New Zealand Data Sheet

1. PRODUCT NAME

SYNERMOX* 600 mg powder for injection
SYNERMOX* 1200 mg powder for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

SYNERMOX 600 mg: each vial contains 100 mg clavulanic acid as potassium clavulanate and 500 mg amoxicillin as amoxicillin sodium. The powder is for reconstitution as an intravenous injection or infusion.

SYNERMOX 1200 mg: each vial contains 200 mg clavulanic acid as potassium clavulanate and 1000 mg amoxicillin as amoxicillin sodium. The powder is for reconstitution as an intravenous injection or infusion.

3. PHARMACEUTICAL FORM

SYNERMOX 600 mg and 1200 mg are sterile white to off-white powders for injection, contained in clear glass vials.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

SYNERMOX should be used in accordance with local official antibiotic prescribing guidelines and local susceptibility data.

SYNERMOX is indicated for the short team treatment of common bacterial infections such as:

- Upper Respiratory Tract Infections (including ENT) e.g. Tonsillitis, sinusitis, otitis media.
- Lower Respiratory Tract Infection 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, post-surgical infections.

SYNERMOX is indicated for 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 SYNERMOX treatment due to its amoxicillin content. Mixed infections caused by amoxicillin susceptible organisms in conjunction with SYNERMOX-susceptible beta-lactamase-producing organisms may, therefore, be treated by SYNERMOX.

4.2. Dose and method of administration

Dose

Adults and Children 40 kg and over:

Usually, 1200 mg 8 hourly. In more serious infections, increase frequency to 6 hourly intervals.

Special populations

Elderly population

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

Renal impairment

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

	Mild impairment (creatinine clearance >30 mL/min)	Moderate impairment (creatinine clearance 10 – 30 mL/min)	Severe impairment (creatinine clearance < 10 mL/min)
Intravenous	No change in dosage	1200 mg IV stat followed by 600 mg IV 12 hourly	1200 mg IV stat followed by 600 mg IV 24 hourly. Dialysis decreases serum concentrations of SYNERMOX. An additional 600 mg IV dose may need to be supplemented at the end of dialysis.

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

	Mild impairment (creatine clearance > 30 mL/min)	Moderate impairment (creatinine clearance 10 – 30 mL/min)	Severe impairment (creatinine clearance < 10 mL/min)
Intravenous	No change in dosage	30 mg/kg 12 hourly	30 mg/kg every 24 hours Dialysis decreases serum concentrations of SYNERMOX. An additional 15 mg/kg may need to be supplemented at the end of dialysis, then 30 mg/kg/day

Hepatic impairment

Dose 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.

Dosage for surgical prophylaxis

Surgical prophylaxis with SYNERMOX 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 1200 mg SYNERMOX intravenous given at induction of anaesthesia. Longer operations require subsequent doses of 1200 mg SYNERMOX intravenous (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 SYNERMOX or oral amoxicillin/clavulanic acid therapy post-operatively.

Paediatric population

Children 0 – 3 months: 30 mg/kg* SYNERMOX every 12 hours in infants < 4 kg and 30 mg/kg* SYNERMOX every 8 hours in infants > 4 kg.

Children 3 months – 12 years: Usually 30 mg/kg* SYNERMOX 8 hourly. In more serious infections, increase frequency to 6 hourly intervals.

* Each 30 mg SYNERMOX provides 5 mg clavulanic acid with 25 mg amoxicillin.

Method of Administration

The combination of amoxicillin/clavulanic acid is to be administered intravenously. It is not suitable for intramuscular injection.

To prepare, dissolve SYNERMOX 600 mg injection in 10 mL of Water for Injection. The final volume will be 10.5 mL. Dissolve SYNERMOX 1200 mg injection in 20 mL of Water for Injection. The final volume will be 20.9 mL.

Reconstituted solutions of SYNERMOX injection are usually a pale straw colour although a transient pink colour may develop and disappear during reconstitution.

After reconstitution, the injection solution should be given by slow intravenous injection over a period of three minutes. The injections should be used within 20 minutes of reconstitution.

If used as an infusion, administer over a period of 30 – 40 minutes within four hours after reconstitution.

4.3. Contraindications

SYNERMOX is contraindicated in individuals:

- with a hypersensitivity to beta-lactam antibiotics (e.g. penicillins and cephalosporins).
- with a previous history of SYNERMOX or amoxicillin-associated jaundice/hepatic dysfunction.
- With a history of acute generalised exanthemous pustulosis (AGEP)

4.4. Special warnings and precautions for use

In general, amoxicillin-clavulanate 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.

Hypersensitivity

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

Anaphylaxis

Serious and occasionally fatal hypersensitivity (anaphylactic) reactions have been reported in patients on penicillin therapy. These reactions are more likely to occur in individuals with a history of penicillin hypersensitivity and/or a history of sensitivity to multiple 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 (see section 4.8 Undesirable effects). Before initiating therapy with any penicillin, careful enquiry should be made concerning previous hypersensitivity reactions to penicillins, cephalosporins, or other allergens. If an allergic reaction occurs, SYNERMOX therapy should be discontinued and appropriate alternative therapy instituted.

Serious anaphylactoid reactions require immediate treatment with adrenaline. Oxygen, intravenous steroids and airway management, including intubation may also be required.

Drug-induced enterocolitis syndrome (DIES)

Drug-induced enterocolitis syndrome (DIES) has been reported mainly in children receiving amoxicillin (see section 4.8). DIES is an allergic reaction with the leading symptom of protracted vomiting (1-4 hours after taking the medicine) in the absence of allergic skin or respiratory symptoms. Further symptoms could comprise abdominal pain, diarrhoea, hypotension or leucocytosis with neutrophilia. In severe cases, drug-induced enterocolitis syndrome can progress to shock.

Infectious mononucleosis

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.

Jarisch-Herxheimer reaction

The Jarisch-Herxheimer reaction has been seen following amoxicillin treatment of Lyme disease (see section 4.8). It results directly from the bactericidal activity of amoxicillin on the causative bacteria of Lyme disease, the spirochaete Borrelia burgdorferi. Patients should be reassured that this is a common and usually self-limiting consequence of antibiotic treatment of Lyme disease.

Micro-organism Overgrowth

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

Pseudomembranous colitis

The use of SYNERMOX could lead to the development of severe colitis as a result of colonization with *C. difficile,* a toxin-producing organism. The colitis, which may or may not be accompanied by the formation of a pseudomembrane in the colon, can be fatal. If significant diarrhoea occurs (this may, however, begin up to several weeks after cessation of antibiotic therapy) SYNERMOX should be discontinued. This may be sufficient treatment in the early stages although cholestyramine orally may help by binding the toxin in the colonic lumen. In severe cases oral vancomycin has proved effective. Vancomycin is not effective if given parenterally.

Prolongation of Prothrombin time

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

Lab Tests

Massive doses of amoxicillin-clavulanate can cause hypokalaemia and sometimes hypernatremia. Use of a potassium-sparing diuretic may be helpful. In patients undergoing high-

dose treatment for more than 5 days, electrolyte balance, blood counts and renal functions should be monitored.

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

Penicillins may interfere with:

- urinary glucose test
- coomb's tests
- tests for urinary or serum proteins
- tests which use bacteria (e.g. Guthrie test)

Hepatic Impairment

SYNERMOX should be used with caution in patients with evidence of hepatic dysfunction.

Changes in liver function tests have been observed in some patients receiving SYNERMOX. The risk is highest in males and elderly patients and may be associated with prolonged treatment. These events have been very rarely reported in children. Cholestatic hepatitis, which may be severe but is usually reversible has been reported. 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. 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 of concomitant medications. Hepatic events subsequent to SYNERMOX have occurred predominantly in adults and elderly patients.

Renal Impairment

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

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

Acute Generalised Exanthemous Pustulosis (AGEP)

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

Crystalluria

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 and acute renal injury (see section 4.9).

Sodium Content

If the parenteral administration of high doses is necessary, the sodium content must be taken into account in patients on a sodium restricted diet.

Other

Fluids, electrolytes and protein replacement therapy should be provided when indicated.

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), SYNERMOX should be discontinued and/or appropriate therapy instituted.

4.5. Interaction with other medicines and other forms of interaction

Probenecid

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

Allopurinol

Concomitant use of allopurinol during treatment with amoxicillin can increase the likelihood of allergic skin reactions. There are no data on the concomitant use if amoxicillin-clavulanate and allopurinol.

Oral Contraceptives

In common with other antibiotics, amoxicillin-clavulanate may affect the gut flora, leading to lower oestrogen reabsorption and reduced efficacy of combined oral contraceptives. The efficacy of oral contraceptives may be impaired under concomitant administration of SYNERMOX, which may result in unwanted pregnancy. Women taking oral contraceptives should be aware of this and should be informed about alternative methods of contraception.

Acenocoumarol and Warfarin

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 of withdrawal of amoxicillin.

Mycophenolate mofetil

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.

Methotrexate

Penicillins reduce the excretion of methotrexate thereby increasing the risk of methotrexate toxicity.

Other

Medicines or drugs that delay peristalsis, e.g. opiates and diphenoxylate with atropine (Lomotil) may prolong and/or worsen the condition and should not be used.

4.6. Fertility, pregnancy and lactation

Pregnancy

Reproduction studies in animals (mice and rats at doses up to 10 times the human dose) with orally and parentally administered amoxicillin-clavulanate have shown no teratogenic effects. In a single study in women with preterm, premature rupture of the foetal membrane (pPROM), it was reported that prophylactic treatment with amoxicillin-clavulanate 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.

Breast-feeding

SYNERMOX 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.

Trace quantities of penicillin can be detected in breast milk with the potential for hypersensitivity reactions (e.g. drug rashes) or gastrointestinal disorders (e.g. diarrhoea or candidosis) in the breast-fed infant. Consequently, breast-feeding might have to be discontinued.

Fertility

No fertility data available.

4.7. Effects on ability to drive and use machines

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

During treatment with SYNERMOX, undesirable effects may occur (e.g. allergic reactions, dizziness, convulsions) which may influence the ability to drive and use machines. Patients should be cautious when driving or operating machinery.

4.8. Undesirable effects

Tabulated summary of adverse reactions

Table 1: Summary of the safety profile

Frequencies are defined as very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000), not known (cannot be estimated from the available data).

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.
Cardiac disorders	
Very rare	Kounis syndrome
Gastrointestinal disorders following intravenous administration	
Very Common	Diarrhoea
Uncommon	Nausea, vomiting, indigestion
Very rare	Antibiotic-associated colitis (including pseudomembranous colitis and haemorrhagic colitis) (see section 4.4) are less likely to occur after parenteral administration. Black hairy tongue. Superficial tooth discolouration^
Not known	Drug-induced enterocolitis syndrome (DIES)
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 cephalosporins (see section 4.4).
Immune system disorders	
Very rare	Angioneurotic oedema, anaphylaxis, serum sickness-like syndrome, hypersensitivity vasculitis.
Not known	Jarish-Herxheimer reaction
Infections and Infestations	
Common	Mucocutaneous candidiasis
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.
Renal and Urinary disorders	
Very rare	Interstitial nephritis, crystalluria that may lead to acute renal injury (see sections 4.4 and 4.9)
Skin and subcutaneous tissue disorders	
Uncommon	Skin rash, pruritus, urticaria
Rare	Erythema multiforme
Very rare	Stevens-Johnson syndrome, toxic epidermal necrolysis, bullous exfoliative-dermatitis, acute generalised exanthemous pustulosis

	(AGEP), and drug reaction with eosinophilia and systematic symptoms (DRESS). Symmetrical drug-related intertriginous and flexural exanthema (SDRIFE) (baboon syndrome) have been reported in patients taking beta-lactam antibiotics. If any hypersensitivity dermatitis reaction occurs, treatment should be discontinued. Linear IgA disease
Vascular disorders	
Rare	Thrombophlebitis at the site of injection.

^ Superficial tooth discolouration has been reported in children. Good oral hygiene may help to prevent tooth discolouration as it can be removed by brushing.

Reporting of suspected adverse reactions

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 reactions https://pophealth.my.site.com/carmreportnz/s/

4.9. Overdose

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).

Amoxicillin has been reported to precipitate in bladder catheters after intravenous administration of large doses. A regular check of patency should be maintained.

Amoxicillin-clavulanate can be removed from the circulation by haemodialysis.

A prospective study of 51 paediatric patients at a poison control centre suggested that overdoses of less than 250 mg/kg of amoxicillin are not associated with significant clinical symptoms and do not require gastric emptying.

Drug abuse and dependence
Drug dependency, addiction and recreational abuse have not been reported as a problem with this compound.

For risk assessment and 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: Amoxicillin and enzyme inhibitor, ATC code: JO1CR02.

Mechanism of action

SYNERMOX (beta-lactam antibacterial penicillin co-formulated with a beta-lactamase inhibitor) is an antibiotic agent with a notably broad spectrum of activity against the commonly occurring bacterial pathogens in general practice and hospital. The beta-lactamase inhibitory action of clavulanate extends the spectrum of amoxicillin to embrace a wider range of organisms, including many resistant to other beta-lactam antibiotics.

Amoxicillin is a semisynthetic with a broad spectrum of antibacterial activity against many gram-positive and gram-negative micro-organisms. Amoxicillin is, however, susceptible to degradation by beta-lactamases and therefore the spectrum of activity of amoxicillin alone does not include organisms which produce these enzymes.

Clavulanic acid is a beta-lactam, structurally related to the penicillins, which possesses the ability to inactivate a wide range of beta-lactamase enzymes commonly found in micro-organisms 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.

The presence of clavulanic acid in SYNERMOX formulations protects amoxicillin from degradation by beta-lactamase enzymes and effectively extends the antibacterial spectrum of amoxicillin to include many bacteria normally resistant to amoxicillin and other penicillins and cephalosporins. Thus, SYNERMOX possesses the distinctive properties of a broad spectrum antibiotic and a beta-lactamase inhibitor.

Pharmacodynamic effects

In the list below, organisms are categorised according to their in-vitro susceptibility to amoxicillin-clavulanate.

In vitro susceptibility of micro-organisms to amoxicillin-clavulanate Where clinical efficacy of amoxicillin-clavulanate has been demonstrated in clinical trials, this is indicated with an aterisk(*). Organisms that do not produce beta-lactamase are identified (with ᵗ). If an isolate is susceptible to amoxicillin, it can be considered susceptible to amoxicillin-clavulanate.
Commonly susceptible species
Gram-positive aerobes: *Bacillius anthracis* *Enterococcus faecalis* *Gardnerella vaginalis* *Listeria monocytogenes* *Nocardia asteroids* *Streptococcus pneumoniae** *Streptococcus pyogenes** *Streptococcus agalactiae** *Viridans group streptococcus* *Streptococcus spp.* (other β-hemolytic)

Staphylococcus aureus (methicillin susceptible) *Staphylococcus saprophyticus* (methicillin susceptible) *Coagulase negative staphylococcus* (methicillin susceptible)
Gram-negative aerobes: *Bordetella pertussis* *Brucella species* *Haemophilus influenzae** *Haemophilus parainfluenzae* *Heliobacter pylori* *Moraxella catarrhalis** *Neisseria gonorrhoeae* *Pasteurella multocida* *Vibrio chloera*
Other: *Borrelia burgdorferi* *Leptospira ictterahaemorrhagiae* *Treponema pallidum*
Gram-positive anaerobes: *Clostridium spp.* *Peptococcus niger* *Peptostreptococcus magnus* *Peptostreptococcus micros* *Peptostreptococcus spp.*
Gram-negative anaerobes: *Bacteroides fragilis* *Bacteroides spp.* *Capnocytophaga spp.* *Eikenella corrodens* *Fusobacterium nucleatum* *Fusobacterium spp.* *Porphyromonas spp.* *Prevotella spp.*
Species for which acquired resistance may be a problem
Gram-negative aerobes: *Escherichia coli** *Klebsiella oxytoca* *Klebsiella pneumoniae** *Klebsiella spp.* *Proteus mirabilis* *Proteus vulgaris* *Proteus spp.* *Salmonella spp.* *Shigella spp.*
Gram-positive aerobes: *Corynebacterium spp.* *Enterococcus faecium*
Inherently resistant organisms
Gram-negative aerobes: *Acinetobacter spp.* *Citrobacter freundii* *Enterobacter spp.*

Hafnia alvei *Legionella pneumophila* *Morganella morganii* *Providencia spp.* *Pseudomonas spp.* *Serratia spp.* *Stentotrophomas maltophilia* *Yersinia enterolitica*
Others: *Chlamydia pneumoniae* *Chlamydia psittaci* *Chlamydia spp.* *Coxiella burnetti* *Mycoplasma spp.*

5.2. Pharmacokinetic properties

Absorption

The two components of SYNERMOX, amoxicillin and clavulanic acid are fully dissociated in aqueous solution at physiological pH. The pharmacokinetic results for studies in which amoxicillin-clavulanate was administered to groups of healthy volunteers as either 500/100 (600 mg) or 1000/200 (1200 mg) given as a bolus intravenous injection are given below:

Amoxicillin Component	Mean Pharmacokinetic Parameters				
	Amoxicillin dose	Mean peak serum conc (mcg/mL)	T ½ (hours)	AUC hours (h.mg/L)	Urinary recovery 0 to 6 hours (%)
Amoxicillin-clavulanate 500/100 mg	500 mg	32.2	1.07	25.5	66.5
Amoxicillin-clavulanate 1000/200 mg	1000 mg	105.4	0.9	76.3	77.4

Clavulanic Acid Component	Mean Pharmacokinetic Parameters				
	Clavulanic Acid dose	Mean peak serum conc (mcg/mL)	T ½ (hours)	AUC hours (h.mg/L)	Urinary recovery 0 to 6 hours (%)
Amoxicillin-clavulanate 500/100 mg	100 mg	10.5	1.12	9.2	46.0
Amoxicillin-clavulanate 1000/200 mg	200 mg	28.5	0.9	27.9	63.8

Distribution

Following intravenous administration therapeutic concentrations of both amoxicillin and clavulanic acid may be detected in the tissues and interstitial fluid. Therapeutic concentrations of both medicines have been found in gall bladder, abdominal tissue, skin, fat, and muscle tissues; fluids found to have therapeutic levels include synovial and peritoneal fluids, bile and pus.

Neither amoxicillin nor clavulanic acid is highly protein bound, studies show that about 13 – 25% of total plasma drug content of each compound is bound to protein. From animal studies there is no evidence to suggest that either component 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.

Biotransformation

Amoxicillin is also partly excreted in the urine as the inactive penicilloic acid in quantities equivalent to 10-25% of the initial dose. Clavulanic acid is extensively metabolised in man to 2,5-dihydro-4-(2-hydroxyethyl)-5-oxo-1H-pyrole-3-carboxylic acid and 1-amino-4-hydroxy-butan-2-one and eliminated in urine and faeces as carbon dioxide in expired air.

Elimination

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 6-70% of the amoxicillin and approximately 40-65% of the clavulanic acid are excreted unchanged in the urine during the first 6 hours after administration of a single 500/100 mg or a single 1000/200 mg bolus intravenous injection.

Concomitant use of probenecid delays amoxicillin excretion but does not delay renal excretion of clavulanic acid (see section 4.5).

5.3. Preclinical safety data

No further information of relevance is available.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

SYNERMOX powder for injection contains no excipients.

6.2. Incompatibilities

SYNERMOX injection should not be mixed with blood products, other proteinaceous fluids such as protein hydrolysates or with intravenous lipid emulsions. If prescribed concomitantly with an aminoglycoside, the antibiotics should not be mixed in the syringe, intravenous fluid container or giving set because of a loss of activity of the aminoglycoside under these conditions.

SYNERMOX solutions should not be mixed with infusions containing glucose, dextran or bicarbonate.

6.3. Shelf life

24 months

6.4. Special precautions for storage

Store below 25°C
See section 6.6 for information on storage of reconstituted solutions.

6.5. Nature and contents of container

SYNERMOX 500 mg/100 mg Powder for Injection is available in packs of 5 and 10 vials.
SYNERMOX 1000 mg/200 mg Powder for Injection is available in packs of 5 and 10 vials.
Not all pack sizes may be marketed

6.6. Special precautions for disposal and other handling

Preparation of intravenous injections and stability:

Vial	Diluent (mL)	Volume Obtained (mL)
600 mg	10	10.5
1200 mg	20	20.9

Water for Injections is the normal diluent. A transient pink colouration may or may not develop during reconstitution. Reconstituted solutions are usually a pale straw colour.

SYNERMOX should be administered within 20 minutes of reconstitution.

Preparation of intravenous infusions and stability:
Add without delay the reconstituted solution of 600 mg (as prepared above – this is a minimum volume) to 50 mL of infusion fluid or of 1200 mg to 100 mL infusion fluid (e.g. using a minibag or inline burette).

Prepared SYNERMOX injections are compatible with the following solvent solutions: physiological solution, M/6 sodium lactate solution for infusion, Ringer Lactate Solution, Hartmann's Solution. The stability period of the reconstituted solutions in the different infusion fluids, at 5° and 25°C, is shown in the following table:

Infusion Fluid	Stability (hours)	
	5°C	25°C
Water for Injections	8	4
Sodium chloride intravenous infusion 0.9%	8	4
Sodium lactate intravenous infusion (M/6)	-	4
Ringers' solution	-	3
Hartmann's solution; Ringer-Lactate solution	-	3
Potassium chloride and Sodium chloride intravenous solution	-	3

Once reconstituted, the solution is to be used once only, discarding any remaining solution.

For storage at 5°C, the reconstituted solutions of 600 mg and 1200 mg may be added to pre-refrigerated infusion bags which may be stored for up to 8 hours. Thereafter, the infusion should be administered immediately after reaching room temperature.

7. MEDICINE SCHEDULE

Prescription Medicine

8. SPONSOR

Douglas Pharmaceuticals Ltd
P O Box 45 027
Auckland 0651
New Zealand
Phone: (09) 835 0660

9. DATE OF FIRST APPROVAL

14 June 2007

10. DATE OF REVISION OF THE TEXT

29 September 2025

* SYNERMOX is a registered trademark in New Zealand and other countries.

Summary table of changes

Section Changed	Summary of new information
4.4	Added information on Kounis syndrome; Drug-induced enterocolitis syndrome (DIES); and Jarisch-Herxheimer reaction. Revised crystalluria information to include possibility of acute renal injury.
4.8	Reformatted table to improve readability. Added Kounis syndrome - Very rare under Cardiac disorders; Black hairy tongue - Very rare, Superficial tooth discolouration (with footnote) - Very rare and Drug-induced enterocolitis syndrome (DIES) - Not known under Gastrointestinal disorders; Jarish-Herxheimer reaction - Not known under Immune system disorders.
4.9	Replaced: “For advice” with: “For risk assessment and advice”.