RANMOXY

Amoxicillin Trihydrate equivalent to Amoxicillin 125mg/5mL and 250mg/5mL Suspension BP

Presentation

RANMOXY 125mg/5mL suspension is a white powder which when reconstituted with water forms an orange suspension with a frutti tutti flavour. Each 5mL of reconstituted suspension contains amoxicillin trihydrate equivalent to 125mg of amoxicillin.

RANMOXY 250mg/5mL suspension is a white powder which when reconstituted with water forms an orange suspension with a frutti tutti flavour. Each 5mL of reconstituted suspension contains amoxicillin trihydrate equivalent to 250mg of amoxicillin.

Uses

Actions

Amoxicillin is a bactericidal penicillin active against both Gram-positive and Gram-negative organisms and is subject to the hydrolytic activity of penicillinase. Amoxicillin differs *in vitro* from benxylpenicillin in the Gram-negative spectrum.

In vitro most strains of *Haemophilus influenzae, Neisseria gonorrhoeae, N. meningitidis, Proteus mirabilis, Amoxicillin*, Salmonellae, alpha- and beta-haemolytic Streptococci, *Diplococcus pneumoniae*, nonpenicillinase producing Staphylococci and *Streptococcus faecalis*, are sensitive to amoxicillin at serum concentrations which may be expected following the recommended doses. However, some of the organisms are sensitive to amoxicillin only at concentrations achieved in the urine (see Indications).

Escherichia coli isolates are becoming increasing resistant to amoxicillin *in vitro* due to the presence of penicillinase producing strains.

Strains of gonococci that are relatively resistant to benzylpenicillin may be sensitive to amoxicillin.

Amoxicillin is not effective against penicillinase producing bacteria, particularly resistant Staphylococci, which now have a high prevalence.

All strains of Pseudomonas, Klebsiella, Enterobacter, indole positive Proteus, *Serratia marcescens*, Citrobacter, penicillinase producing *N. gonorrhoeae* and penicillinase producing *H. influenzae* are also resistant.

Combining Amoxicillin with a beta-lactamase inhibitor such as clavuanic acid effectively broadens its spectrum of activity to include many strains of beta-lactamase producing bacteria.

Like benzylpenicillin, amoxicillin is bactericidal against sensitive organisms during the stage of active multiplication. Amoxicillin exerts its mode of action by interfering with bacterial cell wall synthesis by acylating the enzyme transpeptidase, thus rendering it unable to cross-link muramic acid containing peptidoglycan strands. This inhibition of the biosynthesis of dipeptidoglycan, a substance necessary for cell wall strength and rigidity, results in a defective cell wall.

Pharmacokinetics

Amoxicillin is stable at gastric pH. It is completely absorbed in the upper gastrointestinal tract. Absorption is independent of meals.

Amoxicillin diffuses rapidly into most body tissues and fluids except for the brain and spinal fluid unless the meninges are inflamed. Amoxicillin has been shown to diffuse into saliva and sputum

and is excreted mainly via the urine where it exists in high concentration. The amount to be found in bile is variable depending on normal biliary secretory function.

Amoxicillin is not highly protein bound, with only 17% protein bound in serum.

The serum half-life of amoxicillin is 61.3 minutes but in the absence of renal function it is 7 to 10 hours. The half-life may be longer in neonates and the elderly.

Oral doses of 250mg and 500mg of amoxicillin give average peak serum levels in one to two hours or 5micrograms/mL and 6.6 to 10.8micrograms /mL respectively. Detectable serum levels of amoxicillin are present 8 hours after the ingestion of a single dose.

Amoxicillin is primarily excreted by the renal system and approximately 75% of a 1g dose is excreted within 6 hours in the presence of normal renal function. It is excreted in the urine both unchanged (60%) and as penicilloic acid (15%). However, only about 32% of a 3g dose is excreted via the urine as the biologically active component in 8 hours (by which time most of the urinary excretion is complete). This proportional difference in the amount excreted from the different doses reflects a lack of linearity between doses and extent of absorption with a levelling off at higher doses or oral amoxicillin. Excretion of amoxicillin can be delayed by concurrent administration of probenecid thus prolonging its therapeutic effect.

Indications

Amoxicillin is indicated for the treatment of the following infections due to susceptible strains of sensitive organisms:

Upper Respiratory Infections:

Otitis media, pharyngitis, sinusitis and tonsillitis.

Lower Respiratory Infections:

Bronchitis, bronchopneumonia and lobar pneumonia.

Urinary Tract Infections:

Cystitis, cysto-pyelitis, urethritis, and gonococcal urethritis.

Prophylaxis:

against α-haemolytic (viridans group) and β-haemolytic Streptococci before dental, oral or upper respiratory tract surgery or instrumentation.

Prophylaxis:

of bacterial endocarditis in patients with any of the following conditions: congenital cardiac malformations, rheumatic and other acquired valvular lesions, prosthetic heart valves, previous history of bacterial endocarditis, hypertrophic cardiomyopathy, surgically constructed systemic-pulmonary shunts, mitral valve prolapse with valvular regurgitation or mitral valve prolapse without valvular regurgitation but associated with thickening and/or redundancy of the valve leaflets.

Amoxicillin is further indicated for the treatment of cutaneous infections. In emergency cases where the causative organism is not yet identified, therapy may be initiated with amoxicillin on the basis of clinical judgement, while awaiting the results of bacteriologic studies to determine its antimicrobial sensitivity.

Dosage and Administration

Amoxicillin can be administered orally independent of meals. Therapy should be maintained for a minimum for 5 days. Treatment should be continued for a minimum of 96 hours beyond the time the patient becomes asymptomatic or after evidence of bacterial eradication is observed. At least 10 days treatment is recommended for any infection caused by beta-haemolytic streptococci to prevent the occurrence of acute rheumatic fever or glomerulonephritis.

Infections of the upper respiratory or genitourinary tracts, skin and soft tissues

due to susceptible strains of the causative organism:
Adults: 250 mg every 8 hours.
Children < 20 kg: 25 mg/kg/day in divided doses every 8 hours.

In severe infections

or infections associated with organisms where sensitivity determinations require higher blood concentrations*:*
Adults: 500 mg every 8 hours.
Children < 20 kg: 50 mg/kg/day in divided doses every 8 hours; this dosage should not exceed the recommended adult dosage.

Infections of the lower respiratory tract

due to susceptible strains of the causative organism, and acute otitis media:
Adults: 500 mg every 8 hours.
Children <20 kg: 50 mg/kg/day in divided doses every 8 hours; this dosage should not exceed the recommended adult dosage.

High Dosage Therapy:

An adult dosage of 3g twice daily is recommended in appropriate cases for the treatment of severe or recurrent purulent infection of the respiratory tract.

Urethritis

due to non-penicillinase producing N. Gonorrhoea acquired in area with active monitoring for resistance to penicillin and where the percentage of penicillin-resistant isolates is <3.0%:
Adults and children > 45 kg: 3 g as a single oral dose; 1 g of oral probenecid should be administered concomitantly as well as appropriate therapy for presumptive or proven infection with *C. Trachomatis.*
Children < 45 kg: a single 50 mg/kg dose (maximum 3 g) of amoxicillin given with a single 25 mg/kg (up to 1 g) dose of probenecid. However, probenecid is not recommended in children under 2 years of age. Appropriate therapy of presumptive or proven infection with *C. Trachomatis* should be included as well.

Before prescribing amoxicillin, dark field examinations should be carried out in those cases where syphilis is also suspected and monthly serologic tests should be carried out for a minimum of 4 months.

Acute, uncomplicated lower urinary tract infections:

Adults: 3g as a single dose.
In the treatment of chronic urinary tract infections, frequent bacteriologic and clinical evaluations are necessary. Doses smaller than those recommended above should not be used. In stubborn infections, therapy may be required for several weeks, sometimes at doses higher than those recommended. Concurrent bacteriologic sensitivity monitoring is recommended. It may be necessary to continue clinical and/or bacteriologic follow-up for several months after cessation of therapy.

For prevention of endocarditis:

Patient not having a general anaesthetic**:**
Adults: 3 g orally one hour before the procedure. A second dose may be given 6 hours later if considered necessary.
Children: For children under 5 administer quarter the adult dose and for children aged 5 to 10 administer half the adult dose.

Patient having a general anaesthetic – oral antibiotics appropriate:

Adults: 3g orally 4 hours prior to anaesthesia followed by 3g orally 6 hours after the initial dose.
Children: For children under 5 administer quarter the adult dose and for children aged 5 to 10 administer half the adult dose.

Note: The children's dose is intended for individuals whose weight will not cause dosage to be calculated greater than that recommended for adults. Children weighing more than 20 kg should be dosed according to the adult recommendations.

Dosage in renal failure:

The relative dose interval for amoxicillin is 4 hours; thus, in patients with renal failure in whom the half life is 6 hours the dosage interval is 24 hours and it may be necessary to reduce the total daily dosage. In patients with a creatinine clearance of more than 30mL/min no dosage adjustment is required. For patients with a creatinine clearance between 10 and 30mL/min the maximum recommended dose is 500mg twice daily. For patients with a creatinine clearance of less than 10mL/min the maximum recommended dose is 500mg per day. In patients receiving peritoneal dialysis the maximum recommended daily dose is 500mg. Amoxicillin may be removed from the system by haemodialysis.

Contraindications

Patients with a history of hypersensitivity to beta-lactum antibiotics (e.g. penicillins and cephalosporins).

Amoxicillin 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.

Warnings and Precautions

Amoxicillin is not effective against beta-lactamase-producing (penicillin resistant) staphylococci.

Serious and occasionally fatal hypersensitivity (anaphylactoid) reactions have been reported in patients on parenteral and oral penicillin therapy. These reactions, however, are more likely to occur in individuals with a history of sensitivity to multiple allergens. Therefore, before initiating therapy with amoxicillin or any penicillin, careful inquiry should be made concerning previous hypersensitivity reactions to penicillins, cephalosporins or other allergens. If an allergic reaction occurs, amoxicillin should be discontinued and the appropriate measures instituted. Serious anaphylactoid reactions require immediate emergency treatment with epinephrine, oxygen, intravenous steroids and airway management, as indicated.

As with other penicillins, amoxicillin should be administered with caution in the presence of renal or hepatic insufficiency. Periodic assessment of renal, hepatic and haematopoietic functions should be made during prolonged amoxicillin therapy. Since amoxicillin is excreted mainly by the kidney, the dosage for patients with renal impairment should be reduced when creatinine clearance is <30 mL/min (see Dosage and Administration).

The possibility of superinfections with mycotic organisms or bacterial pathogens should be kept in mind during amoxicillin therapy. If superinfections occur (usually involving Aerobacter, Candida or Pseudomonas), the drug should be discontinued and appropriate measures instituted.

Amoxicillin should not be used if infectious mononucleosis or lympathic leukaemia is suspected since the occurrence of a morbilliform rash in patients with infectious mononucleosis following the use of amoxicillin is well documented. These patients are also very susceptible to ampicillin-induced skin rashes.

Following single dose therapy of acute lower urinary tract infections, the urine should be cultured. A positive culture may be evidence of a complicated or upper urinary tract infection and call for a longer or larger course of therapy.

Adequate fluid intake and urinary output must be maintained in patients receiving high doses of amoxicillin.

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 crystalluria.

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

Amoxicillin should be given with caution to patients who have experienced symptoms of allergy associated with a cephalosporin or penicillin.

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.

Pseudomembranous colitis has been reported with virtually all broad-spectrum antibiotics. It is important to consider this diagnosis in patients who develop severe and persistent diarrhoea during or after receiving amoxicillin. In this situation, even if Clostridium difficile is only suspected, administration of amoxicillin should be discontinued and appropriate treatment given.

Effects on ability to drive and use machines

During treatment with amoxicillin, 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.

Use in Pregnancy

Category A.
Animal studies with amoxicillin have not shown any teratological effects. The product has been used extensively for more than twenty years and its suitability in human pregnancy has been well documented. When antibiotic therapy is required during pregnancy, amoxicillin may be considered appropriate.

Use in Lactation

Amoxicillin is distributed into breast milk in low concentrations and should be used with caution in nursing women.

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, breastfeeding might have to be discontinued.

Adverse Effects

The following convention has been utilised for the classification of undesirable effects:- Very common (more than 1/10), common (more than 1/100, less than 1/10), uncommon (more than 1/1000, less than 1/100), rare (more than 1/10,000, less than 1/1000), very rare (less than 1/10,000).

The majority of the side-effects listed below are not unique to amoxicillin and may occur when using other penicillins.

Unless otherwise stated, the frequency of adverse events (AE's) has been derived from more than 30 years of post-marketing reports.

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 other 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 tooth 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 disorders:

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

Renal and Urinary tract disorders:

Very rare: Interstitial nephritis, crystalluria.

The incidence of these AEs was derived from clinical studies involving a total of approximately 6,000 adults 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/

Interactions

Probenecid decreases the renal tubular secretion of amoxicillin, and concurrent use may result in increased and prolonged blood levels of amoxicillin.

There is an increased risk of skin rashes in patients taking amoxicillin and allopurinol concurrently.

Amoxicillin may reduce the efficiency of oral contraceptives and patients should be warned according.

Tetracyclines and other bacteriostatic drugs may interfere with the bactericidal effects of amoxicillin.

The efficacy of oral contraceptives may be impaired under concomitant administration of amoxicillin, which may result in unwanted pregnancy. Women taking oral contraceptives should be aware of this and should be informed about alternative methods of contraception.

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

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

Penicillins may interfere with:

- Urinary glucose test
- Coomb's tests
- Tests for urinary or serum proteins
- Tests which use bacteria e.g. Guthrie test.

Overdosage

Serious toxicity is unlikely to occur. Acute ingestion of large doses may cause nausea, vomiting, diarrhoea and abdominal pain and should be treated symptomatically. Amoxicillin is removable from the circulation by haemodialysis. For all cases of suspected overdose appropriate supportive measures and symptomatic treatment are recommended.

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

Pharmaceutical Precautions

Store at or below 25°C.
Protect from heat, light and moisture.The reconstituted suspension may be stored in a refrigerator (between 2 and 8°C) for up to 14 days.

The suspension is reconstituted by adding 85mL water to each bottle of powder as supplied (20.4g) to provide 100mL of reconstituted suspension.

Medicine Classification

Prescription-Only Medicine

Package Quantities

RANMOXY 125mg/5mL suspension:
Bottles of powder which when reconstituted with 85mL of water form 100mL of suspension.

RANMOXY 250mg/5mL suspension:
Bottles of powder which when reconstituted with 85mL of water form 100mL of suspension

Further Information

Suspensions contain sorbitol, sodium saccharin, Sunset yellow colorant (CI 15985, E110) and Tutti frutti flavour.

Name and Address

Apotex NZ Ltd
32 Hillside Road
Glenfield, Auckland
Private Bag 102-995
North Shore Mail Centre
Tel: (09) 444-2073
Fax: (09) 444-2951

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