in males and elderly patients and may be associated with prolonged treatment. These side effects are very rarely reported in children.

Signs and symptoms usually occur during or shortly after treatment, but in some cases may not become apparent until several weeks after treatment has ceased. These are usually reversible. Hepatic events may be severe and in extremely rare circumstances, deaths have been reported. These have almost always occurred in patients with a serious underlying disease, or taking concomitant medications know to have the potential for hepatic effects.

In patients with renal impairment, dosage should be adjusted according to the degree of impairment (see section 4.2 Dose and method of administration).

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

The occurrence at treatment initiation of a feverish generalised erythema associated with pustule may be a symptom of acute generalised exanthemous pustulosis (AGEP). This reaction requires Curam discontinuation and is a contraindication to subsequent administration of amoxicillin.

The presence of clavulanic acid may cause a non-specific binding of IgG and albumin by red cell membranes leading to a false positive Coombs test.

Amoxicillin/clavulanic acid suspensions contain aspartame, which is a source of phenylalanine and should be used with caution in patients with phenylketonuria.

In patients with reduced urine output crystalluria has been observed very rarely, predominantly with parenteral therapy. During 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 (refer to Section 4.9 Overdose).

Use in hepatic impairment

Amoxicillin/clavulanic acid should be used with caution in patients with evidence of hepatic dysfunction.

Use in renal impairment

In patients with renal impairment, dosage should be adjusted according to the degree of impairment (refer to Section 4.2 Dose and method of administration).

Use in the elderly

See Section 4.2 Dose and method of administration.

Paediatric use

See Section 4.2 Dose and method of administration.

Effects on laboratory tests

No data available.

4.5. INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Concomitant use of probenecid is not recommended. Probenecid decreases the renal tubular secretion of amoxicillin. Concomitant use with amoxicillin/clavulanic acid may result in increased and prolonged blood levels of amoxicillin, but not of clavulanic acid.

Concomitant use of allopurinol during treatment with amoxicillin can increase the risk of allergic skin reactions. There are no data on the concomitant use of amoxicillin/clavulanic acid and allopurinol.

In common with other antibiotics, amoxicillin/clavulanic acid 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.

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.

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

4.6. FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

There are no data on the effects of amoxicillin trihydrate/potassium clavulanate on fertility in humans. Reproduction studies in animals (mice and rats at doses up to 10 times the human dose) with orally and parenterally administered amoxicillin/clavulanic acid have shown no teratogenic effects.

Use in pregnancy

Category B1

Assigned Category B1 by the Australian Drug Evaluation Committee. This category includes medicines, which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human foetus having been observed. Studies in animals have not shown evidence of an increased occurrence of foetal damage.

In a single study in women presenting preterm, premature rupture of the foetal membrane (pPROM), it was reported that prophylactic treatment with amoxicillin/clavulanic acid may be associated with an increased risk of necrotising enterocolitis in neonates. As with all medicines, use should be avoided in pregnancy, unless considered essential by the physician.

Use in lactation

Amoxicillin/clavulanic acid may be administered during the period of lactation. With the exception of the risk of sensitisation, associated with the excretion of trace quantities in breast milk, there are no known detrimental effects for the breastfed infant.

4.7. EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

This medicine is presumed to be safe or unlikely to produce an effect. Adverse effects on the ability to drive or operate machinery have not been observed.

4.8. UNDESIRABLE EFFECTS

Data from large clinical trials were used to determine the frequency of very common to rare adverse effects. The incidences of all other adverse effects occurring below 1 in 10,000 were mainly determined from post-marketing data and reflect the reporting rate rather than the true incidence.

The following convention has been used for the classification of frequency:-very common ≥1/10, common ≥1/100 and <1/10, uncommon ≥1/1000 and <1/100, rare ≥1/10,000 and <1/1000, very rare <1/10,000.

Infections and infestations:

Common	Mucocutaneous candidiasis
Unknown	Overgrowth of non-susceptible organism

Blood and lymphatic system disorders:

Rare	Reversible leucopenia (including neutropenia) and thrombocytopenia
Very rare	Reversible agranulocytosis and haemolytic anaemia. Prolongation of bleeding time and prothrombin time

Immune system disorders:

Very rare	Angioneurotic oedema, anaphylaxis (see section 4.4 Special warnings and precautions for use), serum sickness-like syndrome, hypersensitivity vasculitis (see also Skin and subcutaneous tissue disorders)

Nervous system disorders:

Uncommon	Dizziness, headache
Very rare	Aseptic meningitis, reversible hyperactivity and convulsions. Convulsions may occur in patients with impaired renal function or in those receiving high doses (refer to Section 4.4 Special warnings and precautions for use).

Cardiac disorders:

Very rare	Kounis syndrome (see section 4.4 Special warnings and precautions for use).

Gastrointestinal disorders following oral administration to adults:

Very common	Diarrhoea
Common	Nausea, vomiting
Uncommon	Indigestion

Very Rare	Antibiotic-associated colitis (including pseudomembranous colitis and haemorrhagic colitis), drug-induced enterocolitis syndrome (see Section 4.4 Special warnings and precautions for use). Black hairy tongue. Superficial tooth discolouration has been reported very rarely in children. Good oral hygiene may help to prevent tooth discolouration as it can usually be removed by brushing.

Gastrointestinal disorders following oral administration to paediatrics:

Common	Diarrhoea, nausea, vomiting
Uncommon	Indigestion
Very Rare	Antibiotic-associated colitis (including pseudomembranous colitis and haemorrhagic colitis) (see Section 4.4 Special warnings and precautions for use). Black hairy tongue. Superficial tooth discolouration has been reported very rarely in children. Good oral hygiene may help to prevent tooth discolouration as it can usually be removed by brushing.

In all populations, nausea is more often associated with higher oral dosages. If gastrointestinal reactions are evident, they may be reduced by taking amoxicillin/clavulanic acid at the start of a meal. Lower gastro-intestinal irritation reactions such as diarrhoea and pruritus have been observed. These side effects are generally of a mild and transitory nature.

Hepatobiliary disorders:

Uncommon	A moderate rise in AST and/or ALT has been noted in patients treated with beta-lactam class antibiotics, but the significance of these findings is unknown.
Very Rare	Hepatitis and cholestatic jaundice. These events have been noted with other penicillins and other beta-lactam antibiotics (see Section 4.4 Special warnings and precautions for use).

Skin and subcutaneous tissue disorders:

Common	Allergic skin reactions occur significantly more often than with other penicillins and generally are maculopapular in nature. In a small majority of cases, "fifth day rash" (a morbilliform exanthema) is reported. This is dependent on the size of the dose and the patient's condition.
Uncommon	Skin rash, pruritus, urticaria and purpura; angio-oedema and anaphylaxis can occur less frequently
Rare	Erythema multiforme
Very rare	Stevens-Johnson syndrome, toxic epidermal necrolysis, bullous exfoliative-dermatitis, acute generalised exanthemous pustulosis (AGEP), drug reaction with eosinophilia and systemic symptoms (DRESS), and symmetrical drug-related intertriginous and flexanthema (SDRIFE) (baboon syndrome) (see also Immune system disorders) If any hypersensitivity dermatitis reaction occurs, treatment should be discontinued. Linear IgA disease.

Renal and urinary disorders:

Very rare Interstitial nephritis, crystalluria (see Section 4.9 Overdose)

Cardiovascular system disorders:

Rare Allergies, which result in anaphylactic shock

Laboratory diagnostic tests

Non-enzymatic methods for glucose determination in urine may give false-positive results.

Clavulanic acid may cause a non-specific binding of IgG and albumin by red cell membranes leading to a false positive Coombs test (refer to Section 4.4 Special warnings and precautions for use).

Reporting suspected adverse effects

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://pophealth.my.site.com/carmreportnz/s/.

4.9. OVERDOSE

Drug dependency, addiction and recreational abuse have not been reported as problems.

Signs and symptoms

Gastrointestinal symptoms and disturbance of fluid and electrolyte balances may be evident.

Complications from amoxicillin crystalluria may present in high doses, in some cases leading to renal failure (refer to Section 4.4 Special warnings and precautions for use). When present at high concentrations in urine at room temperature, amoxicillin may precipitate in bladder catheters. A regular check of patency should be maintained.

Management

Amoxicillin and clavulanic acid can be removed from the circulation by haemodialysis. Gastrointestinal symptoms may be treated symptomatically by attending to the water and electrolyte balance. Treat other symptoms symptomatically. A prospective study of 51 paediatric patients at a poison control centre suggested that overdosages less than 250 mg/kg of amoxicillin are not associated with significant clinical symptoms and do not require gastric emptying.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5. PHARMACOLOGICAL PROPERTIES

5.1. PHARMACODYNAMIC PROPERTIES

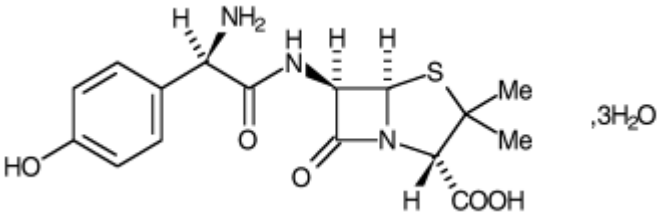
Pharmacotherapeutic group

J01CR02 – Combinations of penicillins, including beta-lactamase inhibitors.

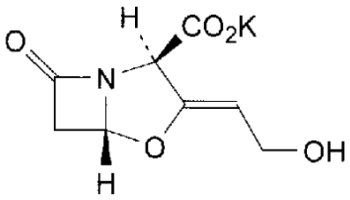
Antibiotic class

Semi-synthetic penicillin compounded with a beta-lactamase inhibitor.

Amoxicillin trihydrate



Potassium clavulanate



Mechanism of action

Curam film-coated tablets and oral suspension are antibiotic preparations compounded for oral administration from amoxicillin trihydrate – a beta-lactam antibacterial penicillin and the potassium salt of clavulanic acid - a beta-lactamase inhibitor. Amoxicillin/clavulanic acid has a notably broad-spectrum of activity against bacterial pathogens of clinical importance to general practice and secondary/tertiary care.

Antibiotic nature and mode of action

Amoxicillin is an aminopenicillin type broad-spectrum antibiotic that possesses activity against many Gram-positive and Gram-negative microorganisms. Amoxicillin is a bactericidal, cell-wall active agent that inhibits bacterial cell wall synthesis by binding to penicillin binding proteins and inhibits the cross-linking of bacterial peptidoglycan. However, amoxicillin is susceptible to degradation by beta-lactamases so it's intrinsic spectrum of activity excludes bacteria producing these enzymes.

Clavulanic acid is a beta-lactam, structurally related to the penicillins. It possesses the ability to inactivate a wide range of beta-lactamase enzymes commonly found in microorganisms resistant to penicillins and cephalosporins. In particular, it has good activity against the clinically important plasmid mediated beta-lactamases frequently responsible for transferred drug resistance. It is generally less effective against chromosomally-mediated type 1 beta-lactamases.

When appropriately combined with amoxicillin, clavulanic acid inhibits the degradation of amoxicillin by beta-lactamase enzymes and effectively extends the antibacterial spectrum of amoxicillin to include many bacteria normally resistant to amoxicillin, other penicillins and cephalosporins.

Susceptibility data

The prevalence of resistance may vary geographically and temporally for selected species. Local resistance information is desirable, particularly when treating severe infections. The

following information only provides approximate guidance on the probabilities that microorganisms will be susceptible to amoxicillin/clavulanic acid.

Susceptible

Susceptible Gram-positive aerobes include *Bacillus anthracis* [1], *Corynebacterium* spp., *Enterococcus faecalis* [1], *Listeria monocytogenes*, *Nocardia asteroides*, *Staphylococcus aureus* [1], Coagulase negative staphylococci [1] (including *Staphylococcus epidermidis* [1]), *Streptococcus* spp.; *Streptococcus pneumoniae*; Group A streptococci (including *Streptococcus pyogenes*); Group B streptococci (including *Streptococcus agalactiae*); Viridans group streptococci.

Susceptible Gram-positive anaerobes include *Clostridium* spp., *Peptococcus* spp., *Peptostreptococcus* spp.

Susceptible Gram-negative aerobes include *Bordetella pertussis*, *Brucella* spp., *Gardnerella vaginalis*, *Haemophilus influenzae* [1], *Helicobacter pylori*, *Legionella* species, *Moraxella catarrhalis* [1], *Neisseria gonorrhoeae* [1], *Neisseria meningitidis* [1], *Pasteurella multocida*, *Proteus mirabilis* [1], *Proteus vulgaris* [1], *Vibrio cholerae*, *Yersinia enterocolitica* [1].

Susceptible Gram-negative anaerobes include: *Bacteroides* spp. [1] *(*including *Bacteroides fragilis)*, *Fusobacterium* spp. [1]

Other susceptible pathogens include *Borrelia burgdorferi*, *Chlamydiae* spp., *Leptospira icterohaemorrhagiae*, *Treponema pallidum*.

Intermediate

Partially susceptible Gram-positive aerobes include *Enterococcus faecium* [1].

Partially susceptible Gram-negative aerobes include *Escherichia coli* [1]; *Klebsiella* spp. [1]; *Klebsiella pneumoniae* [1]; *Klebsiella oxytoca* [1]; *Salmonella* spp. [1]; *Salmonella hadar* [1]; *Salmonella typhimurium* [1]; *Shigella* spp. [1].

Notes:

[1] Some members of these species of bacteria produce beta-lactamase, rendering them insensitive to amoxicillin alone.

Resistance

Although, amoxicillin/clavulanic acid may exhibit *in vitro* activity against methicillin/oxacillin resistant *Staphylococcus aureus* (MRSA) and coagulase-negative staphylococci (MRS) it is not clinically effective and isolates should therefore be considered resistant. Rare beta-lactamase negative, ampicillin resistant (BLNAR) strains of *H. influenzae* should also be considered resistant to amoxicillin/clavulanic acid despite the apparent *in vitro* susceptibility of some BLNAR strains.

Resistant Gram-positive aerobes include *Staphylococcus aureus* (MRSA) and Coagulase-negative staphylococci (MRS).

Resistant Gram-negative aerobes include *Acinetobacter* spp.; *Citrobacter* spp.; *Enterobacter* spp.; *Haemophilus influenzae* (BLNAR); *Morganella morganii*; *Providencia* spp.; *Pseudomonas aeruginosa*; *Serratia* spp.; *Stenotrophomonas maltophilia*.

Other resistant pathogens include *Mycoplasma* spp. and *Rickettsia* spp.

Clinically relevant MIC ranges

According to the US National Committee on Clinical Laboratory Standards (NCCLS) in 2001, the following breakpoints have been defined for amoxicillin/clavulanic acid: *Enterobacteriaceae:* NMT 8/4 mcg/mL susceptible, 16/8 mcg/mL intermediate, NLT 32/16 mcg/mL resistant; *Staphylococcus* spp. and *Haemophilus* spp.: NMT 4/2 mcg/mL susceptible, NLT 8/4 mcg/mL resistant; *Streptococcus pneumoniae:* NMT 2/1 mcg/mL susceptible, 4/2 mcg/mL intermediate, NLT 8/4 mcg/mL resistant; Anaerobic bacteria: NMT 4/2 mcg/mL susceptible, 8/4 mcg/mL intermediate, NLT 16/8 mcg/mL resistant.

No NCCLS breakpoint is stipulated for *Vibrio cholerae*, however, ampicillin susceptibility (NMT 8 mcg/mL susceptible, 16 mcg/mL intermediate, NLT 32 mcg/mL resistant) is representative for amoxicillin/clavulanic acid.

For *Enterococcus* spp. penicillin and ampicillin susceptibility (NMT 8 mcg/mL susceptible, NLT 16 mcg/mL resistant) may be used to predict the susceptibility to amoxicillin/clavulanic acid.

Clinical trials

No data available.

5.2. PHARMACOKINETIC PROPERTIES

Absorption

Amoxicillin and clavulanic acid are fully dissociated in aqueous solution at physiological pH. Both components are rapidly and well absorbed by the oral route of administration. Absorption of amoxicillin/clavulanic acid is optimised when taken at the start of a meal.

Two separate studies measured the mean pharmacokinetic parameters in fasting healthy volunteers for amoxicillin/clavulanic acid 625 mg tablets equivalent to amoxicillin 500 mg and clavulanic acid 125 mg against the two components given separately. Following a single oral dose equivalent to amoxicillin 500 mg: amoxicillin/clavulanic acid 625 mg gave a plasma concentration-time profile characterised by a peak corresponding to C_{max} of 6.5 mg/L at t_{max} of 1.5 hours with AUC of 23.2 mg.h/L and elimination half life of 1.3 hours; amoxicillin 500 mg alone gave a plasma concentration-time profile characterised by a peak corresponding to C_{max} of 6.5 mg/L at t_{max} of 1.3 hours with AUC of 19.5 mg.h/L and elimination half life of 1.1 hours. Similarly, following a single oral dose equivalent to clavulanic acid 125 mg: amoxicillin/clavulanic acid 625 mg gave a plasma concentration-time profile characterised by a peak corresponding to C_{max} of 2.8 mg/L at t_{max} of 1.3 hours with AUC of 7.3 mg.h/L and elimination half life of 0.8 hours; clavulanic acid 125 mg alone gave a plasma concentration-time profile characterised by a peak corresponding to C_{max} of 3.4 mg/L at t_{max} of 0.9 hours with AUC of 7.8 mg.h/L and elimination half life of 0.7 hours. The studies suggest that amoxicillin serum concentrations achieved with amoxicillin/clavulanic acid are similar to those produced by the oral administration of equivalent doses of amoxicillin alone.

Distribution

Intravenous administration of the prescribed dose of amoxicillin/clavulanic acid provides therapeutic levels of both constituents in the tissues and interstitial fluids including gall bladder, skin, abdominal, adipose and muscle tissues, synovial and peritoneal fluids, bile and pus. Neither amoxicillin nor clavulanic acid is highly protein bound; studies show that about 13% to 25% of total plasma drug content of each compound is bound to protein. From animal studies, there is no evidence to suggest that either compound accumulates in any organ.

Amoxicillin, like most penicillins, can be detected in breast milk. Trace quantities of clavulanate can also be detected in breast milk. With the exception of the risk of sensitisation associated with this excretion, there are no known detrimental effects for the breastfed infant.

Reproduction studies in animals have shown that both amoxicillin and clavulanic acid penetrate the placental barrier. However, no evidence of impaired fertility or harm to the foetus was detected.

Metabolism

Amoxicillin is partly metabolised with between 10 to 25% of the initial dose found in the urine as the inactive penicilloic acid. Clavulanic acid is extensively metabolised. The inactive metabolites 2,5-dihydro-4-(2-hydroxyethyl)-5-oxo-1H-pyrrole-3-carboxylic acid and 1-amino-4-hydroxy-butan-2-one are eliminated by urinary and biliary excretion while the terminal metabolite, carbon dioxide, is eliminated in expired air and water.

Excretion

As with other penicillins, the major route of elimination for amoxicillin is via the kidney, whereas for clavulanate it is by both renal and non-renal mechanisms. Approximately 60 to 70% of the amoxicillin content and approximately 40 to 65% of the clavulanic acid content are excreted unchanged in urine during the first 6 hours after administration of a single 500/125 mg tablet.

5.3. PRECLINICAL SAFETY DATA

Genotoxicity

No data available.

Carcinogenicity

No data available.

6. PHARMACEUTICAL PARTICULARS

6.1. LIST OF EXCIPIENTS

Curam tablet:

Microcrystalline cellulose, croscarmellose sodium, talc, povidone, magnesium stearate, titanium dioxide, hypromellose, ethylcellulose, sodium lauryl sulfate, cetyl alcohol, triethyl citrate.

Curam powder for oral suspension:

Colloidal silicon dioxide, guar gum, aspartame, talc, trisodium citrate, citric acid, orange flavour, lemon flavour, peach-apricot flavour.

These medicines do not contain lactose or gluten.

6.2. INCOMPATIBILITIES

None known.

6.3. SHELF LIFE

Unopened container:

Curam tablets: 36 months.

Curam powder for oral suspension: 36 months.

After container first opened:

Not applicable.

After dilution or reconstitution:

Curam tablets: not applicable.

Curam powder for oral suspension: 7 days when stored at 2 to 8°C (refrigerate, do not freeze).

6.4. SPECIAL PRECAUTIONS FOR STORAGE

Store below 25°C. Protect from moisture.

6.5. NATURE AND CONTENTS OF CONTAINER

Curam tablet:

Blisters of 15, 21 and 100 tablets.

Curam Duo 500/125 tablet:

Blisters of 10, 15, 21, 50, 80 and 100 tablets.

Curam powder for oral suspension:

Bottles of 60 and 100 mL with a 5 mL dosing syringe.

All presentations, strengths or pack sizes may not be currently marketed.

6.6. SPECIAL PRECAUTIONS FOR DISPOSAL

Any unused medicine or waste material should be disposed of in accordance with local requirements.

Curam powder for oral suspension reconstitution instructions

Curam powder for oral suspension 125 mg/5 mL: add water 95 mL to make up 100 mL. Curam powder for oral suspension 250 mg/5 mL: add water 90 mL to make up 100 mL.

Close and shake well at once. Store the prepared suspension under refrigeration (2 to 8°C) and use within 7 days of preparation. Shake well before use.

7. MEDICINE SCHEDULE

Prescription Only Medicine

8. SPONSOR

Sandoz New Zealand Limited
12 Madden Street
Auckland 1010
New Zealand

Telephone: 0800 726 369

9. DATE OF FIRST APPROVAL

21 August 2016

10. DATE OF REVISION OF THE TEXT

27 June 2024

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
4.8	New undesirable effects updated