PRODUCT MONOGRAPH

[Pr]pms-AMOXICILLIN
250 mg & 500 mg Capsules, USP
250 mg and 500 mg amoxicillin (as amoxicillin trihydrate)

125 mg/5 mL & 250 mg/5 mL Oral Suspension, USP
125 mg/5 mL amoxicillin (as amoxicillin trihydrate)
250 mg/5 mL amoxicillin (as amoxicillin trihydrate)

Antibiotic

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NAME OF DRUG

[Pr]pms-AMOXICILLIN
(Amoxicillin Trihydrate)

THERAPEUTIC CLASSIFICATION

Antibiotic

ACTION AND CLINICAL PHARMACOLOGY

pms-AMOXICLLIN (amoxicillin) exerts its bactericidal action by interfering with bacterial cell wall synthesis.

INDICATIONS AND CLINICAL USE

pms-AMOXICLLIN (amoxicillin) may be indicated in the treatment of infections due to susceptible strains of the following micro-organisms: Gram-negative organisms: H. influenzae, P. mirabilis and N. gonorrhoeae. Gram-positive organisms: Streptococci (including Streptococcus faecalis and Streptococcus pneumoniae).

Amoxicillin is not active against Pseudomonas aeruginosa, indole-positive Proteus species, Serratia marcescens, Klebsiella and Enterobacter species.

In emergency cases, where the causative organism is not yet identified, therapy may be initiated with amoxicillin on the basis of clinical judgment while awaiting bacteriologic tests to determine its antimicrobial sensitivity.

pms-AMOXICLLIN may be indicated as a prophylaxis against alpha-hemolytic (Viridan's group) Streptococci before dental, oral or upper respiratory tract surgery or instrumentation.

It may be also indicated as a 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.

To reduce the development of drug-resistant bacteria and maintain the effectiveness of pms-AMOXICLLIN and other antibacterial drugs, pms-AMOXICLLIN should be used only to treat 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.

CONTRAINDICATIONS

pms-AMOXICLLIN is contraindicated in patients who are hypersensitive to this drug or to any ingredient in the formulation or component of the container.

A history of a previous hypersensitivity reaction to any of the penicillins or cephalosporins is a contraindication.

pms-AMOXICLLIN (amoxicillin) is also contraindicated in cases where infectious mononucleosis is either suspected or confirmed.

WARNINGS

Serious and occasionally fatal hypersensitivity (anaphylactoid) reactions have been reported in patients on penicillin therapy. Although anaphylaxis is more frequent following parenteral therapy, it has occurred in patients following oral dosing of penicillins. These reactions are more apt to occur in individuals with a history of sensitivity to multiple allergens. There have been well-documented reports of individuals with a history of penicillin hypersensitivity reactions that have experienced severe hypersensitivity reactions when treated with cephalosporins. Before initiating therapy with penicillin, careful inquiry should be made concerning previous hypersensitivity reactions to penicillins, cephalosporins and other allergens. If an allergic reaction occurs, administration of pms-AMOXICLLIN (amoxicillin) should be discontinued and appropriate therapy instituted.

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

Hypersensitivity reactions are more likely to occur in patients with a history of hypersensitivity to beta-lactams.

Abnormal prolongation of prothrombin time (increased international normalized ratio (INR)) has been reported in patients receiving amoxicillin and oral anticoagulants. Appropriate monitoring should be undertaken when amoxicillin and oral anticoagulants are prescribed concurrently, particularly upon initiation or cessation of concurrent administration. Adjustments in the dose of oral anticoagulants may be necessary to maintain the desired level of anticoagulation.

Gastrointestinal

Clostridium difficile-associated disease
Clostridium difficile-associated disease (CDAD) has been reported with use of many antibacterial agents, including amoxicillin (see ADVERSE REACTIONS). CDAD may range in severity from

mild diarrhea to fatal colitis. It is important to consider this diagnosis in patients who present with diarrhea, or symptoms of colitis, pseudomembranous colitis, toxic megacolon, or perforation of colon subsequent to the administration of any antibacterial agent. CDAD has been reported to occur over 2 months after the administration of antibacterial agents.

Treatment with antibacterial agents may alter the normal flora of the colon and may permit overgrowth of Clostridium difficile. C. difficile produces toxins A and B, which contribute to the development of CDAD. CDAD may cause significant morbidity and mortality. CDAD can be refractory to antimicrobial therapy.

If the diagnosis of CDAD is suspected or confirmed, appropriate therapeutic measures should be initiated. Mild cases of CDAD usually respond to discontinuation of antibacterial agents not directed against Clostridium difficile. In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation, and treatment with an antibacterial agent clinically effective against Clostridium difficile. Surgical evaluation should be instituted as clinically indicated, as surgical intervention may be required in certain severe cases.

Susceptibility/Resistance

Development of Drug Resistant Bacteria
Prescribing pms-AMOXICLLIN in the absence of a proven or strongly suspected bacterial infection is unlikely to provide benefit to the patient and risks the development of drug-resistant bacteria.

PRECAUTIONS

Periodic assessment of renal, hepatic and hematopoietic functions should be made during prolonged therapy with pms-AMOXICLLIN (amoxicillin).

Because amoxicillin is excreted mostly by the kidney, the dosage for patients with renal impairment should be reduced in proportion to the degree of loss of renal function.

Use in the Elderly: There are no known specific precautions for the use of amoxicillin in the elderly.

If superinfections with mycotic or bacterial pathogens occur (usually involving Aerobacter, Pseudomonas or Candida) treatment with pms-AMOXICLLIN should be discontinued and appropriate therapy instituted.

The safety of pms-AMOXICLLIN in the treatment of infections during pregnancy has not been established. If the administration of pms-AMOXICLLIN to pregnant patients is considered to be necessary, its use requires that the potential benefits be weighed against the possible hazards to the fetus.

A morbilliform rash following the use of ampicillin in patients with infectious mononucleosis has been well documented and has also been reported to occur following the use of amoxicillin.

ADVERSE REACTIONS

As with other penicillins, it may be expected that untoward reactions will be related to sensitivity phenomena. They are more likely to occur in individuals who have previously demonstrated hypersensitivity to penicillins and cephalosporins 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 pms-AMOXICLLIN:

Gastrointestinal
Nausea, vomiting and diarrhea, hemorrhagic and pseudomembranous colitis. Clostridium difficile-associated disease (CDAD) has been reported with use of many antibacterial agents, including amoxicillin. Glossitis, black "hairy" tongue and stomatitis, mucocutaneous candidiasis, tooth discoloration (brown, yellow or gray staining); most reports occurred in pediatric patients. Discoloration was reduced or eliminated with brushing or dental cleaning in most cases.

Hypersensitivity Reactions
Skin rashes have been reported frequently. Less commonly, a few cases of serum sickness like reactions including urticaria, erythema, erythema multiforme, angioneurotic edema, pruritus have been reported. Rarely, Stevens-Johnson syndrome, toxic epidermal necrolysis, bullous dermatitis, exfoliative dermatitis, acute generalized exanthematous pustulosis, hypersensitivity vasculitis have been reported.

Anaphylaxis
Is the most serious reaction experienced and has usually been associated with the parenteral dosage form.

NOTE: Urticaria, other skin rashes, and serum sickness-like reactions may be controlled with antihistamines and if necessary, systemic corticosteroids. Whenever such reactions occur, pms-AMOXICLLIN (amoxicillin) should be discontinued unless, in the opinion of the physician, the condition being treated is life threatening and amenable only to amoxicillin therapy. Serious anaphylactic reactions require the immediate use of epinephrine, oxygen and intravenous steroids.

Hepatobiliary
A moderate rise in serum glutamic oxaloacetic transaminase (SGOT) has been noted, particularly in infants, but the significance of this finding is not known. Transient increases in serum alkaline phosphatase and lactic dehydrogenase levels have also been observed but they returned to normal on discontinuation of amoxicillin. Reports have also been seen of hepatic dysfunction including cholestatic jaundice, hepatic cholestasis, acute cytolytic hepatitis,

Hemic and Lymphatic Systems
Anemia thrombocytopenia, thrombocytopenic purpura, eosinophilia, leukopenia, neutropenia and agranulocytosis have been reported during therapy with the penicillins. These reactions are usually reversible on discontinuation of therapy and are believed to be hypersensitivity phenomena. Reports have also been seen of anemia including hemolytic anemia.

Central Nervous System
As with other penicillins, acute and chronic toxicity is not a clinical problem. Although penicillins do not normally cross the blood-brain barrier to any substantial extent, if massive doses are given (several grams per day) to elderly patients, patients with inflamed meninges or patients with impaired renal function, toxic reactions are likely to occur. At extremely high doses, convulsions can occur. When penicillin reaches a high concentration in the cerebrospinal fluid, neurotoxic symptoms consisting of myoclonia, convulsive seizures and depressed consciousness may occur. Unless administration of the drug is stopped or its dosage reduced, the syndrome may progress to coma and death. Dizziness, hyperkinesias, hyperactivity, agitation, anxiety, insomnia, confusion, and behavioural changes have also been reported.

Skin and Appendages
Erythematous maculopapular rash.

Renal
Crystalluria. Interstitial nephritis (oliguria, proteinuria, hematuria, hyaline casts, pyuria) and nephropathy are infrequent and usually associated with high doses of parenteral penicillins; however, this has occurred with all of the penicillins. Such reactions are hypersensitivity responses and are usually associated with fever, skin rash and eosinophilia. Elevations of creatinine or blood urea nitrogen may occur.

DRUG INTERACTIONS

Methotrexate
Penicillins compete with renal tubular secretion of methotrexate, resulting in decreased clearance of methotrexate. Concomitant use may increase methotrexate serum concentrations, with increased risk of toxicity.

Probenecid:
Probenecid inhibits the renal tubular excretion of amoxicillin. Concurrent use of amoxicillin and probenecid may result in increased and prolonged blood levels of amoxicillin.

Warfarin
Abnormal prolongation of prothrombin time (increased international normalized ratio [INR]) has been reported in patients receiving amoxicillin and warfarin. Appropriate monitoring should be undertaken when warfarin is prescribed concurrently. Adjustments in the dose of oral anticoagulants may be necessary to maintain the desired level of anticoagulation.

Oral Contraceptives
pms-AMOXICLLIN may affect the gut flora, leading to lower estrogen reabsorption and reduced efficacy of combined oral estrogen/progesterone contraceptives.

Tetracyclines
Bacteriostatic action of tetracyclines may inhibit bactericidal activity of penicillins.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

Treatment of overdosage would likely be needed only in patients with severely impaired renal function, since patients with normal kidneys excrete penicillins at a fast rate. Hemodialysis would, therefore, represent the main form of treatment.

Activated charcoal may be administered to aid in the removal of unabsorbed drug. General supportive measures are recommended.

For management of a suspected drug overdose, contact your regional Poison Control Centre.

DOSAGE AND ADMINISTRATION

Infections of the upper respiratory tract (ear, nose and throat) due to susceptible strains of streptococci (beta-hemolytic and Streptococcus pneumoniae), non-penicillinase-producing staphylococci and H. influenzae.

Infections of the urinary tract due to Proteus mirabilis and Streptococcus faecalis.

Infections of the skin and soft-tissues due to streptococci and staphylococci (non penicillinase producing).

USUAL DOSAGE:

Adults: 250 mg every 8 hours

Children <20 kg: 20 mg/kg/day in divided doses every 8 hours. This dosage should not exceed the recommended adult dosage.

Children weighing 20 kg or more should be dosed according to the adult recommendations.

In severe infections or infections associated with organisms where sensitivity determinations require higher blood concentrations: 500 mg every 8 hours for adults, and 40 mg/kg/day in divided doses every 8 hours for children less than 20 kg may be needed.

Infections of the lower respiratory tract, due to susceptible strains of the causative organism and acute otitis media.

USUAL DOSAGE:

Adults: 500 mg every 8 hours
Children <20 kg: 40 mg/kg/day in divided doses every 8 hours. This dosage should not exceed the recommended adult dosage.
Children weighing 20 kg or more should be dosed according to the adult recommendations.

Urethritis due to non-*penicillinase producing N. gonorrhoeae 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) 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. Cases of gonorrhea with a suspected lesion of syphilis should have dark field examinations before receiving amoxicillin, and monthly serological tests for a minimum of four months.

For prevention of endocarditis

Adults: 3 g orally 1 hour before procedure; then 1.5 g 6 hours after the initial dose.

Children: 50 mg/kg (not to exceed adult dose) orally 1 hour before procedure; then 25 mg/kg 6 hours after the initial dose.

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 and 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 gonorrhoeae, 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 beta-hemolytic streptococci to prevent the occurrence of acute rheumatic fever or glomerulonephritis.

In order to obtain optimal absorption of drug from pms-AMOXICLLIN capsules they should be administered between meals with a glass of water (250 mL or 8 fl. oz.).

PHARMACEUTICAL INFORMATION

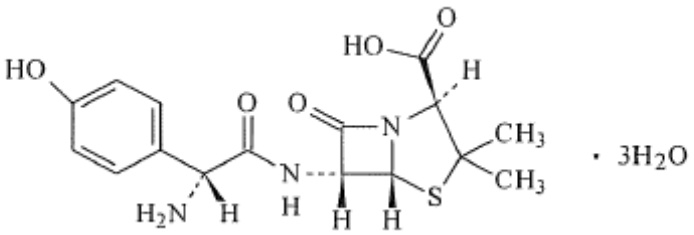
DRUG SUBSTANCE:

Trade Name: pms-AMOXICLLIN

Proper Name: Amoxicillin Trihydrate

Chemical Name: Trihydrate of 6-[D-(-)-alpha-amino-4-hydroxyphenyl-acetamido] penicillanic acid.

Structural Formula:



Molecular Formula: $C_{16}H_{19}N_3O_5S \cdot 3H_2O$

Molecular Weight: 419.5 g/mol

Description: Amoxicillin trihydrate is a white practically odorless crystalline powder, slightly soluble in water and in methanol; insoluble in benzenes, in chloroform and in ether.

STABILITY AND STORAGE RECOMMENDATIONS:

Capsules
Store between 15°C and 30°C. Unit dose strips should be stored between 15°C and 25°C and protected from high humidity.

Granules for Oral Suspension
Store at room temperature (between 15°C -30°C). Keep bottle tightly closed.

Reconstituted Solution
The reconstituted formulation is stable for 14 days under refrigeration (between 2°C -8°C) or 7 days at room temperature (between 15°C -30°C).

DIRECTIONS FOR DISPENSING ORAL SUSPENSION:

Prepare these formulations at the time of dispensing. For ease in preparation, add water to the bottle in two portions and shake well after each addition. Add the total amount of water as directed on the labeling of the package being dispensed.

The reconstituted formulation is stable for 14 days under refrigeration (6°C) or 7 days at room temperature (25°C).

pms-AMOXICLLIN Granules for Oral Suspension 125 mg/5 mL and 250 mg/5 mL: After reconstitution each 5 mL suspension contains amoxicillin trihydrate equivalent to 125 mg or 250 mg amoxicillin. Sugar content/5 mL: 125 mg suspension 2.91 g equivalent to 11.6 cal.; 250 mg suspension 2.75 g equivalent to 11 .0 cal.

AVAILABILITY OF DOSAGE FORMS

Hard Gelatin Capsules:

pms-AMOXICLLIN 250 mg Capsules:
250 mg amoxicillin (as the trihydrate) in # 1 capsules with opaque scarlet cap and opaque gold body, printed in white "AMOXICILLIN" on the gold body and "P/250" on opposing cap of the capsule

pms-AMOXICLLIN 500 mg Capsules:
500 mg amoxicillin (as the trihydrate) in #0 capsules with opaque scarlet cap and opaque gold body, printed in white "AMOXICILLIN" and "P/500" on opposing cap and Body portions.

pms-AMOXICLLIN Granules for Oral Suspension 125 mg/5 mL and 250 mg/5 mL:

Each 5 mL of reconstituted suspension contains amoxicillin trihydrate equivalent to 125 or 250 mg amoxicillin.

125 mg supplied in bottles of 75 mL, 100 mL and 150 mL.

250 mg supplied in bottles of 75 mL, 100 mL and 150 mL.

MICROBIOLOGY

In vitro studies with amoxicillin have demonstrated the susceptibility of the following gram-positive bacteria: beta-hemolytic streptococci, Streptococcus pneumoniae, D. pneumoniae, non-penicillinase-producing staphylococci, and Streptococcus faecalis. It is active in vitro against many strains of Haemophilus influenzae, Neisseria gonorrhoeae and Proteus mirabilis. Because amoxicillin does not resist destruction by penicillinase, it is not effective against penicillinase-producing bacteria, particularly resistant staphylococci.

Amoxicillin is not active against all Pseudomonas aeruginosa, indole-positive Proteus species, Serratia marcescens, Klebsiella, and Enterobacter species.

Disc Susceptibility Tests: Quantitative methods that involve the measurement of the diameters of zones of inhibition can be used to estimate micro-organism sensitivity to a particular antibiotic. A procedure which involves the use of discs impregnated with a particular antibiotic has been described for the ampicillin class of antibiotics. Interpretations correlate diameters of the zones of inhibition with MIC values for amoxicillin. With this procedure, using a 10 pg disc, a zone of 29 mm or more is classified as "susceptible" and indicates that the infecting organism is likely to respond to therapy. A zone of 20 mm or less is classified as "resistant" and indicates that the infecting organism is not likely to respond to therapy. A zone of 21 -28 mm is classified as "intermediate susceptibility" and indicates that the organism would be susceptible if high dosages are used, or if the infection is confined to tissues and fluids (e.g., urine), in which antibiotic levels are attained.

The *in vitro* activity of amoxicillin against selected organisms has been reported by Sutherland et al. and Sabto et al. shown in the following tables:

Table I: *In Vitro* Activity of Amoxicillin Against Gram-Positive Cocci, H. Influenzae and N. Gonorrhoeae

Organism	No. of Strains	Minimum Inhibitory Concentration (μg/mL)								
		.005	0.01	0.02	0.03	0.05	0.12	0.25	0.5	1.0
Staphylococcus aureus	29					3	20	6		
Beta-hemolytic streptococci	28		25	3						
Streptococcus pneumoniae	23		9	6	2	6				
Streptococcus faecalis	53							3	39	11
H. influenzae	98						20	41	29	8
N. gonorrhoeae	13		1	3		3	1	5		

Table II: *In Vitro* Activity of Amoxicillin Against Gram-Negative Bacilli

Organism	No. of Strains	Minimum Inhibitory Concentration (μg/mL)							
		1.25 or less	2.5	5.0	12.5	25	50	100	>100
Proteus mirabilis	90	38	28	11					13
Shigella sonnei	26		4	11	4		1	1	5
Salmonella species	20	10	8						2
Klebsiella-Enterobacter	29		1				1	2	25
Serratia marcescens	18			1		1	3	6	7
E. coli	206	5	13	115	46	2	1	1	23

The minimum inhibitory concentrations of amoxicillin against all micro-organisms with the exception of 5 strains of Streptococcus pneumoniae were measured by serial dilution in agar.[36] The minimum inhibitory concentration against these strains of Streptococcus pneumoniae was estimated using the tube dilution method with Levinthal's medium.[34]

PHARMACOLOGY

Amoxicillin is stable in the presence of gastric acid. pms-AMOXICLLIN is rapidly and well absorbed after oral administration to fasting subjects. It was found in a recent study that peak serum antibiotic levels were reduced by 50% in subjects receiving amoxicillin immediately following a standard meal. Reducing the dose-water volume given with amoxicillin from 250 to 25 mL in fasted subjects also caused a significant reduction in serum amoxicillin levels. This may be due to the low water solubility of amoxicillin trihydrate (1 g in 370 mL water). In addition, food ingestion immediately before dosing also reduced the urinary excretion.

Peak serum levels are attained between 1 and 2 hours after drug administration. Amoxicillin diffuses readily into most body tissues and fluids, with the exception of brain and spinal fluid. Amoxicillin is excreted largely unchanged in the urine while 10-25% of the administered dose is excreted in the form of penicilloic acid. The excretion of amoxicillin can be delayed by concurrent administration of probenecid. Amoxicillin is not highly protein bound. In blood serum, amoxicillin is approximately 17-1 8% protein bound compared to 59% for penicillin G.

The following amoxicillin mean serum levels were found following the administration of 250 mg capsules of pms-AMOXICLLIN to 12 healthy adult volunteers:

Time (hr.)	0.5	1.0	1.5	2	3	4	5	7
Mean Serum Levels (μg/mL)	0.81	2.96	3.17	3.10	2.22	1.12	0.50	0.11

Peak blood serum levels averaged 3.8 mcg/mL (range 2.35 to 6.38) and the T_{max} was 1.50 hr. The mean biological half-life (t ½) was found to be 55.8 minutes with a mean elimination rate constant K_{el} of 0.7456 $hr.^{-1}$.

Twelve normal male subjects participated in a bioavailability study of pms-AMOXICLLIN Granules for Suspension. Each subject was given 5 mL (250 mg) of reconstituted pms-AMOXICLLIN Granules for Suspension in a single dose.

The following amoxicillin mean serum levels were found:

Time (hr.)	0.5	1.0	1.5	2	3	4	5	7
Mean Serum Levels (μg/mL)	3.26	4.19	3.40	2.56	1.65	0.98	0.43	0.10

Peak plasma concentrations from 2.65 to 5.75 mcg/mL were obtained with a mean C_{max} of 4.24 $\pm$ 0.74 mcg/mL. The time required to reach peak concentrations ranged from 0.5 to 1.5 hours, with a T_{max} mean of 1 .00 $\pm$ 0.21 hr.

The AUC's calculated for 0 to 7 hours ranged from 8.475 to 12.865 mcg-hours/mL. The mean AUC was 10.71 3 $\pm$ 1.443 mcg-hours/mL. The mean biological half-life for pms-AMOXICLLIN Granules far Suspension was 26.4 minutes. The mean elimination rate constant (K_{el}) was 1.57 hour ^{1}.

The administration of 500 mg amoxicillin to healthy fasting subjects has been reported to produce peak mean serum levels of 10.8 mcg/mL and 6.75 mcg/mL. Additional studies in healthy volunteers with normal renal function receiving 500 mg doses, indicated that peak serum levels could vary from 5.0 to 10.8 mcg/mL. Serum amoxicillin half-life values reported in the literature vary from 1-1.3 hours. About 60-80% of an oral dose of amoxicillin is excreted in the urine. In the presence of renal impairment the serum half-life increases (between 7 and 10 hours), necessitating a reduction in the dosage administered.

TOXICOLOGY

Acute Toxicity

The fallowing LD_{50} values for amoxicillin expressed in mg/kg of body weight have been reported.

Species	Route of Administration		
	P.O.	I.P.	S.C.
Mouse	> 10,000	4350	> 6,000
Rat	> 8,000	4900	> 6,000
Dog	> 3,000	-	-

Sub-acute Toxicity

Rats

In one study male and female rats were orally administered 500 mg/kg amoxicillin daily for 21 days. With the exception of significantly greater ($p<0.01$) BUN values in the female test group compared with controls, there were no toxic effects on the organs, tissues or fluids of the body, nor any adverse effects on food consumption, weight gain, or efficiency of food utilization reported in the study.

Histopathologic evaluation of tissues revealed a minimal degree of fatty change in livers of treated females. However, this finding was not considered a toxic change but related to a possible alteration in the intestinal flora.

Dogs

One male and one female dog were dosed orally with 250 mg/kg amoxicillin daily for 14 days. During the period of observation, no deaths occurred, no adverse changes in body weight and no effect on food consumption was found. Laboratory values were found within normal limits. At post-mortem, no gross or microscopic abnormalities were reported and organ weights were within normal limits.

Chronic Toxicity

Rats

In one study male and female rats were given oral doses of 200, 500 and 2000 mg/kg/day amoxicillin, 6 days a week for 26 weeks. No apparent disturbances in absolute organ weights of either treated male or female animals were noted nor was any histologic evidence of response to treatment observed.

In another study, 3 groups of Sprague-Dawley rats were given oral doses of 200, 500 and 2000 mg/kg of amoxicillin for a test period of 13-1 5 weeks. There were no gross or histologic changes observed in the treated rats that were considered related to the administration of amoxicillin. Some

of the intermediate and low-dose groups were shown to exhibit body weight gains lower (males) or slightly higher (females) than those of the control animals.

Dogs
It has been reported that amoxicillin was administered orally at doses of 200, 500 and 2000 mg/kg/day to male and female dogs for a period of 6 months. (Groups consisted of 6 male and 6 female dogs initially, but after 3 months dosing, each group was reduced to 3 dogs).

During the first six weeks of treatment, occasional bouts of vomiting, one to four hours after dosing, were reported in dogs receiving 2000 mg/kg/day and 4 bouts of vomiting were recorded in dogs receiving the intermediate dose of 500 mg/kg/day. Grey colored feces were seen on very isolated occasions in dogs treated at high and intermediate dose levels only. On seven occasions it involved dogs receiving the highest dose level (2000 mg/kg/day) and on three occasions dogs receiving the intermediate dose level (500 mg/kg/day).

Body weight gains of treated males were reported to be not significantly different from those of controls, but all dosed females increased in weight at a significantly slower rate than did the controls. This factor was reported to be attributable to excessive weight gain in the control animals. Food and water consumption was not affected. No abnormalities of the eyes were observed attributable to amoxicillin.

In a second study 2 groups of Beagle dogs were given oral doses of 500 mg/kg and 200 mg/kg of amoxicillin for 13 weeks. There were no gross or histologic changes reported in the treated dogs that were considered related to the administration of amoxicillin.

Effects on Fertility and Reproductive Performance

Rats
Daily doses of 200 and 500 mg/kg amoxicillin were administered orally in one reported study. Male rats that had attained a minimum age of 40 days were treated for 63 days and sexually mature females for 14 days prior to mating. Dosing continued throughout the remainder of the investigation. The duration of gestation was unaffected by treatment at either dosage. It was noted that pregnancy rate at 500 mg/kg was slightly lower than that of controls at the first and second matings. At 200 mg/kg, the pregnancy rate was essentially comparable to control values at both matings. The chronologic sequence of mating was comparable for all groups; at 500 mg/kg the total number of animals showing evidence of mating was slightly lower than that of controls at both pairings. Pre- and post-implantation losses were comparable for all groups at the first and second pregnancies.

Among the rats allowed to rear their young, litter sizes, litter weights, mean pup weights and the pup mortality rates for the group dosed at 500 mg/kg amoxicillin were comparable to control values at birth, 4 and 21 days postpartum. Mean pup weights and pup mortality rates were similarly unaffected by 200 mg/kg amoxicillin; but litter sizes and litter weights were lower than control values from birth through lactation. These differences were considered to be unrelated to treatment. No abnormal young were observed.

Effects on Pregnancy

Mice

It has been reported that amoxicillin administered at doses of 200, 500 and 2000 mg/kg/day orally during days 6-1 5 of pregnancy produced no obvious signs of reaction to treatment or deaths among parent animals. Body weight changes of pregnant dams were comparable for all groups, as was the pregnancy rate.

Fetal loss was significantly higher among all test groups than among controls. However, as implantation rates also tended to be higher at the 500 and 2000 mg/kg doses, litter sizes were only marginally, and not significantly, lower than the control value. Litter sizes and implantation rate also tended to lie at or above the upper limit of the laboratory range. Due to the latter factors, the biologic importance of the increased fetal loss was uncertain. It was noted that mean pup weights were comparable for all groups. The distribution of skeletal variants was considered to be unaffected by treatment at any dosage. A significantly higher proportion of pups with cervical ribs was found in the 200 mg/kg dose group. Cervical rib and 14th rib are the prolongations of the transverse processes of the cervical or lumbar vertebrae. Supernumerary ribs have an incidence which depends on the strain of animals. Cervical ribs are not abnormalities and have no pathologic significance.

In this experiment the incidence of cervical ribs was 12% in control rats and 16% in the drug-treated groups if the three groups are calculated together. If the groups are considered individually, then in the lowest dose group (200 mg/kg) the incidence of cervical ribs was 24%, which is, statistically, significantly higher than in the controls. This finding was not considered to be drug related since at the 500 mg/kg dose level the incidence of cervical ribs was significantly lower than in controls. At the highest dose level (2000 mg/kg) the incidence of cervical ribs was 17%, similar to the controls. The incidence of visceral abnormalities was not significantly affected at any dose level.

Rats

Amoxicillin was administered at doses of 200 mg/kg, 500 mg/kg and 1000 mg/kg orally during gestation from day 6 through 15. Amoxicillin did not modify pregnancy, percentage of resorption and did not produce fetal abnormalities as compared with negative control rats.

Effects on Peri- and Post-Natal Development of the Rat

Amoxicillin was administered orally at 200 and 500 mg/kg/day from day 15 of gestation through lactation to 21 days post-partum. Body weight gain, pregnancy rate, and the duration of gestation of parent animals were unaffected by treatment at any dosage. There was a significant dose-related trend to lower litter size and weight at birth. This persisted through lactation to weaning despite reduced pup mortality and increased mean pup weight in the test groups compared with controls. No abnormal young were observed.

REFERENCES

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PART III: CONSUMER INFORMATION

[Pr]pms-AMOXICLLIN
Amoxicillin (as amoxicillin trihydrate)

This leaflet is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about pms-AMOXICLLIN. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:
pms-AMOXICLLIN is used to treat bacterial infections, such as:

- infections of upper respiratory tract (ear, nose, tonsils and throat);
- infections of lower respiratory tract (bronchi and lungs)
- urinary tract infections
- infections of the skin
- Gonorrhea

Antibacterial drugs like pms-AMOXICLLIN treat only bacterial infections. They do not treat viral infections such as the common cold. Although you may feel better early in treatment, pms-AMOXICLLIN should be used exactly as directed. Misuse or overuse of pms-AMOXICLLIN could lead to the growth of bacteria that will not be killed by pms-AMOXICLLIN (resistance). This means that pms-AMOXICLLIN may not work for you in the future. Do not share your medicine.

What it does:
Amoxicillin interferes with the synthesis of the bacterial cell wall, contributing to bacterial death.

When it should not be used:
You should not take pms-AMOXICLLIN if:

- you have ever had an unusual hypersensitivity or allergic reaction to penicillin or to any other component of this product
- have infectious mononucleosis (suspected or confirmed)

What the medicinal ingredient is:
pms-AMOXICLLIN contains the active ingredient called amoxicillin.

What the important nonmedicinal ingredients are:
pms-AMOXICLLIN also contains the following non-medicinal ingredients:

250 mg and 500 mg capsules: Colloidal Silicon Dioxide, EGC Size #2 or Size #0, Dry-Flo Starch, Magnesium stearate, Sodium lauryl sulfate, Talc

125 mg/5 mL and 250 mg/5 mL Granules for Oral Suspension: Artificial Cherry Raspberry Flavor, FD&C Red #40, Silicon Dioxide, Sodium Benzoate, Sodium Citrate, Sucrose, Xanthan Gum

If you are on a special diet, or if you are allergic to any substance, ask your doctor or pharmacist whether any of these ingredients may cause a problem.

What dosage forms it comes in:
pms-AMOXICLLIN is available in four different forms, such as capsules and Granules for Oral Suspension.

- pms-AMOXICLLIN 250 mg Capsules in # 1 capsules with opaque scarlet cap and yellow body
- pms-AMOXICLLIN 500 mg Capsules in #0 capsules with opaque scarlet cap and yellow body
- pms-AMOXICLLIN Granules for Oral Suspension 125 mg/5 mL and 250 mg/5 mL

WARNINGS AND PRECAUTIONS

Serious and occasionally fatal allergic (hypersensitivity) reactions have been reported in patients on penicillin therapy (see Side Effects and Serious Side Effects)

BEFORE you use pms-AMOXICLLIN talk to your doctor or pharmacist if:

- **you have previous hypersensitivity reactions to penicillins and other allergens**
- **you have any allergies to this drug or its ingredients or components of the container**
- **you are taking anticoagulants – please advise of any signs of bleeding including prolonged bleeding from cuts, increased menstrual flow, vaginal bleeding, nosebleeds, bleeds from gums brushing, unusual bleeding or bruising, red or brown urine or red or black stools**
- **you have kidney problems. Your doctor may monitor your kidney and liver functions during prolonged therapy with pms-AMOXICLLIN.**

As the safety of pms-AMOXICLLIN in the treatment of infections in pregnancy is not established, your doctor will determine if pms-AMOXICLLIN treatment is suitable for you.

INTERACTIONS WITH THIS MEDICATION

As with other medicines, interactions with other drugs are possible. Therefore, do not take any other medicines unless you have discussed the matter with your physician or your pharmacist.

Talk to your doctor before taking the following drugs, as there may be interactions:

- Methotrexate (anti-cancer agent), probenecid (gout treatment), tetracyclines (antibiotics), oral contraceptives, anticoagulants (e.g. warfarin).

Before taking pms-AMOXICLLIN make sure your doctor knows about all the medications you are taking, including those not prescribed by your doctor. It may be necessary to change the dose,

take other precautions, or perhaps stop one of the medicines. This applies to both prescription and non-prescription medicines.

PROPER USE OF THIS MEDICATION

Usual dose:
It is very important that you take this medicine exactly as your doctor tells you in order to get the best results and reduce the chance of side effects.

Infections of upper respiratory tract (ear, nose, tonsils and throat) and Infections of urinary tract
The usual dosage for the treatment of upper respiratory tract and urinary infections is one 250 mg every 8 hours for adults.

For children **under 20 kg**, the dose should be calculated by your doctor considering 20 mg/kg/day in divided doses every 8 hours. In severe infections the recommended dose for adults is 500 mg every 8 hours and for children **under 20 kg**, 40 mg/kg/day in divided doses every 8 hours. **For children over 20 kg, the adult dose should be used**.

Infections of lower respiratory tract (bronchi and lungs)
The recommended dose for adults is 500 mg every 8 hours and for children 40 mg/kg/day in divided doses every 8 hours.

The children's dosage should not exceed that recommended for adults. Children weighing more than 20 kg should be dosed according to the adult recommendations.

For the oral suspension, please administer using the syringe provided by your pharmacist to ensure the correct dose is given.

Overdose:

If you think you have taken too much pms-AMOXICLLIN, contact your healthcare professional, hospital emergency department or regional poison control centre immediately, even if there are no symptoms.

Hemodialysis would be the proper treatment in case of severe overdose.

Activated charcoal may be administered to aid in the removal of unabsorbed drug. General supportive measures are recommended.

Missed Dose:
Try to take your dose as per your doctor's recommendations. If you/your child miss a dose, take it as soon as you remember. But, if it is almost time for the next dose, do not take the missed dose. Instead, take the next scheduled dose. Do not try to make up for the missed dose by taking a double dose next time.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Like all medicines, pms-AMOXICLLIN may cause unwanted reactions, so called side effects. Most patients do not experience side effects from pms-AMOXICLLIN. Examples of occasional side effects include:

- Nausea
- Vomiting and diarrhea
- Skin rashes

If you suffer severe, persistent diarrhea (bloody or watery), with or without fever, abdominal pain and vomiting, you may have Clostridium difficile colitis (bowel inflammation). If this happens, stop taking pms-AMOXICLLIN and call your healthcare professional immediately.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect		**Talk with your doctor or pharmacist**		**Stop taking drug and seek immediate emergency medical attention**
		Only if severe	**In all cases**	
Common	*Allergic reactions* Skin rash, skin eruption or other effect on the skin or eyes			✓
Uncommon	*Gastrointestinal (nausea, vomiting, diarrhea, bloody stool)*			✓
	Serious Allergic Reactions- anaphylaxis – (swollen nose, eyes, throat, difficulty breathing, and serious skin reactions such as blistering, peeling skin, rash)			✓
	Kidney disorder (excretion of crystals in the urine – crystalluria)			✓

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect		Talk with your doctor or pharmacist		Stop taking drug and seek immediate emergency medical attention
		Only if severe	In all cases	
	Liver disorder yellowing of the skin and eyes (Jaundice), abdominal pain, nausea, cytolytic hepatitis (destruction of liver cells),			✓
	Oral (glossitis – black "hairy" tongue and stomatitis, tooth discoloration in children (brown, yellow or gray staining)		✓	
	Central Nervous System (dizziness, anxiety, insomnia, confusion, behavioural changes		✓	
	Blood problems such as leukopenia (low white blood cell count), neutropenia (low blood cell count)		✓	

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

REPORTING SIDE EFFECTS

You can report any suspected side effects associated with the use of health products to
Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

HOW TO STORE IT

Do not take *pms-AMOXICLLIN* past the expiry date shown on the pack.

Store your *pms-AMOXICLLIN* as follows:
For Capsules: store between 15ºC and 30ºC. Blister strips should be stored between 15ºC and 30ºC and protected from high humidity.

Granules for oral suspension: store at room temperature between 15ºC and 30ºC. Keep bottle tightly closed.

Reconstituted Solution: The reconstituted solution is stable for 14 days under refrigeration (between 2ºC -8ºC) or 7 days at room temperature (between 15ºC and 30ºC).

Always remember
This medicine has been prescribed to you for your current medical problem only. Do not give it to other people.

Keep out of reach of children.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals, can be obtained by contacting the sponsor, Pharmascience Inc. at, 1-888-550-6060.

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