New Zealand Data Sheet

1. PRODUCT NAME

Synermox 500 mg/125 mg Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Synermox 500 mg/125 mg Tablets:
Each film-coated tablet contains amoxicillin trihydrate equivalent to 500 mg amoxicillin, with potassium clavulanate equivalent to 125 mg clavulanic acid.

Excipient(s) with known effect

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Synermox 500 mg/125 mg Tablets:
White to off-white, oval shaped film-coated tablets, debossed with "RX713" on one side and plain on the other.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Synermox is indicated in adults and children (see sections 4.2, 4.4 and 5.1) for short term 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 those involving:

- Gastro-intestinal tract
- Pelvic cavity

- Head and neck
- Cardiac
- Renal
- Joint replacement
- 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

Duration of treatment should not exceed 14 days without review.

Adults and Children 40 kg and over

One 500 mg/125 mg 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 500 mg/125 mg tablets three times daily.

Special populations

Elderly population

No adjustment needed; dose as for adults. If there is evidence of renal impairment, dose should be adjusted as per Renal impairment section below.

Renal impairment

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

Mild impairment (Creatinine clearance > 30 mL/min)	No dosage adjustments needed
Moderate impairment (Creatinine clearance 10-30 mL/min)	One 500 mg/125 mg tablet taken 12 hourly
Severe impairment (Creatinine clearance < 10 mL/min)	One 500 mg/125 mg tablet once daily. Dialysis decreases serum concentrations of Synermox. An additional dose may need to be supplemented at the end of dialysis.

Hepatic impairment

Dose with caution; monitor hepatic function at regular intervals. There is as yet insufficient data on which to base a dosage recommendation (see sections 4.3 and 4.4).

Paediatric population

Children under 40 kg: Refer to dosing recommendations for a Powder for Suspension presentation.

Method of Administration

Synermox tablets are for oral use.
To minimise any possible gastrointestinal intolerance, administer at the start of a meal, when the absorption of Synermox is optimal.

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

4.3. Contraindications

Synermox is contraindicated in patients who have had previous experience of a major allergy or anaphylaxis to a cephalosporin or penicillin.

Hypersensitivity to any of the excipients.
History of Synermox or amoxicillin-associated jaundice/hepatic dysfunction (see section 4.8).

4.4. Special warnings and precautions for use

Before initiating therapy with Synermox, careful enquiry should be made concerning previous hypersensitivity reactions to penicillins, cephalosporins, or other allergens. Synermox should be given with caution to patients who have experienced symptoms of allergy associated with a cephalosporin or penicillin.

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. There have been reports of individuals with a history of penicillin hyper-sensitivity who have experienced severe reactions when treated with cephalosporins. If an allergic reaction occurs, Synermox 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.

Massive doses of amoxicillin can cause hypokalaemia and sometimes hypernatraemia. 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 use of Synermox could lead to the development of severe colitis as a result of colonization with *C. difficile*, a toxin-producing organism (see section 4.8). 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. Drugs that delay peristalsis, e.g. opiates and diphenoxylate with atropine (Lomotil) may prolong and/or worsen the condition and should not be used. Fluids, electrolytes and protein replacement therapy should be provided when indicated.

Synermox 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.

In general Synermox 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.

Prolongation of prothrombin time has been reported rarely in patients receiving Synermox. Appropriate monitoring should be undertaken when anticoagulants are prescribed concomitantly (see section 4.5 and 4.8).

Synermox should be used with caution in patients with evidence of hepatic dysfunction (see section 4.2).

Dosage should be adjusted in patients with renal impairment (see section 4.2).
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 (see section 4.9).

As with any potent medicine, periodic assessment of organ system functions, including renal, hepatic and haematopoietic function should be made during prolonged therapy or in patients with evidence of hepatic dysfunction.

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 medicine should be discontinued and/or appropriate therapy instituted.

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. 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 or taking concomitant medications known to have the potential for hepatic effects. Hepatic events subsequent to

Synermox have occurred predominantly in adults and elderly patients. These have been very rarely reported in children.

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 (see section 4.8). This reaction requires Synermox discontinuation and is a contraindication to subsequent administration of amoxicillin.

4.5. Interaction with other medicines and other forms of interaction

Methotrexate

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

Tests interference

- Urinary Glucose Test: Oral administration of Synermox will result in high urine concentrations of amoxicillin. Since high urine concentration 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.
- Coomb's Tests: 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
- Tests for urinary or serum proteins
- Tests which use bacteria e.g. Guthrie test

Oral Contraceptive

Following administration of ampicillin to pregnant women a transient decrease in plasma concentration of total conjugated estriol, estradiol has been noted. This effect may also occur with amoxicillin and therefore Synermox. In common with other broad spectrum antibiotics, Synermox may reduce the efficacy of oral contraceptives and patients should be warned accordingly.

Probenecid

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

Allopurinol

The concurrent administration of allopurinol and ampicillin increases substantially the incidence of rashes in patients receiving both medicines as compared to patients receiving ampicillin alone. It is not known whether this potentiation of ampicillin rashes is due to allopurinol or the

hyperuricaemia present in these patients. There are no data with Synermox and allopurinol administered concurrently.

Alcohol

No information is available about the concurrent use of Synermox and alcohol. However, the ingestion of alcohol whilst being treated with the beta-lactam antibiotics latamoxef, cefoperazone and cephamandole 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 Synermox.

Oral Anticoagulant

In the literature there are rare cases of increased international normalised ratio (INR) 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.

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.

4.6. Fertility, pregnancy and lactation

Pregnancy

Reproduction and teratology studies performed so far in animals (mice and rats at doses up to 10 times the human dose) with orally and parentally administered amoxicillin trihydrate/potassium 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 trihydrate/potassium clavulanate may be associated with an increased risk of necrotising enterocolitis in neonates. have revealed no evidence of impaired fertility or harm to the foetus due to Synermox. There is limited experience of the use of Synermox in human pregnancy. As with all medicines, use should be avoided in pregnancy, especially during the first trimester, unless considered essential by the physician.

Breast-feeding

Amoxicillin is excreted in breast milk and trace quantities of clavulanate can also be detected in breast milk. These trace quantities have the potential for hypersensitivity reactions (e.g. drug rashes) or gastrointestinal disorders (e.g. diarrhoea or candidosis) in the breast-fed infant. Consequently, breastfeeding might have to be discontinued. The possibility of sensitisation should be taken into account.

Therefore, Synermox should only be used during breast-feeding after benefit/risk assessment by the physician in charge.

Fertility

There are no data on the effects of amoxicillin trihydrate/potassium clavulanate on fertility in humans.

4.7. Effects on ability to drive and use machines

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

Data from large clinical trials was used to determine the frequency of very common to rare undesirable effects. The frequencies assigned to all other undesirable effects (i.e., those occurring at <1/10,000) were mainly determined using post-marketing data and refer to a reporting rate rather than a true frequency.

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	
Mucocutaneous candidiasis	Common
Blood and lymphatic system disorders	
Reversible leucopenia (including neutropenia)	Rare
Thrombocytopenia	Rare
Reversible agranulocytosis	Very rare
Haemolytic anaemia	Very rare
Prolongation of bleeding time and prothrombin time [1]	Very rare
Immune system disorders	
Angioneurotic oedema	Very rare
Anaphylaxis	Very rare
Serum sickness-like syndrome	Very rare
Hypersensitivity vasculitis	Very rare
Nervous system disorders	
Dizziness	Uncommon
Headache	Uncommon
Aseptic meningitis	Very rare
Reversible hyperactivity and convulsions [2]	Very rare
Gastrointestinal disorders following oral administration to adults [3]	
Diarrhoea	Very common
Nausea	Common
Vomiting	Common
Indigestion	Uncommon
Antibiotic-associated colitis [4]	Very Rare

Black hairy tongue	Very Rare
Superficial tooth discolouration [5]	Very Rare
Gastrointestinal disorders following oral administration to paediatrics [3]	
Diarrhoea	Common
Nausea	Common
Vomiting	Common
Indigestion	Uncommon
Antibiotic-associated colitis [4]	Very Rare
Black hairy tongue	Very Rare
Superficial tooth discolouration [5]	Very Rare
Hepatobiliary disorders	
A moderate rise in AST and/or ALT [6]	Uncommon
Hepatitis [7]	Very Rare
Cholestatic jaundice [7]	Very Rare
Skin and subcutaneous tissue disorders	
Skin rash	Uncommon
Pruritus	Uncommon
Urticaria	Uncommon
Erythema multiforme	Rare
Stevens-Johnson syndrome	Very rare
Toxic epidermal necrolysis	Very rare
Bullous exfoliative-dermatitis	Very rare
Acute generalised exanthemous pustulosis (AGEP)	Very rare
Drug reaction with eosinophilia and systemic symptoms (DRESS)	Very rare
Renal and urinary disorders	
Interstitial nephritis	Very rare
Crystalluria [8]	Very rare

[1, 2] see section 4.4

[2] convulsions may occur in patients with impaired renal function or in those receiving high doses

[3] in all populations nausea is more often associated with higher oral dosages. If gastrointestinal reactions are evident, they may be reduced by taking Synermox at the start of a meal (see section 4.4).

[4] including pseudomembranous colitis and haemorrhagic colitis [of note, these undesirable effects are less likely to occur after parenteral administration in comparison to oral administration]

[5] 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.

[6] 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.

[7] these events have been noted with other penicillins and cephalosporins (see section 4.4).

[8] see section 4.9

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://nzphvc.otago.ac.nz/reporting/

4.9. Overdose

Symptoms

Gastrointestinal symptoms and disturbance of the fluid and electrolyte balances may be evident. Amoxicillin crystalluria, in some cases leading to renal failure, has been observed (see section 4.4). When present at high concentrations in urine at room temperature, amoxicillin may precipitate in bladder catheters. A regular check of potency should be maintained.

Treatment

Gastrointestinal symptoms may be treated symptomatically, with attention to the water/electrolyte balance.

Synermox can be removed from the circulation by haemodialysis.
A prospective study of 51 paediatric patients at a poison control centre suggested that overdosages of less than 250 mg/kg of amoxicillin are not associated with significant clinical symptoms and do not require gastric emptying.

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

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: Combinations of penicillins, incl. beta-lactamase inhibitors; amoxicillin and enzyme inhibitor; ATC code: J01CR02

Mechanism of action

Amoxicillin is a semi synthetic antibiotic with a broad spectrum of antibacterial activity against many gram-positive and gram-negative micro-organisms. It inhibits one or more enzymes (often referred to as penicillin-binding proteins, PBPs) in the biosynthetic pathway of bacterial peptidoglycan, which is an integral structural component of the bacterial cell wall. Inhibition of peptidoglycan synthesis leads to weakening of the cell wall, which is usually followed by cell lysis and death.
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.

Synermox is bactericidal to a wide range of organisms including:

Gram-positive aerobes	
*Bacillus anthracis**	Coagulase negative *staphylococci** (including *Staphylococcus epidermidis**)
Corynebacterium species	*Streptococcus agalactiae*
*Enterococcus faecalis**	*Streptococcus pneumoniae*
*Enterococcus faecium**	*Streptococcus pyogenes*
Listeria monocytogenes	*Streptococcus species*
Nocardia asteroides	*Streptococcus viridans*
*Staphylococcus aureus**	
Gram-positive anaerobes	
Clostridium species	*Peptostreptococcus* species
Peptococcus species	
Gram-negative aerobes	
Bordetella pertussis	*Neisseria gonorrhoeae**
Brucella species	*Neisseria meningitidis**
*Escherichia coli**	*Pasteurella multocida*
Gardnerella vaginalis	*Proteus mirabilis**
*Haemophilus influenzae**	*Proteus vulgaris**
Helicobacter pylori	*Salmonella* species*
Klebsiella species*	*Shigella* species*
Legionella species	*Vibrio cholerae*
*Moraxella catarrhalis** (*Branhamella catarrhalis*)	*Yersinia enterocolitica**
Gram-negative anaerobes	
*Bacteroide*s species* (including *Bacteroides fragilis*)	*Fusobacterium* species*
Others	
Borrelia burgdorferi	Leptospira icterohaemorrhagiae
Chlamydiae	Treponema pallidum

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

5.2. Pharmacokinetic properties

Absorption

The two components of Synermox, 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 orally administered Synermox is optimised when taken at the start of a meal.

Amoxicillin serum concentrations achieved with Synermox are similar to those produced by the oral administration of equivalent doses of amoxicillin alone. Doubling the dosage of Synermox approximately doubles the serum levels achieved.

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 (see section 4.6).

Reproduction studies in animals have shown that both amoxicillin and clavulanic acid penetrate the placental barrier (see section 4.6).

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-pyrrole-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 60-70% of the amoxicillin and approximately 40-65% of the clavulanic acid are excreted unchanged in urine

during the first 6 hours after administration of a single 500/125 tablet or 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).

Special populations

Renal impairment

In patients with moderate or severe renal impairment, Synermox dosage should be adjusted as recommended in section 4.2.

Hepatic impairment

Synermox should be used with care in patients with severe hepatic dysfunction. Synermox dosage should be adjusted as recommended in section 4.2.

5.3. Preclinical safety data

Non-clinical data reveal no special hazard for humans based on studies of safety pharmacology, genotoxicity and toxicity to reproduction. Repeat dose toxicity studies performed in dogs with amoxicillin/clavulanic acid demonstrate gastric irritancy and vomiting, and discoloured tongue. Carcinogenicity studies have not been conducted with amoxicillin/clavulanic acid or its component.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Synermox 500 mg/125 mg tablets contain: microcrystalline cellulose, colloidal anhydrous silica, povidone K30, sodium starch glycolate, Eudragit E100, magnesium stearate, macrogol 400 Opadry 03B58965 white (hypromellose, titanium dioxide, macrogol 400, talc).

6.2. Incompatibilities

Not applicable.

6.3. Shelf life

24 months from date of manufacture.

6.4. Special precautions for storage

Store at or below 25°C.

6.5. Nature and contents of container

HDPE bottles containing 30 and 100 tablets.
Not all pack sizes may be marketed.

6.6. Special precautions for disposal and other handling

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

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

27 May 1999

10. DATE OF REVISION OF THE TEXT

7 February 2020

Summary table of changes

Section Changed	Summary of new information
4.2	Dosing information revised
4.5	Interaction with mycophenolate mofetil included
4.8	Adverse event updated
5.2	Effect of concomitant probenecid use moved under 'Elimination'