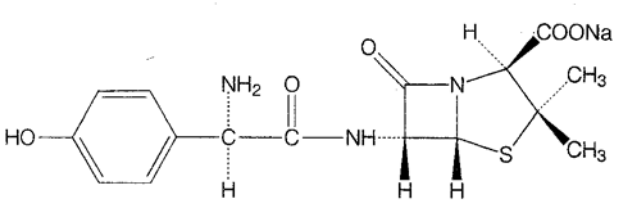
1 PRODUCT NAME

FISAMOX®

Amoxicillin (as amoxicillin sodium)

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

FISAMOX® (amoxicillin sodium) has the chemical name of d-(-)-α-amino-p-hydroxybenzylpenicillin sodium. Amoxicillin sodium has the following structure:



$C_{16}H_{18}N_3NaO_5S$

Amoxicillin sodium has a molecular weight of 387.4 and a CAS registry number, 34642-77-8.

FISAMOX® Powder for Injection is a fine white to off-white homogenous powder, soluble in water. Each one gram of monograph substance represents about 2.6 mmol of sodium. The injection is prepared by the addition of the appropriate volume of Water for Injections to give the desired concentration of amoxicillin

3 PHARMACEUTICAL FORM

Powder for Injection

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

FISAMOX® is indicated in the treatment of infections due to susceptible strains of the organisms listed below:

Gram-negative organisms	**Gram- positive organisms**
Haemophilius influenza	Streptococcus species
Escherichia coli	Streptococcus penumoniae
Proteus mirabilis	Non-penicillinase- producing staphylococci
Neisseria gonorrhoea	

FISAMOX® Powder for Injection is intended for use where the patient's condition precludes the administration of the oral form.

Therapy should be guided by bacteriological studies, including sensitivity tests, and by clinical response. However in emergency cases where the causative organism has not yet been identified, therapy with amoxicillin may be useful. Clinical judgement will decide whether combination with another antibiotic would provide a sufficiently broad spectrum of activity pending sensitivity test results.

Prophylaxis of Endocarditis

FISAMOX® may be used for the prevention of bacteraemia, associated with procedures such as dental extraction, in patients at risk of developing bacterial endocarditis.

4.2 Dose and method of administration

FISAMOX® may be given by intramuscular injection, by intravenous infusion or by **SLOW** intravenous injection.

Normal Renal Function

Upper respiratory tract infections; genito-urinary tract infection; skin and skin structure infections

Adults - 250mg every 8 hours, depending on the patient's condition.

Children (under 20kg) - 20mg/kg/day in equally divided doses every 8 hours.

In severe infections, or those caused by less susceptible organisms, 500mg every 8 hours for adults and 50mg/kg/day in equally divided doses every 8 hours for children may be needed.

Lower respiratory tract infections

Adults - 500mg every 8 hours.

Children (under 20kg) - 50mg/kg/day in equally divided doses every 12 hours.

Prophylaxis of Endocarditis- Dental Procedures: Prophylaxis for patients undergoing extraction, scaling or surgery involving gingivial tissues who have not received a penicillin in the previous month.

Note: For patients fulfilling the criteria listed below, referral to a hospital is recommended and oral antibiotics are considered inappropriate.

Patients to be given a general anaesthetic who have been given a penicillin in the previous month.

Patients to be given a general anaesthetic who have a prosthetic heart valve.

Patients who have had one or more attacks of Endocarditis.

Appropriate parenteral therapy is:

Adults -	Initially 1g of FISAMOX® with 120 mg gentamicin I.M. immediately prior to anaesthesia (if given) or 15 minutes prior to dental procedure.
Children -	(under 10) The doses should be half the adult dose; the dose of gentamicin should be 2 mg/ kg.

Consult the appropriate datasheet for gentamicin. FISAMOX® and gentamicin should not be mixed in the same syringe.

Patients having a general anaesthetic in whom oral antibiotics are considered inappropriate should be treated with a parenteral antibiotic.

Adults -	1g FISAMOX® immediately before induction with 500 mg of an oral antibiotic 6 hours later
Children -	(under 10) half the adult dose

Note: the children's dose is intended for individuals whose weight will not cause dosage to be calculated greater than the recommended for adults.

Children weighting more than 20 kg should be dosed according to the adult recommendations.

In renal impairment the excretion of the antibiotic will be delayed and, depending on the degree of impairment, it may be necessary to reduce the total daily dose.

Treatment should be continued for a minimum of 48 to 72 hours beyond the time that the patient becomes asymptomatic or evidence of bacterial eradication has been obtained.

It is recommended that there be at least 10 days treatment for any infection caused by haemolytic streptococci to prevent the occurrence of rheumatic fever or glomerulonephritis.

Amoxicillin sodium is unstable in concentrated solutions and, when prepared for injection, should be administered immediately.

Reconstitution of Vials: Solutions should be thoroughly mixed by vigorous shaking and checked for absence of particulate matter before use.

Routes of Administration

Intramuscular Injection:	Reconstitute with water for injections. Shake immediately after adding the diluent. Add 2 mL to 500 mg vials and 4 mL to 1 g vials and inject the total volume produced
Intravenous Injection:	Reconstitute with 5 mL of water for injections and shake immediately after adding the diluent.

A transient pink colouration or slight opalescence may appear during reconstitution.

If pain is experienced on intramuscular injection, a 0.5% solution of procaine hydrochloride or a 1% solution of lignocaine hydrochloride may be used in place of Water for Injections.

Directly into infusion tubing: administer by slow injection (at least over a period of 3 to 4 minutes, preferably 10 to 15 minutes) into the injection site of the giving set of infusions listed below. More rapid administration may result in convulsive seizures.

Reconstitution of Part Doses: Because the dry powder in the vial displaces a set volume once it is in solution, this must be allowed for by calculating the volume of diluent to be added to ensure the correct dose is given.

500 mg of stated activity displaces 0.4 mL of diluent

1000 mg of stated activity displaces 0.8 mL of diluent

For example, add 4.6 mL of diluent to a 500 mg vial to produce 500 mg in 5 mL or add 4.2 mL of diluent to a 1 g vial to produce 1 g in 5 mL.

When the whole vial dose is to be given either add 5 mL and withdraw and administer the entire contents, or calculate the displacement and add a lesser volume of 5 mL.

Solutions should be thoroughly mixed by vigorous shaking and checked for absence of particulate matter before use.

4.3 Contraindications

Amoxicillin is a penicillin and should not be given to patients with a history of a hypersensitivity to beta-lactam antibiotics (eg. penicillins, cephalosporins).

4.4 Special warnings and precautions for use

In patients with reduced urine output crystalluria has been observed very rarely, predominantly with parental therapy. During the 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 crysalluria.

Prolongation of prothrombin time has been reported rarely in patients receiving amoxicillin. Appropriate monitoring should be undertaken when anticoagulants are prescribed concurrently.

Serious, and occasionally fatal, hypersensitivity reactions (anaphylaxis) have been reported in patients receiving beta-lactam antibiotics eg. Penicillins. Although anaphylaxis is more frequent following parenteral therapy, it has occurred in patients on oral therapy. Before commencing therapy with any beta-lactam antibiotic, careful enquires should be made concerning previous hypersensitivity reactions to penicillins, cephalosporins or other allergens. If a hypersensitivity reaction occurs, appropriate therapy should be instituted and FISAMOX® therapy discontinued.

Before commencing therapy with any penicillin, careful enquiry should be made concerning previous hypersensitivity reactions to penicillins, cephalosporins, cephamycins or penicillamine. Caution should also be taken in patients with a history of allergy, such as eczema, asthma, hay fever, and hives. If any allergic reaction occurs, appropriate therapy should be instituted and FISAMOX® therapy discontinued.

Serious anaphylactoid reactions require emergency treatment with adrenaline. Oxygen, intravenous steroids and airway management including intubation, should also be administered as indicated.

4.5 Interaction with other medicines and other forms of interaction

FISAMOX® should not be mixed with blood products or proteinaceous fluids such as protein hydrolysates, nor with intravenous lipid emulsions.

Amoxicillin with:

PROBENECID: Probenecid decreases renal tubular secretion of penicillins when used concurrently, resulting in increased and more prolonged amoxicillin serum concentrations and prolonged elimination half-life.

CHLORAMPHENICOL, ERTHROMYCIN, SULFONAMIDES OR TETRACYCLINES: Since bacteriostatic agents may interfere with the bactericidal effect of penicillins in the treatment of meningitis or other situations where a rapid bactericidal effect is necessary, it is best to avoid concurrent therapy.

OESTROGEN CONTAINING ORAL CONTRACEPTIVES: Concurrent administration with amoxicillin may decrease the effectiveness of oral contraceptives. Patients should be advised to use an alternative or additional method of contraception.

ALLOPURINOL: There has been report of an increased incidence of skin rash on concurrent administration.

DIAGNOSTIC INTERFERENCE: FISAMOX® interferes with positive direct antiglobulin (Comb's) test. It may also interfere with urine glucose determinations, due to high concentrations of amoxicillin in the urine.

It has also be found the serum alanine aminotransferase (ALT[SGOT]) and serum asparate aminotransferase (AST[SGOT]) concentrations may be increased, following amoxicillin administration.

Total conjugated estriol, estriol-glucuronide, conjugated estrone and estradiol concentrations may be transiently decreased following FISAMOX® administration to pregnant women.

4.6 Fertility, pregnancy and lactation

Pregnancy and Breast-feeding

Safety for use in pregnancy has not been established, although amoxicillin is known to diffuse across placenta. The potential benefit should, therefore, be weighed against the potential risk before use. Very little amoxicillin appears in breast milk. Caution is, however, required as there may be a possibility of sensitisation, diarrhoea, candidiasis and skin rash in the infant.

As with any potent medicine, periodic assessment of renal, hepatic and haematopoietic function should be made during prolonged therapy. 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.

FISAMOX® should be given with caution to patients with infectious mononucleosis or lymphatic leukaemia since they are especially susceptible to ampicillin induced skin rashes.

Labour and Delivery

Studies in guinea pigs have shown that intravenous administration of ampicillin decreases uterine tone and the frequency, strength and duration of contractions. However it is not known whether the use of amoxicillin in humans during labour or delivery has any immediate or delayed adverse effects on the foetus, prolongs the duration of labour or increases the likelihood that forceps delivery or other obstetrical intervention or resuscitation of the newborn will be necessary.

Fertility
No data available

4.7 Effects on ability to drive and use machines

The effects of this medicine on a person's ability to drive and use machines were not assessed as part of its registration.

4.8 Undesirable effects

As with other penicillins, it may be expected that untoward reactions will be essentially limited to sensitivity phenomena.

They are more likely to occur in individuals who have previously demonstrated hypersensitivity to penicillins. The following adverse reactions have been reported as associated eith the use of amoxicillin.

Blood and Lymphatic System Disorders

Very rare: Reversible leucopenia (including severe neutropenia or agranulocytosis), reversible thrombocytopenia and haemolytic anaemia.

Prolongation of bleeding time and prothrombin time.

Immune System Disorders

Very rare: As with the antibiotics, severe allergic reactions, including angioneurotic oedema, anaphylaxis, serum sickness and hypersensitivity vasculitis.

If a hypersensitivity reaction is reported, the treatment must be discontinued.

Nervous System Disorders

Very rare: Hyperkinesia, dizziness and convulsions. Convulsions may occur in patients with impaired renal function or in those receiving high doses.

Infections and Infestations

Very rare: Mucocutaneous candidiasis

Gastrointestinal Disorders

Common: Diarrhoea and nausea.

Uncommon: Vomiting

Very rare: Antibiotic associated colitis (including pseudomembraneous colitis and haemorrhagic colitis). Black hairy tongue. Superficial tooth discolouration has been reported in children. Good oral hygiene may help to prevent both discolouration as it can usually be removed by brushing.

Hepato-biliary Disorders

Very rare: Hepatitis and cholestatic jaundice. A moderate rise in AST and/or ALT. The significance of a rise in AST and/or ALT is unclear.

Skin and Subcutaneous Tissue Disorder

Common: Skin rash.

Uncommon: Urticaria and pruritus.

Very rare: Skin reactions such as erythema multiforme, Stevens- Johnson syndrome, toxic epidermal necrolysis, bullous and exfoliative dermatitis and acute generalised exanthematous pustulosis (AGEP).

HYPERSENSITIVITY REACTIONS: Erythematous maculopapular rashes, pruritus and urticaria have been reported. Urticaria has occasionally been reported in association with glandular fever and some other viral diseases. Rarely, skin reactions such as erythema multiforme and Stevens-Johnson syndrome, toxic epidermal necrolysis, bullous and exfoliative dermatitis, acute generalised exanthematous pustulosis (AGEP) and drug reaction with eosinophilia and systemic symptoms (DRESS) have been reported. As with other antibiotics, severe allergic reactions including angioneurotic oedema, anaphylaxis, serum sickness, hypersensitivity

vasculitis and interstitial nephritis have been reported rarely. When such reactions occur, FISAMOX® should be discontinued.

NOTE: Urticaria, other skin rashes, and serum sickness-like reactions may be controlled with antihistamines and, if necessary, systemic corticosteroids. Anaphylaxis is the most serious reaction experienced. A macular rash, which is not believed to be a hypersensitivity reaction, occurs predominantly in patients with infectious mononucleosis 4 to 5 days after beginning therapy with amoxicillin.

Renal and Urinary Tract Disorders

Very rare: Interstitial nephritis, crystalluria

The incidence if these adverse events was derived from clinical studies involving a total of approximately 6,000 adult and paediatric patients taking amoxicillin.

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 adverse reactions https://nzphvc.otago.ac.nz/reporting/

4.9 Overdose

Problems of overdosage are unlikely to occur. If encountered, gastro-intestinal effects such as nausea, vomiting and diarrhoea may be evident and should be treated symptomatically with attention to the water/electrolyte balance. Crystalluria may also occur. As with other penicillins, amoxicillin in overdosage has the potential to cause neuromuscular hyperirritability or convulsive seizures. As the blood brain barrier becomes more permeable in meningitis, toxic symptoms may be precipitated by lower levels of amoxicillin in patients with meningitis.

Amoxicillin may be removed from the circulation by haemodialysis. General supportive measures should be instituted.

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: Anti infectives for systemic use ATC code: J01CA04

Microbiology

Amoxicillin has the same spectrum of activity as ampicillin. It is bactericidal and is active against a wider range of Gram-negative organisms than benzylpenicillin. It is less active than benzylpenicillin against Gram-positive organisms but is active *in vitro* against *Streptococcus pyogenes* and many strains of *Streptococcus pneumoniae, Streptococcus viridans*, non-penicillinase producing Staphylococci and *Enterococcus faecalis*. There are strains of *Escherichia coli* that are sensitive to amoxicillin but isolates are becoming increasingly resistant to amoxicillin *in vitro* due to the presence of penicillinase-producing strains. Many strains of *Haemophilus influenzae, Neisseria gonorrhoeae, Neisseria meningitidis, Proteus mirabilis* and Salmonellae are sensitive to amoxicillin, although the increasing incidence of beta-lactamase activity in *H. influenzae* and *E. coli* is reducing the capacity of amoxicillin to treat diseases caused by these organisms. Some of the above organisms are sensitive to amoxicillin only at concentrations achieved in the urine.

Amoxicillin is not effective against penicillinase producing bacteria, particularly resistant Staphylococci, which are now common. All strains of Pseudomonas, indole-positive Proteus, *Serratia marascens*, Enterobacter, Klebsiella and Citrobacter are resistant.

Like benzylpenicillin, amoxicillin is bactericidal to sensitive organisms during the stage of active cell division. It is believed to act through the inhibition of cell wall synthesis.

<u>Susceptibility tests</u>
Dilution or diffusion techniques – either quantitative (MIC) or breakpoint, should be used following a regularly updated, recognised and standardised method (eg. NCCLS). Standardised susceptibility test procedures require the use of laboratory control microorganisms to control the technique aspects of the laboratory procedures.

A report of "Susceptible" indicates that the pathogen is likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations achievable. A report of "Intermediate" indicates that the result should be considered equivocal, and if the microorganism is not fully susceptible to alternative, clinically feasible drugs, the test should be repeated. This category implies possible clinical applicability in body sites where the drug is physiologically concentrated or in situations where high dosage of drug can be used. This category also provides a buffer zone, which prevents small-uncontrolled technical factors from causing major discrepancies in interpretation. A report of "Resistant" indicates that the pathogen is not likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations usually achievable; other therapy should be selected.

Note: The prevalence of resistance may vary geographically for selected species and local information on resistance is desirable, particularly when treating severe infections.

5.2 Pharmacokinetic properties

Absorption and blood levels

Following intramuscular injection of 250 or 500mg of FISAMOX® Powder for Injection, peak serum levels of approximately 5.5 mg/L or 10 mg/L are achieved within 60 minutes of injection and correspond to the peak values obtained after the same dose given orally. Absorption from the intramuscular site is almost complete.

Following intravenous injection over a 3 to 4 minute period, serum levels at 1 hour were similar to those seen at 1 hour after the same dose given intramuscularly. Serum levels immediately after the IV injection were however, higher. The serum half-life measured as unchanged (active) antibiotic in the excretory phase, is approximately 1 hour in the presence of normal renal function, rising to about 7 hours with a creatinine clearance of 13 mL/minute without dialysis. The elimination half-life does not appear to change until creatinine clearance reaches approximately 30 mL/minute. In patients with a creatinine clearance of 10 mL/minute, elimination half-life has been shown to vary between 7.5 and 21 hours after a 2g intravenous dose.

Distribution

In keeping with other penicillins, penetration into the CSF is poor in the absence of inflammation. Some penetration occurs though inflamed meninges but maximum CSF levels are very much lower than peak serum levels.

Bile levels vary with the functional integrity of secretory mechanisms, being absent in the presence of biliary tract obstruction.

Protein Binding

Amoxicillin is not highly bound to human serum protein. The degree of binding, as measured by ultrafiltration or equilibrium dialysis, is 17%.

Excretion

The major route of excretion is renal (by glomerular filtration and tubular secretory mechanisms). The secretory mechanisms may be inhibited by the concurrent administration of probenecid, leading to prolonged and some elevation of serum levels.

If renal function is normal, approximately 70% of a dose administered by intramuscular or rapid intravenous injection will be excreted unchanged within six hours, and approximately 20% will be excreted as the penicilloic acid derivative in the same time. In patients with renal failure, renal excretion falls in relation to the glomerular filtration rate but therapeutic levels are still maintained in the urine.

Results of studies in man, employing thin layer chromatography and bioautography, show that amoxicillin is not changed *in vivo* into substances with antibacterial activity.

There appears to be only one metabolic breakdown product, namely, penicilloic acid.

5.3 Preclinical safety data

No data available

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

FISAMOX® Powder for Injection contains no antiseptics or buffering agents nor are there any excipients.

6.2 Incompatibilities

FISAMOX® Powder for Injection is compatible with commonly used intravenous solutionsThis medicine must not be mixed with other medicines except those mentioned in section 6.4. However, it should not be mixed with blood products or proteinaceous fluids such as protein hydrolysates, nor with intravenous lipid emulsions.

6.3 Shelf life

FISAMOX® Powder for Injection should be stored below 25°C, protected from light.

Dry powder:	Store below 25°C until the expiry date printed on the carton and individual vial
Solutions:	When prepared for intramuscular or direct intravenous injection, FISAMOX® should be administered immediately after reconstitution.

6.4 Special precautions for storage

Intravenous fluids:	Infusions should be administered within 60 minutes even though FISAMOX® maintains a satisfactory degree of activity at room temperature in various infusion fluids listed below.

If the solutions listed below are stored under refrigeration (2-8°C), they will remain stable for the time periods indicated (see **Table 3**).

Table 3: Storage of Intravenous Fluids at 2-8°C

Intravenous Solution	Stability Period (hours)
Sodium chloride injection (normal saline)	6
Compound sodium chloride injection (Ringers solution)	6
Sodium lactate injection	3
Compound sodium lactate injection (Hartmann's solution)	3
Dextrose injection	1
Sodium chloride and (4%) dextrose injection	1

Since FISAMOX® Powder for Injection is relatively less stable in carbohydrate solutions, it is preferable to avoid adding it to them. However, it may be injected into the drip tubing of such an infusion or incorporated into a small volume of the solution and infused over a period of 30 to 60 minutes.

As there is some loss of potency during storage at 2-8°C, solutions that have been stored at 2-8°C for periods within the limits stated above, should be used immediately once they have been brought to room temperature.

6.5 Nature and contents of container <and special equipment for use, administration or implantation>

FISAMOX® Powder for Injection is available in vials containing 500mg or 1 g of amoxicillin (as amoxicillin sodium) in boxes of 5 vials.

6.6 Special precautions for disposal

In New Zealand, any unused medicine or waste material should be disposed of in accordance with local requirements.

7 MEDICINE SCHEDULE

Prescription Medicine

8 SPONSOR

Pharmacy Retailing (NZ) Limited
trading as Healthcare Logistics
58 Richard Pearse Drive
Airport Oaks
Auckland
New Zealand

9 DATE OF FIRST APPROVAL

27 February 2014

10 DATE OF REVISION OF THE TEXT

18 March 2019

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
All document	New document to SmPC format 4.8 Adverse effects (Undesirable effects) - acute generalised exanthematous pustulosis (AGEP) and drug reaction with eosinophilia and systemic symptoms (DRESS)