PRODUCT MONOGRAPH

MYLAN-AMOXICILLIN

(Amoxicillin Trihydrate)

Capsules

BP

ANTIBIOTIC

Mylan Pharmaceuticals ULC

85 Advance Road

Etobicoke, Ontario

Canada M8Z 1S6

Date of Preparation:

June 8, 2009

Control #: 129875

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(Amoxicillin Trihydrate)

Capsules

BP

THERAPEUTIC CLASSIFICATION

Antibiotic

ACTIONS AND CLINICAL PHARMACOLOGY

MYLAN-AMOXICILLIN (amoxicillin trihydrate) is effective orally against Gram-positive organisms as well as against a variety of Gram-negative organisms.

Amoxicillin exerts a bactericidal 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.

MYLAN-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 trihydrate results in peak blood serum levels averaging 8 pg/mL. Following a 500 mg dose, measurable serum levels are present at 8 hours. The half life of amoxicillin trihydrate is approximately an hour. Amoxicillin trihydrate is excreted mostly unchanged in the urine, but its excretion can be delayed by concurrent administration of Probenecid.

Pharmacokinetics

A two-way, single dose, comparative, fasting bioavailability study of MYLAN-AMOXICILLIN 500 mg capsules against the Canadian Reference amoxicillin 500 mg capsules in normal, healthy male volunteers was conducted. The pharmacokinetic data calculated for MYLAN-AMOXICILLIN and the Canadian Reference Product are presented below.

Summary table of the Comparative Data for Amoxicillin Capsules

(1 x 500 mg)

Parameter	**Geometric Mean Arithmetic Mean (% C.V.)**		**Ratio (%) Geometric Means**
	Mylan	Amoxil **	
AUC (0-t hours) (mgc.hr/mL)	20.49 20.62 (11.65)	18.87 19.06 (13.54)	108.54
AUC (0-infinity) (mgc.hr/mL)	21.00 21.13 (11.44)	19.39 19.56 (13.08)	108.31
C_{max} (mcg/mL)	7.80 8.00 (23.45)	7.60 7.85 (25.01)	102.60
T_{max} (hours)*	1.67 (44.10)	1.54 (31.14)	---
$t_{1/2}$ (hours)*	1.04 (16.87)	1.02 (19.09)	---
k_{el}, (hour-^{1})*	0.683 (16.717)	0.699 (17.523)	---

** The reference product Amoxil-500 Wyeth-Ayerst, was purchased in Canada.

* These are arithmetic means (% C.V.)

INDICATIONS AND CLINICAL USES

MYLAN-AMOXICILLIN (amoxicillin trihydrate) may be indicated in the treatment of infections due to susceptible strains of the following organisms: gram-negative: *Haemophilus influenzae, Escherichia colt Proteus mirabilis* and *Neisseria gonorrhoeae;* gram-positive: *Streptococci, Diplococcus pneumoniae* and non-P-lactamase-producing staphylococci.

MYLAN-AMOXICILLIN may be indicated in the prophylaxis against alpha-haemolytic (viridans group) streptococci before dental, oral or upper respiratory tract surgery or instrumentation.

MYLAN-AMOXICILLIN may be 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 with MYLAN-AMOXICILLIN, based on clinical judgment while awaiting the results of bacteriologic studies to isolate the infecting organism, and to determine its sensitivity.

CONTRAINDICATIONS

The use of this drug 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 MYLAN-AMOXICILLIN (amoxicillin trihydrate) or any other penicillin, careful inquiry should be made concerning previous hypersensitivity reactions to penicillins, cephalosporins, or other allergens. If an allergic reaction occurs, MYLAN-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 MYLAN-AMOXICILLIN therapy

MYLAN-AMOXICILLIN (amoxicillin trihydrate) 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 MYLAN-AMOXICILLIN (amoxicillin trihydrate) 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. MYLAN-AMOXICILLIN may therefore be contraindicated in cases where infectious mononucleosis is suspected or confirmed.

Use in the Elderly

There are no known specific precautions for the 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, MYLAN-

AMOXICILLIN should be discontinued unless, in the opinion of the physician, the condition is life-threatening and amenable only to MYLAN-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 cases 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-I3- 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-13-lactamase-producing staphylococci and H. *influenzae;* 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-13-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%:

	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.
Adults and 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.
Children <45 kg:	Appropriate therapy of presumptive or proven infection with C. *trachomatis* should be included as well.

Before prescribing MYLAN-AMOXICILLIN, 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 the 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 becomes 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

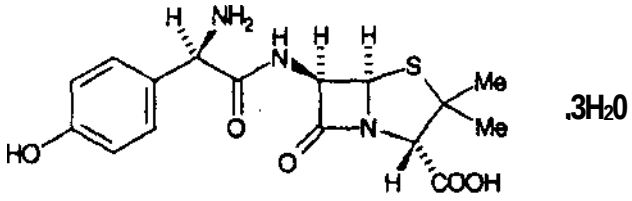
DRUG SUBSTANCE

PROPER NAME: Amoxicillin trihydrate

CHEMICAL NAME:

6-[(-)-a-Amino-p-hydroxyphenylacetamido]-penicillanic acid trihydrate.

STRUCTURAL FORMULA:



MOLECULAR FORMULA:	$C_{16}1\text{-}1_{19}N_30_5S.3H_20$
MOLECULAR WEIGHT:	419.47
DESCRIPTION:	Amoxicillin trihydrate is a white or slightly off-white highly hygroscopic powder.
SOLUBILITY:	Slightly soluble in water and in ethanol (95%); practically insoluble in chloroform, in ether, and in fixed oils. It dissolves in dilute solutions of acids and of alkali hydroxides.
pKa:	7.4
pH:	3.5 to 5.5 (0.2% solution of amoxicillin trihydrate in water)

COMPOSITION

Each capsule, Gold OP body and red OP cap, contains 250 or 500 mg of amoxicillin and the following non-medicinal ingredients: talc, sodium starch glycollate, colloidal silicon dioxide, magnesium stearate, FD&C Blue # 1, D&C Yellow # 10, FD&C Yellow # 6, D&C Red # 28, D&C Red # 33, titanium dioxide, and gelatin.

STABILITY AND STORAGE RECOMMENDATIONS

MYLAN-AMOXICILLIN CAPSULES:

Store in tightly closed, light-resistant containers at room temperature (15 to 30°C).

AVAILABILITY

CAPSULES

MYLAN-AMOXICILLIN 250 - each capsule contains amoxicillin trihydrate equivalent to 250 mg amoxicillin, in bottles of 100 and 1000. MYLAN-AMOXICILLIN 250 mg capsules are hard gelatin capsules with gold opaque body, printed with "AX250" in black, and red opaque cap, printed with " G " in black. The capsule fill is an off - white powder.

MYLAN-AMOXICILLIN 500 - each capsule contains amoxicillin trihydrate equivalent to 500 mg amoxicillin, in bottles of 100 and 500. MYLAN-AMOXICILLIN 500 mg capsules are hard gelatin capsules with gold opaque body, printed with "AX500" in black, and red opaque cap, printed with " G " in black. The capsule fill is an off-white powder.

MICROBIOLOGY

Amoxicillin trihydrate differs *in vitro* from benzylpenicillin in its gram-negative spectrum. It is highly effective *in vitro* against most strains of *H. influenzae,* non-13-lactamase-producing *N. gonorrhoeae, N. meningitides, E. coli, P. mirabilis, BruceIla* species, *Salmonellae* and *Shigellae.*

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

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-13-lactamase producing staphylococci, *B. anthracis,* and most strains of *Enterococci* and *Clostridia.* Amoxicillin trihydrate is not effective against f3-lactamase-producing organisms, particularly resistant staphylococci and recently described P-lactamase-producing strains of gonococci. All strains of *Pseudomonas* and most strains of *Klebsiella* and *Enterobacter* are also resistant. To estimate the *in vitro* susceptibility of organisms to amoxicillin trihydrate, the standard Bauer-Kirby sensitivity disc method is recommended (using standard ampicillin sensitivity discs).

ACTIVITY OF AMOXICILLIN TRIHYDRATE AGAINST GRAM-NEGATIVE ORGANISMS

M.I.C. (pg/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	10	59	10	5	
Proteus mirabilis	27	7							41	33	19	
Kiebsiella 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
Neisseria** gonorrhoeae	5											100

** Serial dilution in agar except for H. *influenzae* - in chocolate blood agar Cultured strains, M.I.C. and % of strains 0.25 pg/mL (40%) and 0.05 pg/mL (60%). One additional strain tested had a M.I.C. greater than 5 pg/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 TRIHYDRATE AGAINST STAPHYLOCOCCI, STREPTOCOCCI, PNEUMOCOCCI AND ENTEROCOCCI

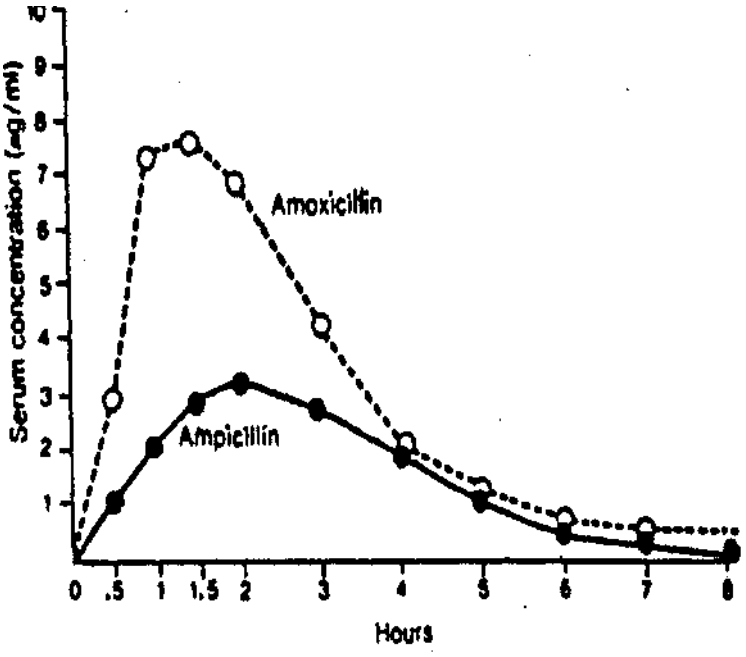
Organism	**No. of strains**	**M.I.C.* (pg/mL) and % of strains**							
		1.25	0.5	0.25	0.12	0.05	0.02	0.012	0.005
S. aureus	24			17	79	4			
8-haemolytic Streptococcus *(S. pyogenes)*	20						15	85	
S. pneumoniae	12					50	42	8	
S. faecalis	16	69	31						

*Serial dilution in agar

PHARMACOLOGY

Amoxicillin trihydrate 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 trihydrate. The half-lives of amoxicillin trihydrate and ampicillin of approximately one hour are virtually identical. Amoxicillin trihydrate is excreted unchanged in the urine; but its excretion can be delayed by concurrent administration of probenecid. Amoxicillin trihydrate is not highly protein bound. In blood serum, amoxicillin trihydrate is only 17% protein bound compared with 59% for penicillin G. A 500 mg dose of amoxicillin trihydrate results in peak blood serum levels averaging 8 pg/mL, whereas the average peak serum level of a 500 mg dose of ampicillin is 4 pg/mL. A 500 mg oral dose of amoxicillin trihydrate gives a peak serum level of approximately that obtained with the same Intramucular 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 trihydrate is twice that of ampicillin.

Using a special skin window technique to determine antibiotic concentrations, therapeutic levels of amoxicillin trihydrate were found in tissue fluid. About 60% -70% of an oral dose of amoxicillin trihydrate 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 trihydrate, with identical half-lives for both antibiotics, all reflect much better absorption of amoxicillin trihydrate than that of ampicillin.

Amoxicillin trihydrate and ampicillin in serum levels of fasting volunteers after 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
		1/2 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 Trihydrate	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 trihydrate.

** 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:

Rats 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 postmortem 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 trihydrate 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 postmortem, 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 trihydrate 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 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 histologic changes attributable to treatment.

Dogs: Amoxicillin trihydrate 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 trihydrate.

Effect on Pregnancy

Mouse: Amoxicillin trihydrate 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 rates 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 was 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 14th 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 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 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 trihydrate 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 a 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 postimplantation 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 the 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.

BIBLIOGRAPHY

1. Pullen H.: British Medical Journal, 1973, 2, p. 350.

2. Mulroy R.: British Medical Journal, Mar. 3, 1973, p. 554.

3. Neu H.C. and E.B. Winshell: Pharmacological Studies of 6 D(-)--Amino-p-Hydroxyphenylacetamido Penicillanic Acid in Humans. Antimicrobial Agents and Chemotherapy, 1970, American Society for Microbiology, Bethesda, 1971, 423-426.

4. Croydon E.A.P. and R. Sutherland: -Amino-p-Hydroxybenzylpenicillin (BRL 2333), A New Semisynthetic Penicillin: Absorption and Excretion in Man, Antimicrobial Agents and Chemotherapy, 1970, American Society for Microbiology, Bethesda, 1971, pp. 427-430.

5. Gordon R.C. and C. Regamey and W.M.M. Kirby: Comparative Clinical Pharmacology of Amoxicillin and Ampicillin Administered Orally, Antimicrobial Agents and Chemotherapy, 1972, American Society for Microbiology, Bethesda, 1972, pp. 504-507.

6. Tan J.S., A. Trott, J.P. Phair, and C. Watanakunakorn: Journal of Infectious diseases, 1972, 126, p. 492.

7. Neu H.C. and E.B. Winshell: In vitro Antimicrobial Activity of 6 D(-)--Amino-p-Hydroxyphenylacetamido Penicillanic Acid, A new Semisynthetic Penicillin, Antimicrobial Agents and Chemotherapy, 1970, American Society for Microbiology, Bethesda, 1971, pp. 407-410.

8. Sutherland R. and G.N. Rolinson. -Amino-p-Hydroxybenzylpenicillin (BRL 2333). a New Semisynthetic Penicillin: In vitro Evaluation, Antimicrobial Agents and Chemotherapy, 1970, American Society for Microbiology, Bethesda, 1971, pp. 411-415.

9. Acred P., P.A. Hunter, L. Mizen, and G.N. Rolinson: -Amino-p-Hydroxybenzylpenicillin (BRL 2333), a New Broad spectrum Semi-Synthetic Penicillin: In vivo Evaluation, Antimicrobial Agents and Chemotherapy, 1970, American Society for Microbiology, Bethesda, 1971, pp. 416-422.

10. Amoxil Product Monograph, Ayerst Laboratories (Canada) [8HN730019P].