PRESCRIBING INFORMATION
For the use only of a Registered Medical Practitioner

RANOXYL CAPSULES

(Amoxicillin Capsules BP)

To reduce the development of drug-resistant bacteria and maintain the effectiveness of amoxicillin and other antibacterial drugs, amoxicillin should be used only to treat or prevent infections that are proven or strongly suspected to be caused by bacteria.

COMPOSITION

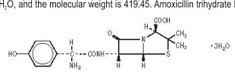
RANOXYL CAPSULE 250 mg
Each capsule contains:
Amoxicillin trihydrate BP
equivalent to anhydrous Amoxicillin .....250 mg

RANOXYL CAPSULE 500 mg
Each capsule contains:
Amoxicillin trihydrate BP
equivalent to anhydrous Amoxicillin .....500 mg

Excipients: Sodium lauryl sulphate, Colloidal silicon dioxide, Purified talc, Magnesium stearate.

DESCRIPTION[1]

RANOXYL CAPSULE contains amoxicillin, which is a semisynthetic antibiotic, an analog of ampicillin, with a broad spectrum of bactericidal activity against many Gram-positive and Gram-negative microorganisms. Chemically, amoxicillin trihydrate is designated as (2S,5R,6R)-6-[(2R)-2-amino-2-(4-hydroxyphenyl)acetamido]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid trihydrate. For amoxicillin trihydrate, the molecular formula is $C_{16}H_{19}N_3O_5S \cdot 3H_2O$, and the molecular weight is 419.45. Amoxicillin trihydrate has following structural formula:



AMOXICILLIN TRIHYDRATE

INDICATIONS[1,2]

Amoxicillin is indicated for the treatment of infections due to susceptible (only β-lactamase-negative) strains of the designated microorganisms in the conditions listed below.

Infections of the ear, nose, and throat – due to Streptococcus spp. (α- and β-hemolytic strains only), S. pneumoniae, Staphylococcus spp., or H. influenzae.

Infections of the genitourinary tract – due to E. coli, P. mirabilis, or E. faecalis.

Infections of the skin and skin structure – due to Streptococcus spp. (α- and β-hemolytic strains only), Staphylococcus spp., or E. coli.

Infections of the lower respiratory tract – due to Streptococcus spp. (α- and β-hemolytic strains only), S. pneumoniae, Staphylococcus spp., or H. influenzae.

Gonorrhea, acute uncomplicated (ano-genital and urethral infections) – due to N. gonorrhoeae (males and females).

Amoxicillin is also indicated for the treatment of below mentioned infections caused by susceptible organisms:

Peritonitis
Intra-abdominal sepsis
Septicaemia
Bacterial endocarditis
Typhoid and paratyphoid fever
Osteomyelitis
Bacteriuria in pregnancy
Dental abscess (as an adjunct to surgical management)

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

H. pylori eradication- to reduce the risk of duodenal ulcer recurrence

Triple Therapy: amoxicillin / clarithromycin / lansoprazole
Amoxicillin, in combination with clarithromycin plus lansoprazole as triple therapy, is indicated for the treatment of patients with H. pylori infection and duodenal ulcer disease (active or 1-year history of a duodenal ulcer) to eradicate H. pylori. Eradication of H. pylori has been shown to reduce the risk of duodenal ulcer recurrence.

Dual Therapy: amoxicillin / lansoprazole
Amoxicillin, in combination with lansoprazole delayed-release capsules as dual therapy, is indicated for the treatment of patients with H. pylori infection and duodenal ulcer disease (active or 1-year history of a duodenal ulcer) who are either allergic or intolerant to clarithromycin or in whom resistance to clarithromycin is known or suspected. Eradication of H. pylori has been shown to reduce the risk of duodenal ulcer recurrence.

In children with urinary tract infection the need for investigation should be considered.

To reduce the development of drug-resistant bacteria and maintain the effectiveness of amoxicillin and other antibacterial drugs, amoxicillin should be used only to treat or prevent infections that are proven or strongly suspected to be caused by susceptible bacteria. When culture and susceptibility information are available, they should be considered in selecting or modifying antibacterial therapy. In the absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy.
Consideration should be given to official local guidance (e.g. national requirements) on the appropriate use of antibacterial agents.

Indicated surgical procedures should be performed.

DOSAGE AND ADMINISTRATION[1,2]

Amoxicillin may be given without regard to meals.

Adults and Pediatric Patients >3 Months

Infection	Severity*	Usual Adult Dose	Usual Dose for Children > 3 Months†
Ear/Nose/Throat	Mild/Moderate	500 mg every 12 hours **or** 250 mg every 8 hours	25 mg/kg/dawy in divided doses every 12 hours **or** 20 mg/kg/day in divided doses every 8 hours
	Severe	875 mg every 12 hours **or** 500 mg every 8 hours	45 mg/kg/day in divided doses every 12 hours **or** 40 mg/kg/day in divided doses every 8 hours
Lower Respiratory Tract	Mild/Moderate or Severe	875 mg every 12 hours **or** 500 mg every 8 hours	45 mg/kg/day in divided doses every 12 hours **or** 40 mg/kg/day in divided doses every 8 hours
Skin/Skin Structure	Mild/Moderate	500 mg every 12 hours **or** 250 mg every 8 hours	25 mg/kg/day in divided doses every 12 hours **or** 20 mg/kg/day in divided doses every 8 hours
	Severe	875 mg every 12 hours **or** 500 mg every 8 hours	45 mg/kg/day in divided doses every 12 hours **or** 40 mg/kg/day in divided doses every 8 hours
Genitourinary Tract	Mild/Moderate	500 mg every 12 hours **or** 250 mg every 8 hours	25 mg/kg/day in divided doses every 12 hours **or** 20 mg/kg/day in divided doses every 8 hours
	Severe	875 mg every 12 hours **or** 500 mg every 8 hours	45 mg/kg/day in divided doses every 12 hours **or** 40 mg/kg/day in divided doses every 8 hours
Gonorrhea Acute, uncomplicated ano-genital, and urethral infections in males and females		3 grams as single oral dose	Prepubertal children: 50 mg/kg amoxicillin, combined with 25 mg/kg probenecid as a single dose. **Note: Since probenecid is contraindicated in children less than 2 years, do not use this regimen in these cases.**

* Dosing for infections caused by less susceptible organisms should follow the recommendations for severe infections.
† The children's dosage is intended for individuals whose weight is less than 40 kg. Children weighing 40 kg or more should be dosed according to the adult recommendations.

Prophylaxis of endocarditis:

CONDITION		ADULTS' DOSAGE (INCLUDING ELDERLY)	CHILDREN'S DOSAGE (< 40 kg)	NOTES
Dental procedures: prophylaxis for patients undergoing extraction, scaling or surgery involving gingival tissues and who have not received a penicillin in the previous month. (N.B. Patients with prosthetic heart valves should be referred to hospital - see below).	Patient not having general anaesthetic.	3 g Amoxicillin orally, 1 hour before procedure. A second dose may be given 6 hours later, if considered necessary.	50 mg amoxicillin/kg body weight given as a single dose one hour preceding the surgical procedure.	Note 1. If prophylaxis with Amoxicillin is given twice within one month, emergence of resistant streptococci is unlikely to be a problem. Alternative antibiotics are recommended if more frequent prophylaxis is required, or if the patient has received a course of treatment with a penicillin during the previous month. Note 2. To minimise pain on injection, Amoxicillin injection may be given as two injections.
	Patient having general anaesthetic: Si les antibiotiques oraux sont considérés comme appropriés,	Initially 3 g Amoxicillin orally 4 hours prior to anaesthesia, followed by 3 g orally (or 1 g IV or IM if oral dose not tolerated) as soon as possible after the operation.		
	Patient having general anaesthetic: if oral antibiotics not appropriate.	1 g Amoxicillin IV or IM immediately before induction; with 500 mg orally, 6 hours later.		
Dental procedures: patients for whom referral to hospital is recommended: a) Patients to be given a general anaesthetic who have been given a penicillin in the previous month. b) Patients to be given a general anaesthetic who have a prosthetic heart valve. c) Patients who have had one or more attacks of endocarditis.		Initially: 1 g Amoxicillin IV or IM with 120 mg gentamicin IV or IM immediately prior to anaesthesia (if given) or 15 minutes prior to dental procedure. Followed by (6 hours later): 500 mg Amoxicillin orally.	50 mg amoxicillin/kg body weight given as a single dose one hour preceding the surgical procedure.	See Note 2. Note 3. Amoxicillin and gentamicin injections should not be mixed in the same syringe. Note 4. Please consult the appropriate data sheet/ prescribing information for full prescribing information on gentamicin.
Genitourinary Surgery or Instrumentation: prophylaxis for patients who have no urinary tract infection and who are to have genito-urinary surgery or instrumentation under general anaesthesia. In the case of *Obstetric and Gynaecological Procedures* and *Gastrointestinal Procedures*– routine prophylaxis is		Initially: 1 g Amoxicillin IV or IM with 120 mg gentamicin IV or IM, immediately before induction. Followed by (6 hours later): 500 mg Amoxicillin		See Notes 2, 3 and 4 above.

Treatment of other infections (like Peritonitis, Intra-abdominal sepsis, Septicaemia, Bacterial endocarditis, Typhoid and paratyphoid fever, Osteomyelitis, Bacteriuria in pregnancy, Dental abscess)

Adult dosage (including elderly patients)

Oral: Standard adult dosage: 250 mg three times daily, increasing to 500 mg three times daily for more severe infections.

High dosage therapy (maximum recommended oral dosage 6 g daily in divided doses): A dosage of 3 g twice daily is recommended in appropriate cases for the treatment of severe or recurrent purulent infection of the respiratory tract.

Short course therapy: Simple acute urinary tract infection: two 3 g doses with 10 to 12 hours between the doses. Dental abscess: two 3 g doses with 8 hours between the doses. Gonorrhoea: single 3 g dose.

Children weighing <40kg

Amoxicillin Suspension is recommended for children under six months of age.

The daily dosage for children is 40 to 90 mg/kg/day in two to three divided doses* (not exceeding 3 g/day) depending on the indication, severity of the disease and the susceptibility of the pathogen.

PK/PD data indicate that dosing three times daily is associated with enhanced efficacy, thus twice daily dosing is only recommended when the dose is in the upper range.

Children weighing more than 40 kg should be given the usual adult dosage.

Special dosage recommendation

Tonsillitis: 50 mg/kg/day in two divided doses.

Acute otitis media: In areas with high prevalence of pneumococci with reduced susceptibility to penicillins, dosage regimens should be guided by national/local recommendations. In severe or recurrent acute otitis media, especially where compliance may be a problem, 750 mg twice a day for two days may be used as an alternative course of treatment in children aged 3 to 10 years.

Early Lyme disease (isolated erythema migrans): 50 mg/kg/day in three divided doses, over 14 to 21 days.

Neonates and Infants Aged ≤ 12 Weeks (≤ 3 Months)

Due to incompletely developed renal function affecting elimination of amoxicillin in this age group, the recommended upper dose of amoxicillin is 30 mg/kg/day divided q12h.

General

It should be recognized that in the treatment of chronic urinary tract infections, frequent bacteriological and clinical appraisals are necessary. Smaller doses than those recommended above should not be used. Even higher doses may be needed at times. In stubborn infections, therapy may be required for several weeks. It may be necessary to continue clinical and/or bacteriological follow-up for several months after cessation of therapy. Except for gonorrhea, 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 *Streptococcus pyogenes* to prevent the occurrence of acute rheumatic fever.

All patients with gonorrhea should be evaluated for syphilis. Larger doses may be required for stubborn or severe infections.

H. pylori Eradication to Reduce the Risk of Duodenal Ulcer Recurrence

Triple Therapy: **Amoxicillin** / clarithromycin / lansoprazole
The recommended adult oral dose is 1 gram **Amoxicillin**, 500 mg clarithromycin, and 30 mg lansoprazole, all given twice daily (q12h) for 14 days (see INDICATIONS).

Dual Therapy: **Amoxicillin** / lansoprazole
The recommended adult oral dose is 1 gram **Amoxicillin** and 30 mg lansoprazole, each given three times daily (q8h) for 14 days (see INDICATIONS).

Please refer to clarithromycin and lansoprazole full prescribing information for CONTRAINDICATIONS and WARNINGS, and for information regarding dosing in elderly and renally impaired patients.

Dosing Recommendations for Adults with Impaired Renal Function

Patients with impaired renal function do not generally require a reduction in dose unless the impairment is severe. Severely impaired patients with a glomerular filtration rate of <30 mL/min should not receive the 875-mg formulation. Patients with a glomerular filtration rate of 10 to 30 mL/min should receive 500 mg or 250 mg every 12 hours, depending on the severity of the infection. Patients with a less than 10 mL/min glomerular filtration rate should receive 500 mg or 250 mg every 24 hours, depending on severity of the infection.

Hemodialysis patients should receive 500 mg or 250 mg every 24 hours, depending on severity of the infection. They should receive an additional dose both during and at the end of dialysis.

Dosing Recommendations during Renal Impairment in Children under 40 kg

Creatinine clearance ml/min	Dose	Interval between administration
> 30	Usual dose	No adjustment necessary
10 to 30	Usual dose	12 hour (corresponding to 2/3 of the dose)
< 10	Usual dose	24 hour (corresponding to 1/3 of the dose)

CONTRAINDICATIONS[1,2]

A history of allergic reaction to amoxicillin or to any of the penicillins or to any of the excipients of the formulation is a contraindication. Amoxicillin is a penicillin and should not be given to penicilin-hypersensitive patients. Attention should be paid to possible cross-sensitivity with other beta-lactam antibiotics eg. cephalosporins.

WARNINGS AND PRECAUTIONS[1,2]

Warnings

SERIOUS AND OCCASIONALLY FATAL HYPERSENSITIVITY (ANAPHYLACTIC) REACTIONS HAVE BEEN REPORTED IN PATIENTS ON PENICILLIN THERAPY. ALTHOUGH ANAPHYLAXIS IS MORE FREQUENT FOLLOWING PARENTERAL THERAPY, IT HAS OCCURRED IN PATIENTS ON ORAL PENICILLINS. 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 HYPERSENSITIVITY WHO HAVE EXPERIENCED SEVERE REACTIONS WHEN TREATED WITH CEPHALOSPORINS. BEFORE INITIATING THERAPY WITH AMOXICILLIN, 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 APPROPRIATE THERAPY INSTITUTED. **SERIOUS ANAPHYLACTIC REACTIONS REQUIRE IMMEDIATE EMERGENCY TREATMENT WITH EPINEPHRINE, OXYGEN, INTRAVENOUS STEROIDS, AND AIRWAY MANAGEMENT, INCLUDING INTUBATION, SHOULD ALSO BE ADMINISTERED AS INDICATED.**

Clostridium difficile associated diarrhea (CDAD) has been reported with use of nearly all antibacterial agents, including amoxicillin, and may range in severity from mild diarrhea to fatal colitis. Treatment with antibacterial agents alters the normal flora of the colon leading to overgrowth of *C. difficile*.

C. difficile produces toxins A and B which contribute to the development of CDAD. Hypertoxin producing strains of *C. difficile* cause increased morbidity and mortality, as these infections can be refractory to antimicrobial therapy and may require colectomy. CDAD must be considered in all patients who present with diarrhea following antibiotic use. Careful medical history is necessary, since CDAD has been reported to occur over two months after the administration of antibacterial agents.

If CDAD is suspected or confirmed, ongoing antibiotic use not directed against *C. difficile* may need to be discontinued. Appropriate fluid and electrolyte management, protein supplementation, antibiotic treatment of *C. difficile*, and surgical evaluation should be instituted as clinically indicated.

In patients with reduced urine output, crystalluria has been observed very rarely, predominantly with parenteral 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.

In patients with renal impairment, the rate of excretion of amoxicillin will be reduced depending on the degree of impairment and it may be necessary to reduce the total daily unit amoxicillin dosage accordingly.

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.

Precaution should be taken in premature children and during the neonatal period: renal, hepatic and haematological functions should be monitored.

General Precautions

The possibility of superinfections with mycotic or bacterial pathogens should be kept in mind during therapy. If superinfections occur, amoxicillin should be discontinued and appropriate therapy instituted.

A high percentage of patients with mononucleosis who receive ampicillin develop an erythematous skin rash. Thus, ampicillin-class antibiotics should not be administered to patients with mononucleosis.

Prescribing amoxicillin in the absence of a proven or strongly suspected bacterial infection or a prophylactic indication is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria.

Laboratory Tests: As with any potent drug, periodic assessment of renal, hepatic, and hematopoietic function should be made during prolonged therapy. All patients with gonorrhea should have a serologic test for syphilis at the time of diagnosis. Patients treated with amoxicillin should have a follow-up serologic test for syphilis after 3 months.

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

Information for Patients

Amoxicillin may be taken every 8 hours or every 12 hours, depending on the strength of the product prescribed.

Patients should be counseled that antibacterial drugs, including amoxicillin should only be used to treat bacterial infections. They do not treat viral infections (e.g., the common cold). When amoxicillin is prescribed to treat a bacterial infection, patients should be told that although it is common to feel better early in the course of therapy, the medication should be taken exactly as directed. Skipping doses or not completing the full course of therapy may: (1) decrease the effectiveness of the immediate treatment, and (2) increase the likelihood that bacteria will develop resistance and will not be treatable by amoxicillin or other antibacterial drugs in the future.

Diarrhea is a common problem caused by antibiotics which usually ends when the antibiotic is discontinued. Sometimes after starting treatment with antibiotics, patients can develop watery and bloody stools (with or without stomach cramps and fever) even as late as 2 or more months after having taken the last dose of the antibiotic. If this occurs, patients should contact their physician as soon as possible.

USE IN SPECIAL POPULATION[1]

Pregnancy

Teratogenic Effects: US-FDA Pregnancy Category B. Reproduction studies have been performed in mice and rats at doses up to 10 times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to amoxicillin. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Labor and delivery: Oral ampicillin-class antibiotics are poorly absorbed during labor. Studies in guinea pigs showed that intravenous administration of ampicillin slightly decreased the uterine tone and frequency of contractions but moderately increased the height and duration of contractions. However, it is not known whether use of amoxicillin in humans during labor or delivery has immediate or delayed adverse effects on the fetus, prolongs the duration of labor, or increases the likelihood that forceps delivery or other obstetrical intervention or resuscitation of the newborn will be necessary.

Lactation

Penicillins have been shown to be excreted in human milk. Amoxicillin use by nursing mothers may lead to sensitization of infants. Caution should be exercised when amoxicillin is administered to a nursing woman.

Pediatrics

Because of incompletely developed renal function in neonates and young infants, the elimination of amoxicillin may be delayed. Dosing of amoxicillin should be modified in pediatric patients 12 weeks or younger (< 3 months). Precaution should be taken in premature children and during the neonatal period: renal, hepatic and haematological functions should be monitored.

Geriatrics

An analysis of clinical studies of amoxicillin was conducted to determine whether subjects aged 65 years and over respond differently from younger subjects. Of the 1,811 subjects treated with capsules of amoxicillin, 95% were <60 years old, 15% were ≥ 61 years old and 7% were ≥ 71 years old. This analysis and other reported clinical experience have not identified differences in responses between the elderly and younger patients, but a greater sensitivity of some older individuals cannot be ruled out.

This drug is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function.

DRUG INTERACTIONS[1,2]

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

Chloramphenicol, macrolides, sulfonamides, and tetracyclines may interfere with the bactericidal effects of penicillin. This has been demonstrated in vitro; however, the clinical significance of this interaction is not well documented.

In common with other antibiotics, amoxicillin may affect the gut flora, leading to lower estrogen reabsorption and reduced efficacy of combined oral estrogen/progesterone contraceptives.

Concurrent administration of allopurinol during treatment with amoxicillin can increase the likelihood of allergic skin reactions.

Abnormal prolongation of prothrombin time (increased international normalized ratio [INR]) has been reported rarely in patients receiving amoxicillin and oral anticoagulants (e.g. acenocoumarol or warfarin). If co-administration is necessary, the prothrombin time or international normalised ratio should be carefully monitored with the addition or withdrawal of amoxicillin. Adjustments in the dose of oral anticoagulants may be necessary to maintain the desired level of anticoagulation.

Drug / Laboratory Test Interactions: High urine concentrations of ampicillin may result in false-positive reactions when testing for the presence of glucose in urine using Benedict's Solution or Fehling's Solution. Since this effect may also occur with amoxicillin, it is recommended that glucose tests based on enzymatic glucose oxidase reactions be used.

Following administration of ampicillin to pregnant women, a transient decrease in plasma concentration of total conjugated estriol, estriol-glucuronide, conjugated estrone, and estradiol has been noted. This effect may also occur with amoxicillin.

ADVERSE REACTIONS[1,2]

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 and in those with a history of allergy, asthma, hay fever, or urticaria. The following adverse reactions have been reported as associated with the use of penicillins:

Infections and Infestations: Mucocutaneous candidiasis.
Gastrointestinal: Nausea, vomiting, diarrhea, black hairy tongue and hemorrhagic / pseudomembranous colitis. Onset of pseudomembranous colitis symptoms may occur during or after antibiotic treatment.

Hypersensitivity Reactions: Severe allergic reactions including angioneurotic oedema, anaphylaxis, serum sickness-like reactions, erythematous maculopapular rashes, erythemia multiforme, stevens-Johnson syndrome, bullous dermatitis, exfoliative dermatitis, toxic epidermal necrolysis, acute generalized exanthematous pustulosis, hypersensitivity vasculitis, skin rash, pruritus and urticaria have been reported.

Note: These hypersensitivity reactions may be controlled with antihistamines and, if necessary, systemic corticosteroids. Whenever such reactions occur, amoxicillin should be discontinued unless, in the opinion of the physician, the condition being treated is life threatening and amenable only to amoxicillin therapy.

Liver: A moderate rise in AST (SGOT) and/or ALT (SGPT) has been noted, but the significance of this finding is unknown. Hepatic dysfunction including cholestatic jaundice, hepatic cholestasis and acute cytolytic hepatitis has been reported.

Renal: Interstitial nephritis. Crystalluria has also been reported (see OVERDOSAGE).

Hemic and Lymphatic Systems: Anemia, including hemolytic anemia, thrombocytopenia, thrombocytopenic purpura, eosinophilia, leukopenia, severe neutropenia, agranulocytosis and prolongation of bleeding time and prothrombin time have been reported during therapy with penicillins. These reactions are usually reversible on discontinuation of therapy and are believed to be hypersensitivity phenomena.

Central Nervous System: Reversible hyperactivity, agitation, anxiety, insomnia, confusion, convulsions, behavioral changes, hyperkinesia, and/or dizziness have been reported rarely. Convulsions may occur in patients with impaired renal function or in those receiving high doses.

Miscellaneous: Tooth discoloration (brown, yellow, or gray staining) has been rarely reported. Most reports occurred in pediatric patients. Discoloration was reduced or eliminated with brushing or dental cleaning in most cases.

Combination Therapy with Clarithromycin and Lansoprazole: In clinical trials using combination therapy with amoxicillin plus clarithromycin and lansoprazole, and amoxicillin plus lansoprazole, no adverse reactions peculiar to these drug combinations were observed. Adverse reactions that have occurred have been limited to those that had been previously reported with amoxicillin, clarithromycin, or lansoprazole.

Triple Therapy: Amoxicillin / Clarithromycin / Lansoprazole: The most frequently reported adverse events for patients who received triple therapy were diarrhea (7%), headache (6%), and taste perversion (5%). No treatment-emergent adverse events were observed at significantly higher rates with triple therapy than with any dual therapy regimen.

Dual Therapy: Amoxicillin / Lansoprazole: The most frequently reported adverse events for patients who received amoxicillin three times daily plus lansoprazole three times daily dual therapy were diarrhea (8%) and headache (7%). No treatment-emergent adverse events were observed at significantly higher rates with amoxicillin three times daily plus lansoprazole three times daily dual therapy than with lansoprazole alone.

For more information on adverse reactions with clarithromycin or lansoprazole, refer to their package inserts/ prescribing information.

OVERDOSAGE[1,2]

In case of overdosage, discontinue medication, treat symptomatically, and institute supportive measures as required. If the overdosage is very recent and there is no contraindication, an attempt at emesis or other means of removal of drug from the stomach may be performed. A prospective study of 51 pediatric patients at a poison-control center suggested that overdosages of less than 250 mg/kg of amoxicillin are not associated with significant clinical symptoms and do not require gastric emptying.

Gastrointestinal effects such as nausea, vomiting and diarrhoea may be evident and should be treated symptomatically with attention to the water / electrolyte balance.

Interstitial nephritis resulting in oliguric renal failure has been reported in a small number of patients after overdosage with amoxicillin.

Crystalluria, in some cases leading to renal failure, has also been reported after amoxicillin overdosage in adults and pediatric patients. In case of overdosage, adequate fluid intake and diuresis should be maintained to reduce the risk of amoxicillin crystalluria.

Renal impairment appears to be reversible with cessation of drug administration. High blood levels may occur more readily in patients with impaired renal function because of decreased renal clearance of amoxicillin. Amoxicillin may be removed from circulation by hemodialysis.

PHARMACOLOGY[1,2]

Mechanism of Action and Antibacterial Spectrum

Amoxicillin is similar to ampicillin in its bactericidal action against susceptible organisms during the stage of active multiplication. It acts through the inhibition of biosynthesis of cell wall mucopeptide. Amoxicillin has been shown to be active against most strains of the following microorganisms, both in vitro and in clinical infections as described in the INDICATIONS section.

Aerobic Gram-Positive Microorganisms
Enterococcus faecalis
*Staphylococcus spp.** (β-lactamase-negative strains only)
Streptococcus pneumoniae
Streptococcus spp. (α- and β-hemolytic strains only)
*Staphylococci which are susceptible to amoxicillin but resistant to methicillin/oxacillin should be considered as resistant to amoxicillin.

Aerobic Gram-Negative Microorganisms
Escherichia coli (β-lactamase-negative strains only)
Haemophilus influenzae (β-lactamase-negative strains only)
Neisseria gonorrhoeae (β-lactamase-negative strains only)
Proteus mirabilis (β-lactamase-negative strains only)

Helicobacter
Helicobacter pylori

Pharmacokinetics

Amoxicillin is stable in the presence of gastric acid and is rapidly absorbed after oral administration. The effect of food on the absorption of amoxicillin from the tablets and suspension of amoxicillin has been partially investigated. The 400-mg and 875-mg formulations have been studied only when administered at the start of a light meal. However, food effect studies have not been performed with the 200-mg and 500-mg formulations. Amoxicillin diffuses readily into most body tissues and fluids, with the exception of brain and spinal fluid, except when meninges are inflamed. The half-life of amoxicillin is 61.3 minutes. Most of the amoxicillin is excreted unchanged in the urine; its excretion can be delayed by concurrent administration of probenecid. In blood serum, amoxicillin is approximately 20% protein-bound.

Orally administered doses of 250 mg and 500 mg amoxicillin capsules result in average peak blood levels 1 to 2 hours after administration in the range of 3.5 g/ml to 5.0 g/ml and 5.5 g/ml to 7.5 g/ml, respectively.

Orally administered doses of amoxicillin suspension, 125 mg/5 ml and 250 mg/5 ml, result in average peak blood levels 1 to 2 hours after administration in the range of 1.5 g/ml to 3.0 g/ml and 3.5 g/ml to 5.0 g/ml, respectively.

Mean amoxicillin pharmacokinetic parameters from an open, two-part, single-dose crossover bioequivalence study in 27 adults comparing 875 mg of amoxicillin with 875 mg of amoxicillin/clavulanate potassium showed that the 875-mg tablet of amoxicillin produces an $AUC_{0-\infty}$ of 35.4 ± 8.1 mcg.hr/mL and a Cmax of 13.8 ± 4.1 mcg/mL. Dosing was at the start of a light meal following an overnight fast.

Oral administration of single doses of 400-mg chewable tablets and 400 mg/5 mL suspension of amoxicillin to 24 adult volunteers yielded comparable pharmacokinetic data:

Dose*	$AUC_{0-\infty}$ (mcg.hr/mL)	C_{max} (mcg/mL)†
Amoxicillin	Amoxicillin (±S.D.)	Amoxicillin (±S.D.)
400 mg (5 mL of suspension)	17.1 (3.1)	5.92 (1.62)
400 mg (1 chewable tablet)	17.9 (2.4)	5.18 (1.64)

* Administered at the start of a light meal.
† Mean values of 24 normal volunteers. Peak concentrations occurred approximately 1 hour after the dose.

Detectable serum levels are observed up to 8 hours after an orally administered dose of amoxicillin. Following a 1 gram dose and utilizing a special skin window technique to determine levels of the antibiotic, it was noted that therapeutic levels were found in the interstitial fluid. Approximately 60% of an orally administered dose of amoxicillin is excreted in the urine within 6 to 8 hours.

In preterm infants with gestational age 26 to 33 weeks, the total body clearance after intravenous dosing of amoxicillin, day 3 of life, ranged between 0.75 to 2 ml/min, very similar to the inuline clearance (GFR) in this population. Following oral administration, the absorption pattern and the bioavailability of amoxicillin in small children may be different to that of adults. Consequently, due to the decreased CL, the exposure is expected to be elevated in this group of patients, although this increase in exposure may in part be diminished by decreased bioavailability when given orally.

PRECLINICAL TOXICITY[1]

Carcinogenesis / Mutagenesis / Impairment of Fertility

Long-term studies in animals have not been performed to evaluate carcinogenic potential. Studies to detect mutagenic potential of amoxicillin alone have not been conducted; however, the following information is available from tests on a 4:1 mixture of amoxicillin and potassium clavulanate. Amoxicillin and potassium clavulanate was non-mutagenic in the Ames bacterial mutation assay, and the yeast gene conversion assay. Amoxicillin and potassium clavulanate was weakly positive in the mouse lymphoma assay, but the trend toward increased mutation frequencies in this assay occurred at doses that were also associated with decreased cell survival. Amoxicillin and potassium clavulanate was negative in the mouse micronucleus test, and in the dominant lethal assay in mice. Potassium clavulanate alone was tested in the Ames bacterial mutation assay and in the mouse micronucleus test, and was negative in each of these assays. In a multi-generation reproduction study in rats, no impairment of fertility or other adverse reproductive effects were seen at doses up to 500 mg/kg (approximately 3 times the human dose in mg/m2).

STORAGE
Store below 25ºC, protected from moisture.

SUPPLY
Box of 10's, 2x10's, 10x20's, 24x20's, 100x10's.

KEEP ALL MEDICINES OUT OF REACH OF CHILDREN

REFERENCES

1. US Prescribing Information of Amoxil, GlaxoSmithKline, NC, USA, September 2009.
2. UK Summary of Product Characteristics for Amoxil Capsules and Pediatric Suspension, GlaxoSmithKline, UK, text revision in November 2010.

Information compiled in March 2013

RANOXYL is a Trademark of Sun Pharmaceutical Ind. Ltd.
AMOXIL is a Trademark of GlaxoSmithKline, and is not trademark of Sun Pharmaceutical Ind. Ltd. The maker of this brand is not affiliated with and does not endorse Sun Pharmaceutical Ind. Ltd. or its products.

Manufactured in India by
Sun Pharmaceutical Ind. Ltd.
Industrial Area - 3
Dewas - 455 001

INFORMATIONS POSOLOGIQUES
À être utilisé uniquement par un médecin agréé

RANOXYL GÉLULES

(Gélules d'amoxicilline BP)

Pour réduire le développement de bactéries résistantes aumédicament et maintenir l'efficacité de l'amoxicilline et d'autres médicaments antibactériens, l'utilisation de l'amoxicilline doit servir uniquement à traiter ou prévenir les infections qui sont confirméesou fortement suspectées d'être d'origine bactérienne.

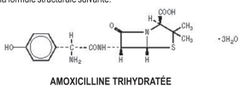
COMPOSITION
RANOXYL GÉLULE 250 mg
Chaque gélule contient :
Amoxicilline trihydrateèBP
Équivalent à amoxicillineanhydre .....250 mg

RANOXYL GÉLULE 500 mg
Chaque gélule contient:
Amoxicilline trihydratèeBP
Équivalent à amoxicilline anhydre .....500 mg

Excipients: Laurylsulfate de sodium, dioxyde de silice colloïdale, talc purifié, stéarate de magnésium.

DESCRIPTION [1]

RANOXYLGÉLULEcontient de l'amoxicilline, qui est un antibiotique semi-synthétique, un analogue del'ampicilline, avec un large spectre d'activité bactéricide contre de nombreux micro-organismes à Gram positif et à Gram négatif. Le nom chimique de l'amoxicillinetrihydratée est,(2S,5R,6R)-6-[(2R)-2-amino-2-(4-hydroxyphenyl)acetamido]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-acide carboxyliquetrihydraté.
La formule moléculaire de l'amoxicillinetrihydratéest $C_{16}H_{19}N_3O_5S \cdot 3H_2O$, et le poids moléculaire estde 419,45.
L'amoxicillinetrihydratéea la formule structurale suivante:



AMOXICILLINE TRIHYDRATÉE

INDICATIONS [1,2]

L'amoxicilline est indiquée dans le traitement des infections dues à des souches sensibles (non productrices de β-lactamasesseulement) des microorganismes désignés dans les conditions sous-mentionnées:

Infections des oreilles, du nez, et de la gorge– causées par *Streptococcusspp.* (souches α- etβ-hémolytiques seulement),*S. pneumoniae, Staphylococcus spp.*, ou *H. influenzae*.

Infections de l'appareil génito-urinaire – causées par *E. coli, P. mirabilis, ou E. faecalis*.

Infections de la peau et de la structure de la peau– causées par *Streptococcus spp.* (souches α- et β-hémolytiques seulement), *Staphylococcusspp., ouE. coli*.

Infections des voies respiratoires inférieures– causées *parStreptococcusspp.* (souches α- et β-hémolytiques seulement), *S. pneumoniae, Staphylococcus spp., ou H. influenzae*.

Gonorrhée, aiguë noncompliquée (infection ano-génitale et infection de l'urètre)– causée *parN. gonorrhoeae* (hommes et femmes).

L'amoxicilline est également indiquée dans le traitement des infections mentionnées ci-dessous causées par des organismes sensibles:

Péritonite
Septicémie intra-abdominale
Septicémie
Endocardite infectieuse
Fièvre typhoïde et paratyphoïde
Ostéomyélite
Bactériuriependant la grossesse
Abcès dentaire (en complémentd'un traitement chirurgical)

Prophylaxie del'endocardite: L'amoxicilline peut être utilisée dans la préventionde la bactériémie, associée à des procédures telles que l'extraction dentaire, chez les patients à risque de développer une endocardite infectieuse.

Éradication de H. pylori-Pour minimiser le risque de réapparition d'un ulcère duodénal.

Trithérapie: Amoxicilline / Clarithromycine / Lansoprazole
La trithérapie associant l'amoxicilline avec