

# DATA SHEET

## SYNERMOX

Amoxicillin/clavulanic acid

### Presentation

SYNERMOX 375 mg Tablets: White oval biconvex film coated tablets engraved "R-375" on one side. Each tablet contains potassium clavulanate equivalent to 125 mg clavulanic acid with amoxicillin trihydrate equivalent to 250 mg amoxicillin.

SYNERMOX 625 mg Tablets: White oval biconvex film coated tablets engraved "R-625" on one side. Each tablet contains potassium clavulanate equivalent to 125 mg clavulanic acid with amoxicillin trihydrate equivalent to 500 mg amoxicillin.

SYNERMOX Syrup 125: Bottles of white to off-white powder for the preparation of 100 mL suspension. When reconstituted each 5 mL contains potassium clavulanate equivalent to 31.25 mg clavulanic acid and amoxicillin trihydrate equivalent to 125 mg amoxicillin. When reconstituted the suspension is white to off-white in colour with a characteristic flavour.

SYNERMOX Syrup 250: Bottles of white to off-white powder for the preparation of 100 mL suspension. When reconstituted each 5 mL contains potassium clavulanate equivalent to 62.5 mg clavulanic acid and amoxicillin trihydrate equivalent to 250 mg amoxicillin. When reconstituted the suspension is white to off-white in colour with a characteristic flavour.

SYNERMOX 600 mg Intravenous: Each vial of sterile white to off-white powder 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 1.2 g Intravenous: Each vial of sterile white to off-white powder 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.

### Uses

#### *Actions*

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.

#### **Pharmacodynamic properties**

**Microbiology:** Amoxicillin is a semi synthetic antibiotic 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. SYNERMOX is bactericidal to a wide range of organisms including:

- **Gram-positive aerobes:**

- Bacillus anthracis*\*

- Corynebacterium* species

- Enterococcus faecalis* \*

- Enterococcus faecium* \*

- Listeria monocytogenes*

- Nocardia asteroides*

- Staphylococcus aureus*\*

- Coagulase negative staphylococci*\* (including *Staphylococcus epidermidis*\*)

- Streptococcus agalactiae*

- Streptococcus pneumoniae*

- Streptococcus pyogenes*

- Streptococcus* species

- Streptococcus viridans*

- **Gram-positive anaerobes:**

- Clostridium* species

- Peptococcus* species

- Peptostreptococcus* species

- **Gram-negative aerobes:**

- Bordetella pertussis*

- Brucella* species

- Escherichia coli*\*

- Gardnerella vaginalis*

- Haemophilus influenzae*\*

- Helicobacter pylori*

- Klebsiella* species\*

- Legionella* species

- Moraxella catarrhalis*\* (*Branhamella catarrhalis*)

- Neisseria gonorrhoeae*\*

- Neisseria meningitidis* \*

- Pasteurella multocida*

- Proteus mirabilis*\*

- Proteus vulgaris*\*

- Salmonella* species\*

- Shigella* species\*

- Vibrio cholerae*

- Yersinia enterocolitica*\*

- **Gram-negative anaerobes:**

- Bacteroides* species\* (including *Bacteroides fragilis*)

- Fusobacterium* species\*

- **Others:**  
*Borrelia burgdorferi*  
*Chlamydiae*  
*Leptospira icterohaemorrhagiae*  
*Treponema pallidum*

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

### **Pharmacokinetics**

**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.

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

**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.

**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.

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-hydroxybutan-2-one and eliminated in urine and faeces as carbon dioxide in expired air.

In patients with moderate or severe renal impairment, SYNERMOX dosage should be adjusted as recommended in the Dosage and Administration section. SYNERMOX may be taken at the start of meals with no effect on its absorption. SYNERMOX should be used with care in patients with severe hepatic dysfunction.

Doubling the dosage of SYNERMOX approximately doubles the serum levels achieved.

### **Indications**

SYNERMOX is indicated for the 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 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 organism in conjunction with SYNERMOX-susceptible beta-lactamase-producing organisms may therefore be treated by SYNERMOX.

## **Dosage and Administration**

### **Synermox Syrup**

Premature: No dosage recommendations are made.

Children 3-9 months: 1.25 mL of SYNERMOX Syrup 125 three times a day.

Children 9 months - 2 years: 2.5 mL of SYNERMOX Syrup 125 three times a day.

Children 2-6 years: 5 mL of SYNERMOX Syrup 125 three times a day. In severe infections this may be increased to 10 mL SYNERMOX Syrup 125 three times a day.

Children 7-12 years: 5 mL of SYNERMOX Syrup 250 three times daily. In severe infections this may be increased to 10 mL of SYNERMOX Syrup 250 three times a day.

Each 5 mL of SYNERMOX Syrup 125 contains 6.25 mg potassium

### **Reconstitution:**

SYNERMOX Syrup 125: add 83 mL of water in two portions to the dry mixture in the bottle. Shake well after each addition. When reconstituted, each 5 mL contains amoxicillin trihydrate equivalent to 125 mg amoxicillin and potassium clavulanate equivalent to 31.25 mg clavulanic acid.

SYNERMOX Syrup 250: add 80 mL of water in two portions to the dry mixture in the bottle. Shake well after each addition. When reconstituted, each 5 mL contains amoxicillin trihydrate equivalent to 250 mg amoxicillin and potassium clavulanate equivalent to 62.5 mg clavulanic acid.

SYNERMOX Syrup 125 and SYNERMOX Syrup 250 is not primarily intended for use in adults.

When first reconstituted, allow to stand for 5 minutes to ensure full dispersion.

Once reconstituted, the suspension must be stored in a refrigerator (at 2 °C to 8 °C) and used within 7 days.

Shake well before taking each dose.

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

To minimise any possible gastrointestinal intolerance, administer at the start of a meal, when the absorption of SYNERMOX is optimal.

Duration of treatment should not exceed 14 days without review.

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

For administration to children up to 2 years old, SYNERMOX suspensions may be diluted to half-strength using water.

### ***Synermox Tablets***

Adults and Children over 12 years: The recommended dosage of SYNERMOX 375 mg tablets is three times a day. For lower respiratory tract infections, complicated urinary tract infections or severe infections at other sites, the dosage can be increased to 1 to 2 SYNERMOX 625 mg tablets three times daily.

SYNERMOX 375 mg and 625 mg tablets are not recommended for children 12 years and under.

To minimise any possible gastrointestinal intolerance, administer at the start of a meal, when the absorption of SYNERMOX is optimal.

Duration of treatment should not exceed 14 days without review.

### ***Synermox Intravenous***

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 > 4kg

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

Adults and Children 40 kg and over: Usually 1.2 g 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.

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

**Reconstitution:**

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.

**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 1.2 g SYNERMOX Intravenous given at induction of anaesthesia. Longer operations require subsequent doses of 1.2 g 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 or oral SYNERMOX therapy post-operatively.

**Dosage in 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)
Tablet	No change in dosage	One 625 mg tablet 12 hourly	One 625 mg tablet once daily. Dialysis decreases serum concentrations of SYNERMOX. An additional 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 (creatinine clearance >30 mL/min)	Moderate Impairment (creatinine clearance 10- 30 mL/min)	Severe Impairment (creatinine clearance <10 mL/min)
Oral Solution (in the majority of cases,	No change in dosage	15/3.75 mg/kg given 12 hourly (maximum 500/125 mg twice	15/3.75 mg/kg given as a single daily dose. (maximum 500/125 mg).

	Mild Impairment (creatinine clearance >30 mL/min)	Moderate Impairment (creatinine clearance 10- 30 mL/min)	Severe Impairment (creatinine clearance <10 mL/min)
parenteral therapy, where available, may be preferred).		daily).	Dialysis decreases serum concentrations of SYNERMOX. 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

**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	1.2 g IV stat followed by 600 mg IV 12 hourly	1.2 g 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 (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	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

**Dosage in 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 in 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).

## Contraindications

SYNERMOX is contraindicated in individuals with a history of hypersensitivity to beta-lactam antibiotics (e.g. penicillins and cephalosporins).

SYNERMOX is contraindicated in patients with a previous history of SYNERMOX or amoxicillin-associated jaundice/hepatic dysfunction.

## Warnings and Precautions

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

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. 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 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.

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.

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.

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

Dosage should be adjusted in patients with renal impairment (see dosage and administration). 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 Overdosage).

SYNERMOX Suspensions contain aspartame, which is a source of phenylalanine and should be used with caution in patients with phenylketonuria.

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 drug 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 concomitant medications. Hepatic events subsequent to SYNERMOX have occurred predominantly in adults and elderly patients.

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 exanthematous pustulosis (AGEP). This reaction requires Synermox 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.

Use in Pregnancy: Reproduction and teratology studies performed so far in mice and rats 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.

Use in Lactation: Amoxicillin is excreted in breast milk; there are no data on the excretion of clavulanic acid in human milk. Therefore, caution should be exercised when SYNERMOX is administered to a nursing woman.

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

## **Adverse Reactions**

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  $\geq 1/10$ , common  $\geq 1/100$  and  $<1/10$ , uncommon  $\geq 1/1000$  and  $<1/100$ , rare  $\geq 1/10,000$  and  $<1/1000$ , very rare  $<1/10,000$ .

**Infections and infestations:**

Common Mucocutaneous candidiasis

**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, serum sickness-like syndrome, hypersensitivity vasculitis

**Nervous system disorders:**

Uncommon Dizziness, headache  
Very rare Reversible hyperactivity and convulsions. Convulsions may occur in patients with impaired renal function or in those receiving high doses.

**Vascular disorders:**

Rare Thrombophlebitis at the site of injection

**Gastrointestinal disorders following intravenous administration:**

Common Diarrhoea  
Uncommon Nausea, vomiting, indigestion  
Very Rare Antibiotic-associated colitis (including pseudomembranous colitis and haemorrhagic colitis) are less likely to occur after parenteral administration.

**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). 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). 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 SYNERMOX at the start of a meal.

**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.

Hepatic events have been reported predominantly in males and elderly patients and may be associated with prolonged treatment. These events have been 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 serious underlying disease or taking concomitant medications known to have the potential for hepatic effects.

**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)

If any hypersensitivity dermatitis reaction occurs, treatment should be discontinued.

**Renal and urinary disorders:**

Very rare	Interstitial nephritis, crystalluria (see Overdosage)
-----------	---

**Interactions**

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 Clinistix, Benedict's Solution or Fehling's Solution, it is recommended that glucose tests based on enzymatic glucose oxidase reactions (such as Clinistix or Testape) be used.

Following administration of ampicillin to pregnant women a transient decrease in plasma concentration of total conjugated oestriol, oestradiol 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 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. 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.

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 cephmandole 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.

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.

## Overdosage

**Overdosage:** 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 Warnings and Precautions).

When present at high concentrations in urine at room temperature, amoxicillin may precipitate in bladder catheters. A regular check of potency should be maintained.

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

## Pharmaceutical Precautions

### Shelf life

SYNERMOX 375 mg Tablets: 18 months from date of manufacture stored at or below 25°C.

SYNERMOX 625 mg Tablets: 24 months from date of manufacture stored at or below 25°C.

SYNERMOX Syrup 125 and 250 (Dry powder): 18 months from date of manufacture stored at or below 25°C.

SYNERMOX Syrup 125 and 250 (Reconstituted): 7 days when stored at 2°C to 8°C (Refrigerate, do not freeze) and protected from light.

SYNERMOX Intravenous 600 mg and 1.2 g: 24 months from date of manufacture stored at or below 25°C.

All SYNERMOX preparations should be stored in a dry place, protected from light and moisture.

### SYNERMOX Intravenous

#### Incompatibilities

SYNERMOX Intravenous 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 loss of activity of the aminoglycoside under these conditions.

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

### Instructions for Use/Handling

Preparation of intravenous injections and stability		
Vial	Diluent (mL)	Volume Obtained (mL)
600 mg	10	10.5
1.2 g	20	20.9

Water for Injections is the normal diluent. A transient pink colouration may or may not develop during reconstitution. Reconstituted solutions are normally colourless or 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 50mL of infusion fluid or of 1.2 g to 100mL infusion fluid (e.g. using a minibag or in-line 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 infusion	-	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 1.2 g 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.

## **Medicine Classification**

Prescription Medicine.

## **Package Quantities**

SYNERMOX 375 mg Tablets:	Quantities of 30 and 100 tablets packed in HDPE bottles.
SYNERMOX 625 mg Tablets:	Quantities of 30 and 100 tablets packed in HDPE bottles.
SYNERMOX Syrup 125:	Bottles of powder for 100 mL suspension
SYNERMOX Syrup 250:	Bottles of powder for 100 mL suspension
SYNERMOX Injection 600 mg:	Packs of 10 vials

SYNERMOX Injection 1.2 g:

Packs of 10 vials

## **Further Information**

Other ingredients of the tablets are: microcrystalline cellulose, colloidal anhydrous silica, croscarmellose sodium, butylated hydroxy toluene, talc, magnesium stearate, hypromellose, titanium dioxide, macrogol 400.

Other ingredients of the syrups are: sorbitol (E420), sodium benzoate (E211), sodium citrate, aspartame (E591), butyl hydroxy toluene (E321), xanthan gum, monosodium citrate, passion fruit flavour.

The only ingredients in the injections are amoxicillin as amoxicillin sodium and clavulanic acid as potassium clavulanate.

## **Name and Address**

Douglas Pharmaceuticals Ltd  
PO Box 45-027  
Auckland 0651

Ph: (09) 835-0660  
Fax: (09) 835-0665

## **Date of Preparation**

25 October 2011