PRODUCT MONOGRAPH

[Pr]phl-AMOXICILLIN

(Amoxicillin Trihydrate USP)

Capsules 250 and 500 mg

and

Granules for Oral Suspension

125 mg/5mL and 250 mg/5mL

Antibiotic

PHARMEL INC.
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Montréal, Québec
H1Z 2X4

Date of Preparation :
December 17, 2004

Control #: 095791

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THERAPEUTIC CLASSIFICATION

Antibiotic

ACTIONS AND CLINICAL PHARMACOLOGY

Amoxicillin trihydrate exerts its bactericidal action by interfering with bacterial cell wall synthesis.

INDICATIONS AND CLINICAL USE

Amoxicillin trihydrate 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 trihydrate 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 trihydrate on the basis of clinical judgment while awaiting bacteriologic tests to determine its antimicrobial sensitivity.

Amoxicillin trihydrate 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.

CONTRAINDICATIONS

A history of a previous hypersensitivity reaction to any of the penicillins or cephalosporins is a contraindication. Amoxicillin trihydrate 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 who have experienced severe hypersensitivity reactions when treated with cephalosporins. Before initiating therapy with

a penicillin, careful inquiry should be made concerning previous hypersensitivity reactions to penicillins, cephalosporins and other allergens. If an allergic reaction occurs, administration of amoxicillin trihydrate 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.

PRECAUTIONS

Periodic assessment of renal, hepatic and hematopoietic functions should be made during prolonged therapy with amoxicillin trihydrate. Because amoxicillin trihydrate 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 trihydrate in the elderly.

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

The safety of amoxicillin trihydrate in the treatment of infections during pregnancy has not been established. If the administration of amoxicillin trihydrate 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 trihydrate.

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 amoxicillin trihydrate.

Gastrointestinal: Nausea, vomiting and diarrhea.

Hypersensitivity Reactions: Skin rashes and urticaria have been reported frequently. A few cases of exfoliative dermatitis and erythema multiforme 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, amoxicillin trihydrate should be discontinued unless, in the opinion of the physician, the condition being treated is life threatening and amenable only to amoxicillin trihydrate therapy. Serious anaphylactic reactions require the immediate use of epinephrine, oxygen and intravenous steroids.

Liver: 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 trihydrate.

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 a hypersensitivity phenomena.

Oral: Glossitis, black "hairy" tongue and stomatitis.

CNS Reactions: As with other penicillins, acute and chronic toxicity is not a clinical problem. 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. 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, the above toxic reactions are likely to occur.

TREATMENT OF OVERDOSE

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.

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 nonpenicillinase 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 darkfield examinations before receiving amoxicillin trihydrate, 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 gonorrhoea, 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 amoxicillin trihydrate capsules they should be administered between meals with a glass of water (250 mL or 8 fl. oz.).

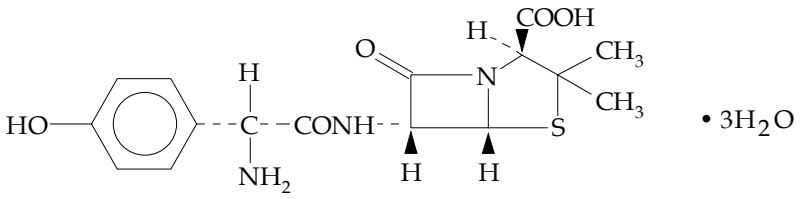
PHARMACEUTICAL INFORMATION

DRUG SUBSTANCE:

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

Description: Amoxicillin trihydrate is a white practically odourless 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° and 30°C.

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

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

DIRECTIONS FOR DISPENSING ORAL SUSPENSION:

Prepare this formulation 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).

phl-AMOXICILLIN (amoxicillin trihydrate) 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

phl-AMOXICILLIN (amoxicillin trihydrate) Hard Gelatin Capsules:

250 mg Capsules: 250 mg amoxicillin (as the trihydrate) in #1 capsules with opaque scarlet cap and yellow body, imprinted “P 250" on cap and “Amoxicillin"on body. Bottles of 500 and 1000.

500 mg Capsules: 500 mg amoxicillin (as the trihydrate) in #0 capsules with opaque scarlet cap and yellow body, imprinted “P 500" on cap and “Amoxicillin"on body. Bottles of 250 and 500.

phl-AMOXICILLIN 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 100 mL and 150 mL.
250 mg supplied in bottles of 100 mL and 150 mL.

MICROBIOLOGY

In vitro studies with amoxicillin trihydrate 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 trihydrate does not resist destruction by penicillinase, it is not effective against penicillinase producing bacteria, particularly resistant staphylococci.

Amoxicillin trihydrate 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 trihydrate. With this procedure, using a 10 µg 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 to 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 trihydrate against selected organisms has been reported by Sutherland *et al.* and Sabto *et al.* as shown in the following tables:

Table 1. *In vitro* Activity of Amoxicillin trihydrate Against Gram-Positive Cocci, H. Influenzae and N. Gonorrhoeae[34,36]

Organism	No. of Strains	Minimum Inhibitory Concentration (µg/mL)								
		0	0	0	0	0	0,1	0,3	0,5	1
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. gonorrhoeae13		1	3		3	1	5			

Table 1. *In vitro* Activity of Amoxicillin Trihydrate Against Gram-Negative Bacilli[36]

Organism	No. of Strains	Minimum Inhibitory Concentration (µg/mL)							
		1.25 or less	2,5	5	13	25	50	100	>100
Proteus mirabilis	90	38	28	11					13
Shigella sonnei26		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 trihydrate against all micro organisms with the exception of 5 strains of Streptococcus pneumoniae were measured by serial dilution in agar.[6] The minimum inhibitory concentration against these strains of Streptococcus pneumoniae was estimated using the tube dilution method with Levinthal's medium.[34]

PHARMACOLOGY

Amoxicillin trihydrate is stable in the presence of gastric acid. Amoxicillin trihydrate 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 trihydrate immediately following a standard meal. Reducing the dose-water volume given with amoxicillin trihydrate from 250 to 25 mL in fasted subjects also caused a significant reduction in serum amoxicillin trihydrate 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 trihydrate diffuses readily into most body tissues and fluids, with the exception of brain and spinal fluid. Amoxicillin trihydrate is excreted largely unchanged in the urine while 10 to 25% of the administered dose is excreted in the form of penicilloic acid. The excretion of amoxicillin trihydrate can be delayed by concurrent administration of probenecid. Amoxicillin trihydrate is not highly protein bound. In blood serum, amoxicillin trihydrate is approximately 17 to 18% protein bound compared to 59% for penicillin G.

The following amoxicillin trihydrate mean serum levels were found following the administration of 250 mg capsules of amoxicillin trihydrate 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 µg/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 amoxicillin trihydrate Granules for Suspension. Each subject was given 5 mL (250 mg) of reconstituted amoxicillin trihydrate Granules for Suspension in a single dose.

The following amoxicillin trihydrate 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 µg/mL were obtained with a mean C_{max} of 4.24 ± 0.74 µg/mL. The time required to reach peak concentrations ranged from 0.5 to 1.5 hours, with a T_{max} mean of 1.00 ± 0.21 hr.

The AUC's calculated for 0 to 7 hours ranged from 8.475 to 12.865 µg-hours/mL. The mean AUC was 10.713 ± 1.443 µg-hours/mL. The mean biological half-life for amoxicillin trihydrate Granules for Suspension was 26.4 minutes. The mean elimination rate constant (K_{el}) was 1.57 hour $^{-1}$.

The administration of 500 mg amoxicillin trihydrate to healthy fasting subjects has been reported to produce peak mean serum levels of 10.8 µg/mL and 6.75 µg/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 µg/mL. Serum amoxicillin trihydrate half-life values reported in the literature vary from 1 1.3 hours. About 60 80% of an oral dose of amoxicillin trihydrate 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 following LD_{50} values for amoxicillin trihydrate expressed in mg/kg of body weight have been reported.

SPECIES	ROUTE OF ADMINISTRATION		
	P.O.	I.P.	S.C.
Mouse	>10,000	4350	> 6000
Rat	> 8,000	4900	> 6000
Dog	> 3,000		

Sub-acute Toxicity

Rats:

In one study male and female rats were orally administered 500 mg/kg amoxicillin trihydrate 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 trihydrate 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 trihydrate, 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 trihydrate for a test period of 13 to15 weeks. There were no gross or histologic changes observed in the treated rats that were considered related to the administration of amoxicillin trihydrate. 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 trihydrate 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 coloured 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 trihydrate.

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

Effects on Fertility and Reproductive Performance

Rats:

Daily doses of 200 and 500 mg/kg amoxicillin trihydrate 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 trihydrate 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 trihydrate; 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 trihydrate administered at doses of 200, 500 and

2000 mg/kg/day orally during days 6 to 15 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 trihydrate was administered at doses of 200 mg/kg, 500 mg/kg and 1000 mg/kg orally during gestation from day 6 through 15. Amoxicillin trihydrate 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 trihydrate 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.

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