# PRODUCT MONOGRAPH

## AMOXICILLIN CAPSULES

**Amoxicillin Capsules BP**

**250 mg & 500 mg Capsules**

**250 mg amoxicillin as amoxicillin trihydrate**
**500 mg amoxicillin as amoxicillin trihydrate**

**ANTIBIOTIC**

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250 mg amoxicillin as amoxicillin trihydrate
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## THERAPEUTIC CLASSIFICATION

Antibiotic

## ACTIONS AND CLINICAL PHARMACOLOGY

AMOXICILLIN CAPSULES (Amoxicillin Capsules BP) are effective orally against Gram-positive organisms as well as against a variety of Gram-negative organisms.

Amoxicillin exerts a bacterial action against sensitive organisms during the stage of active multiplication. This action involves the inhibition of the biosynthesis of the bacterial cell wall mucopeptide. The growing cell wall is thus weakened and undergoes lysis. This inhibitory action is similar for ampicillin and benzyl penicillin. Because it is destroyed by beta-lactamase, amoxicillin is not effective against beta-lactamase-producing bacteria, particularly resistant staphylococci and beta-lactamase-producing strains of gonococci. All strains of *Pseudomonas* and most strains of *Klebsiella* and *Enterobacter* are resistant.

Amoxicillin is rapidly and well absorbed orally and diffuses readily into most body tissues and fluids with the exception of the brain and spinal fluid. A 500 mg oral dose of amoxicillin results in peak blood serum levels averaging 8 μg/mL. Following a 500 mg dose, measurable serum levels are present at 8 hours. The half life of amoxicillin is approximately an hour. Amoxicillin is excreted mostly unchanged in the urine. but its excretion can be delayed by concurrent administration of probenecid.

The bioequivalence of AMOXICILLIN CAPSULES and WYETH-AYERST AMOXIL® CAPSULES was assessed in a comparative, randomized, single dose, 2-way crossover bioavailability study, which compared the bioavailability of 500 mg strength capsules from each manufacturer, under fasting conditions in 24 young healthy male volunteers. Results are tabulated below and demonstrate that the two products are bioequivalent.

Summary of Table of Measured Comparative Bioavailability Data – Amoxicillin Capsules 500 mg

| Parameter | Geometric Mean and Arithmetic Mean (CV)[1] | | Ratio of Geometric Means (%) (CI)[2] |
|---|---|---|---|
| | Test Amoxicillin Capsules 500 mg (L) 132 FEB exp. 3/99 | Reference Amoxil® of Wyeth Ayerst 500 mg (L) 2AVE-15 exp 98 SEP | |
| $AUC_T$ (mg.h/mL) | 24.43 (19.7)<br>24.003 (19.1) | 25.11 (15.3)<br>24.803 (16.6) | 98.4 (93.3 – 101.0) |
| $AUC_I$ (mg.h/mL) | 24.88 (19.9)<br>24.441 (19.3) | 25.16 (15.3)<br>24.855 (16.4) | 98.2 (94.0 – 102.6) |
| $C_{MAX}$ (mg/mL) | 8.688 (28.9)<br>30.5 (24) | 9.804 (29.6)<br>32.0 (24) | 90.4 (80.9 – 101.0) |
| $T_{MAX}$ (h) | 1.715 (36.0) | 1.826 (43.3) | |
| T ½ (h) | 1.1149 (13.1) | 1.0688 (12.2) | |

INDICATIONS AND CLINICAL USES

AMOXICILLIN CAPSULES (Amoxicillin Capsules BP) are indicated in the treatment of infections due to susceptible strains of the following organisms: gram-negative: *Haemophilus influenzae, Escherichia coli, Proteus mirablis and Neisseria gonorrhoeae*; gram-positive: *Streptococci, Diplococcus pneumoniae* and non-ß-lactamase-producing staphylococci.

AMOXICILLIN CAPSULES (Amoxicillin Capsules BP) are indicated in the prophylaxis against alpha-haemolytic (viridans group) streptococci before dental, oral or upper respiratory tract surgery or instrumentation.

AMOXICILLIN CAPSULES (Amoxicillin Capsules BP) are indicated in the 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.

In emergency cases, before the causative organism is identified, therapy may be initiated, based on clinical judgement while awaiting the results of bacteriologic studies to isolate the infecting organism, and to determine its sensitivity.

## CONTRAINDICATIONS

The use of AMOXICILLIN CAPSULES (Amoxicillin Capsules BP) is contraindicated in individuals with a history of an allergic reaction to the penicillins or cephalosporins.

## WARNINGS

Serious and occasionally fatal hypersensitivity (anaphylactoid) reactions have been reported in patients on penicillin therapy. Although anaphylaxis occurs more frequently following parenteral therapy, it has happened in patients on oral penicillins. These reactions are more apt to occur in individuals with a history of sensitivity to multiple allergens. It has also been reported that individuals with a history of penicillin hypersensitivity have had severe reactions when treated with cephalosporins. Before initiating therapy with amoxicillin or any other penicillin, careful inquiry should be made concerning previous hypersensitivity reactions to penicillins, cephalosporins, or other allergens. If an allergic reaction occurs, amoxicillin therapy 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 used as indicated.

## PRECAUTIONS

Periodic assessment of renal, hepatic and haematopoietic function should be made during prolonged therapy with AMOXICILLIN CAPSULES (Amoxicillin Capsules BP).

Amoxicillin is excreted mostly by the kidney. The dosage administered to patients with renal impairment should be reduced proportionately to the degree of loss of renal function.

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

Evidence is lacking concerning safety of amoxicillin in the treatment of infections during pregnancy. Benefits of the drug should then be weighed against its possible hazards to the mother and child. Morbilliform rashes following the use of ampicillin and amoxicillin in patients with infectious mononucleosis are well documented. AMOXICILLIN CAPSULES (Amoxicillin Capsules BP) may therefore be contraindicated in cases where infectious mononucleosis is suspected or confirmed.

## Use in the Elderly

There are no known specific precautions for use of amoxicillin in the elderly. However, elderly patients are more likely to have an age-related decrease in renal function, which may require an adjustment in dosage.

## ADVERSE REACTIONS

As with other penicillins, presumably the most common untoward reactions will be related to sensitivity phenomena, similar to those observed with ampicillin. 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 amoxicillin trihydrate.

Gastrointestinal – nausea, vomiting and diarrhoea.

Hypersensitivity Reactions – erythematous maculopapular rashes and urticaria.

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 therapy should be discontinued unless, in the opinion of the physician, the condition is life-threatening and amenable only to amoxicillin.

Liver – moderate rises in serum glutamic oxaloacetic transaminase (SGOT), alkaline phosphatase and lactic dehydrogenase have been noted, but the significance of these findings is unknown.

Haemic and Lymphatic Systems – anaemia, thrombocytopenia, thrombocytopenic purpura, eosinophilia, leucopenia, 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.

## TREATMENT OF OVERDOSAGE

The 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. Dialysis is, therefore, the main form of treatment.

In case of severe allergic reactions, general supportive measures (if the patient is in shock) or symptomatic therapy similar to that applied to all cases of hypersensitivity are recommended.

## DOSAGE AND ADMINISTRATION

Infections of the ear, nose and throat due to streptococci, pneumococci, and non-β-lactamase-producing staphylococci. Infections of the upper respiratory tract due to H. influenzae;

Infections of the genitourinary tract due to *E.coli, P. mirabilis* and *S.faecalis*;

Infections of the skin and soft tissues due to streptococci, non-beta-lactamase producing staphylococci, and *E.coli*:

Usual Dose

| | |
|---|---|
| Adults and Children >20 kg: | 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. |

In severe infections, or infections where sensitivity determinations indicate higher blood levels may be advisable:

| | |
|---|---|
| Adults and Children >20 kg: | 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. |

Infections of the lower respiratory tract due to streptococci, pneumococci, non-β-lactamase-producing staphylococci and *H. influenzas*; and acute otitis media:

Usual Dose

| | |
|---|---|
| Adults and Children >20 kg: | 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. |

Urethritis due to non-β-lactamase-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 dose 50mg/kg dose (maximum 3 g) given with a single 25 mg/kg (up to 1 g) dose of probenecid.<br>However, probenecid is not recommended in children under 2 years of age. Appropriate therapy of presumptive or proven infection with *C.trachomatis* should be included as well. |

Before prescribing AMOXICILLIN CAPSULES (Amoxicillin Capsules BP), a dark field examination should be done in patients in whom syphilis is also suspected, and monthly serologic tests should be carried out for at least 4 months.

In treatment of chronic urinary tract infections, frequent bacteriologic and clinical evaluations are essential. Smaller doses than those recommended above should not be used. In stubborn infections, therapy may be required for several weeks, sometimes at doses higher than those recommended above. Concurrent bacteriologic sensitivity monitoring is recommended. It may be necessary to continue clinical and/or bacteriologic follow-up for several months after cessation of therapy.

Treatment must be continued for 48 to 72 hours beyond the time the patient has become asymptomatic or evidence of bacterial eradication has been obtained. At least 10 days' treatment is recommended for infections caused by Group A beta-haemolytic streptococci to prevent acute rheumatic fever or glomerulonephritis.

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. |

## PHARMACEUTICAL INFORMATION

### DRUG SUBSTANCE

PROPER NAME: Amoxicillin trihydrate

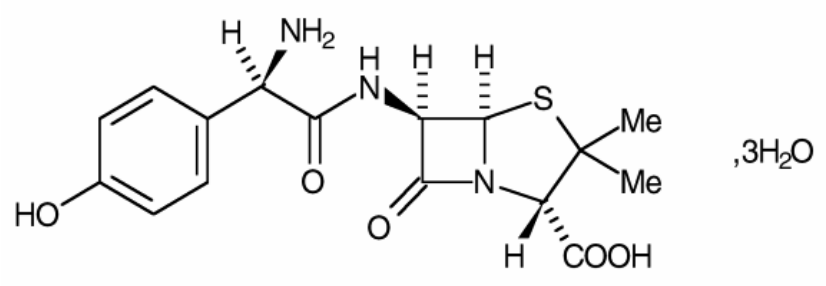
CHEMICAL NAME:

1. 4-Thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid, 6-[[amino(4-hydroxyphenyl)acetyl]amino]-3, 3-dimethyl-7-oxo-,trihydrate[2S-[2∝,5∝,6β(S*)]]-

2. (2S,5R,6R)-6-[(R)-( - )-2-Amino-2-(p-hydroxyphenyl) acetamido]-3, 3-dimethyl-7-oxo-4-thia-1-azabicyclo [3.2.0]heptane-2-carboxylic acid trihydrate.

MOLECULAR FORMULA: $C_{16}H_{19}N_3O_5S.3H_2O$

STRUCTURAL FORMULA




MOLECULAR WEIGHT: 419.46

DESCRIPTION: Amoxicillin trihydrate is a white or slightly off-white highly hygroscopic powder.

## DOSAGE FORMS

### COMPOSITION

AMOXICILLIN CAPSULES (Amoxicillin Capsules BP) contain amoxicillin as amoxicillin trihydrate 250 mg or 500 mg, with magnesium stearate and sodium lauryl sulphate in a gelatin capsule.

### STABILITY AND STORAGE RECOMMENDATIONS

AMOXICILLIN CAPSULES (Amoxicillin Capsules BP) should be stored at controlled room temperature (15°C – 25°C) protected from light and moisture. Keep out of reach of children.

### AVAILABILITY

AMOXICILLIN CAPSULES (Amoxicillin Capsules BP) 250 mg strength, is supplied as a size 2 green and white capsule imprinted 250 SP, in bottles of 100 and 500 capsules.

AMOXICILLIN CAPSULES (Amoxicillin Capsules BP) 500 mg strength, is supplied as a size 0 green and white capsule imprinted 500 SP, in bottles of 100 and 500 capsules.

## MICROBIOLOGY

Amoxicillin differs in vitro from benzylpenicillin in its gram-negative spectrum. It is highly effective in vitro against most strains of *H. influenzas*, non-β-lactamase-producing *N. gonorrhoeae, N. meningitides, E. coli, P. mirabilis, Brucella* species, *Salmonellae* and *Shigellae*.

Strains of gonococci which are relatively resistant to benzylpenicillin are more sensitive to amoxicillin.

In vitro studies have also demonstrated the sensitivity of most strains of the following gram-positive organisms: alpha-and beta- haemolytic streptococci, *D. pneumoniae*, non-β-lactamase producing staphylococci *B. anthracis*, and most strains of *Enterococci* and *Clostridia*. Amoxicillin is not effective against β-lactamase-producing organisms, particularly resistant staphylococci and recently described β-lactamase-producing strains of gonococci. All strains of *Pseudomonas* and most strains of *Klebsiella* and *Aerobacter* are also resistant. To estimate the in vitro susceptibility of organisms to amoxicillin, the standard Bauer-Kirby sensitivity disc method is recommended (using standard ampicillin sensitivity discs).

ACTIVITY OF AMOXICILLIN AGAINST GRAM-NEGATIVE ORGANISMS

M.I.C. (μg/mL) and % of strains.

| Organism | No. of Strains | 500 | 500 | 250 | 125 | 50 | 25 | 125 | 5.0 | 2.5 | 1.25 | 1.25 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| *E. Coli* | 84 | 13 | 1 | | | 1 | 1 | 10 | 59 | 10 | 5 | |
| *Proteus mirabilis* | 27 | 7 | | | | | | | 41 | 33 | 19 | |
| *Klebsiella aerogenes* | 22 | 59 | 18 | 5 | 9 | 4.5 | | | | 4.5 | | |
| *Pseudomonas aeruginosa* | 8 | 88 | | 12 | | | | | | | | |
| *Proteus species (1)* | 18 | 33 | 16.8 | 16.8 | 16.8 | 16.8 | | | | | | |
| *Salmonella species (2)* | 10 | | | | | | | | | | 80 | 20 |
| *Shigella sonnei* | 16 | | | 19 | 6 | 6 | | 2 | 38 | 19 | | |
| *Haemophilus influenzae* | 25 | | | | | | | | 8 | | 8 | 84<br>100 |
| *Neisseria** gonorrhoeae* | 5 | | | | | | | | | | | |

Serial dilution in agar except for *H.influenzae* – in chocolate blood agar

** Cultured strains, M.I.C. and % of strains 0.25 μg/ml (40%) and 0.5 μg/ml (60%).

One additional strain tested had a M.I.C greater than 5 μg/ml.

(1) 6 strains of *P.morganii*, 5 strains of *P. rettgeri* and 7 strains of *P. vulgaris.*

(2) *S.typhi* (2), *S.paratyphi A* (1), *S. paratyphi B* (1), *S. typhimurium* (4), *S. London* (1), *S.choleraesuis* (1).

ACTIVITY OF AMOXICILLIN AGAINST STAPHYLOCOCCI, STREPTOCOCCI, PNEUMOCOCCI AND ENTEROCOCCI

| Organism | No. of Strains | M.I.C.* (μg/mL) and % of strains | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | 1.25 | 0.5 | 0.25 | 0.12 | 0.05 | 0.02 | 0.012 | 0.005 |
| *S. aureus* | 24 | | | 17 | 79 | 4 | | | |
| β-haemolytic Streptococcus (*S.pyogenes)* | 20 | | | | | | 15 | 85 | |
| *S.pneumoniae* | 12 | | | | | 50 | 42 | 8 | |
| *S. facecalis* | 16 | 69 | 31 | | | | | | |

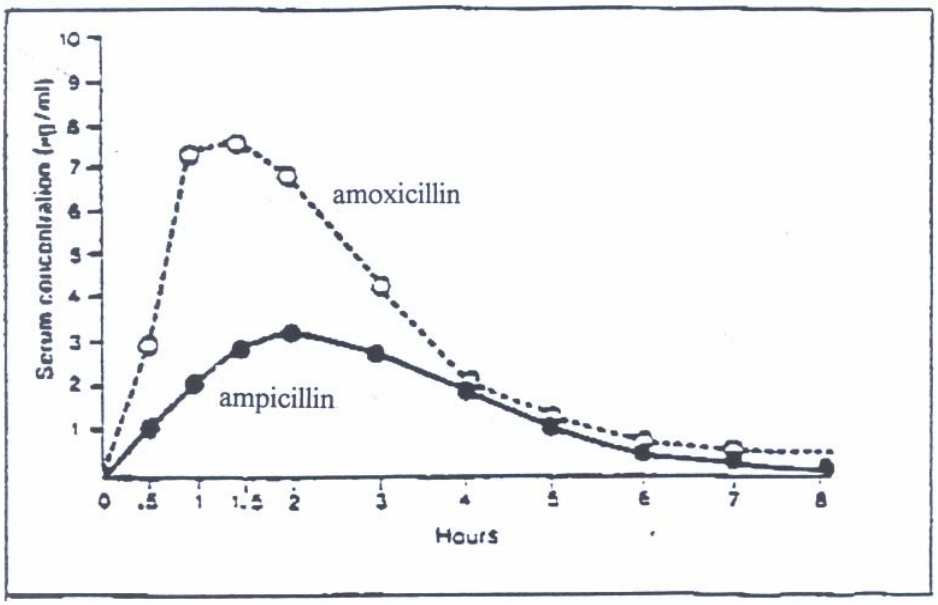
* Serial dilution in agar

## PHARMACOLOGY

Amoxicillin is stable in gastric acid and may be given without regard to meals. It is rapidly and well absorbed orally and diffuses readily into most body tissues and fluids, except the brain and spinal fluid.

Inflammation generally increases the permeability of the meninges to penicillins. This may also apply to amoxicillin. The half-lives of amoxicillin and ampicillin of approximately one hour are virtually identical. Amoxicillin is excreted unchanged in the urine; but its excretion can be delayed by concurrent administration of probenecid. Amoxicillin is not highly protein bound. In blood serum, amoxicillin is only 17% protein bound compared with 59% for penicillin G. A 500 mg dose of amoxicillin results in peak blood serum levels averaging 8 μg/mL, whereas the average peak serum level of a 500 mg dose of ampicillin is 4 μg/mL. A 500 mg oral dose of amoxicillin gives a peak serum level of approximately that obtained with the same intramuscular dose of ampicillin. Following a 500 mg dose, measurable serum levels are present even at 8 hours.

Mean Serum concentrations of ampicillin and amoxicillin for eight fasting volunteers after 500 mg oral doses




The "area under the curve" for amoxicillin is twice that of ampicillin.

Using special skin window technique to determine antibiotic concentrations, therapeutic levels of amoxicillin were found in tissue fluid. About 60% - 70% of an oral dose of amoxicillin is excreted in the urine compared with 30% - 40% of ampicillin. The finding of higher peak serum concentrations, larger "area under the curve", and greater urinary excretion of amoxicillin, with identical half-lives for both antibiotics, all reflect much better absorption of amoxicillin than that of ampicillin.

Amoxicillin and ampicillin in serum levels of fasting volunteers after oral administration of 500 mg, area under the curve and urinary excretion**

| Antibiotic | Oral Dose | Serum Blood Levels mcg/ml | | | | | | Area Under Curve | Urinary Excretion 0.8 hr |
|---|---|---|---|---|---|---|---|---|---|
| | | ½ hr | 1 hr | 2 hr | 4 hr | 6 hr | 8 hr | | |
| Ampicillin | 500 mg | 0.9 | 2.0 | 3.2 | 1.9 | 0.4 | 0.1 | 50.3%* | 33.8% |
| Amoxicillin | 500 mg | 3.0 | 7.5 | 7.0 | 2.0 | 0.5 | 0.2 | 100.0% | 60.2% |

* The relative area under the curve for ampicillin was expressed as a percentage of the area for amoxicillin.

** Adapted from Gordon, R.C., Regamey, C. and Kirby, W.M.M.

## TOXICOLOGY

### Acute animal Toxicity

The $LD_{50}$ values of amoxicillin trihydrate expressed in mg/kg of body weight are as follows:

| | | |
|---|---|---|
| Rat and Mice | oral | 5000 mg/kg |
| | subcutaneous | 5000 mg/kg |
| | intramuscular | 5000 mg/kg |

Dogs were given single doses of 10, 15 and 20 g/kg, with intervals of one week between doses. During the seven-day period of observation, no deaths occurred, no adverse changes in body weight were noted, and food consumption remained unaffected. Occasional vomiting was noted, usually 1 – 3 hours after dosing. At post-mortem examination, no abnormalities were detected and organ weights were within normal limits.

## Short-Term Oral Studies

Beagle 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 were noted and food consumption was not affected. Laboratory values were within normal limits. At post-mortem, no gross or microscopic abnormalities were noted and organ weights were within normal limits.

Rats: Male and female rats were administered 500 mg/kg amoxicillin daily for 21 days. Except for significantly greater ($p<0.01$) BUN values in the female test group, compared with controls, no toxic effects on the organs, tissues or body fluids were observed, nor any adverse effects on food consumption, weight gain, or efficiency of food utilization. Histopathologic evaluation 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.

## Long-Term Oral Studies

Rats: Male and female rats were given 250, 500 and 200 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, not histologic changes attributable to treatment.

Dogs: Amoxicillin was administered orally at doses of 200, 500 and 2000 mg/kg/day to male and female dogs for 6 months. (Groups consisted of 6 male and female dogs initially. After 3 months dosing, each group was reduced to 3 dogs).

During the first 6 weeks of treatment, occasional bouts of vomiting, one to four hours after dosing, were seen in dogs receiving 2000 mg/kg/day; 4 bouts of vomiting were recorded at the intermediate dose level (500 mg/kg/day). Grey-coloured faeces were seen on isolated occasions in dogs treated at high and intermediate dose levels. 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 not significantly different from the controls, but all dosed females increased in weight at a significantly slower rate than the controls. This is probably due to excessive weight gain in the control animals. Food and water consumption were not affected. No abnormalities of the eyes were observed attributable to amoxicillin.

## Effect on Pregnancy

Mouse: Amoxicillin was administered at doses of 200, 500 and 2000 mg/kg/day orally during days 6-15 of pregnancy. No obvious signs of reaction to treatment and no deaths among parent animals were observed. 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 rate also tended to be higher at 500 and 2000 mg/kg, litter sizes were only marginally, but not significantly, lower than in the controls. 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.

Mean pup weights were comparable in all groups. The distribution of skeletal variants were considered to be unaffected by treatment at any dosage. A significantly higher proportion of pups with cervical ribs were found in the 200 mg/kg dose group. Cervical rib and 14$^{th}$ rib are the prolongations of the transverse process of the cervical or lumbar vertebrae. The incidence of supernumerary ribs depends on the strain of animals. Cervical ribs are not abnormalities and have no pathologic significance. In the present 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 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 500 mg/kg dose level the incidence of cervical ribs was found to be significantly lower than in controls. At the highest dose level (2000 mg/kg), the incidence of cervical ribs was 17%, similar to the control group. The incidence of visceral abnormalities was not significantly affected at any dose.

## Effect on Peri- and Postnatal 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 postpartum. Body weight gain, pregnancy rate and the duration of gestation of parent animals were unaffected by treatment at any dosage. There was significant dose-related trend to lower litter size and weight at birth. This persisted through the lactation period to weaning despite reduced pup mortality and increased mean pup weight in the test groups compared with controls. No abnormal young were observed.

## Effect on Fertility and General Reproductive Performance of the Rat

Daily doses of 200 and 500 mg/kg were administered orally. Male rats with a minimum age of 40 days were treated for 63 days before mating. Sexually mature females were treated for 14 days before mating. Dosing continued throughout the remainder of the investigation. The duration of gestation was unaffected by treatment at either dosage. 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 with 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.

At 500 mg/kg, among the rats allowed to rear their young, litter sizes, litter weights, mean pup weights and pup mortality rates were comparable with control values at birth, 4 and 21 days postpartum. At 200 mg/kg, mean pup weights and pup mortality rates were similarly unaffected. But litter sizes and litter weights were lower than control values from birth through lactation. These differences were considered unrelated to treatment.

No abnormal young were observed.

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