PRODUCT MONOGRAPH

[Pr]AURO-AMOXICILLIN

Amoxicillin for Oral Suspension

USP

125 mg / 5 mL and 250 mg / 5 mL Amoxicillin (as Amoxicillin Trihydrate)

Antibiotic

Auro Pharma Inc.
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CANADA

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THERAPEUTIC CLASSIFICATION

Antibiotic

ACTIONS AND CLINICAL PHARMACOLOGY

Amoxicillin is a bactericidal penicillin active against both Gram-positive and Gram-negative organisms and is subject to the hydrolytic activity of penicillinase. Amoxicillin exerts its mode of action by interfering with bacterial cell wall synthesis by acylating the enzyme transpeptidase, thus rendering it unable to cross-link muramic acid containing peptidoglycan strands. This inhibition of the biosynthesis of dipeptidoglycan, a substance necessary for cell wall strength and rigidity, results in a defective cell wall.

INDICATIONS AND CLINICAL USE

AURO-AMOXICILLIN (amoxicillin trihydrate) is indicated for the treatment of the following infections due to susceptible strains of sensitive organisms.

Upper Respiratory Infections:

Otitis media, pharyngitis, sinusitis and tonsillitis.

Lower Respiratory Infections:

Bronchitis, bronchopneumonia and lobar pneumonia.

Urinary Tract Infections:

Cystitis, cysto-pyelitis, urethritis, gonococcal urethritis.

AURO-AMOXICILLIN is also indicated in the following:

- prophylaxis against alpha-hemolytic (viridans group) Streptococci before dental, oral or upper respiratory tract surgery or instrumentation.

- 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.

AURO-AMOXICILLIN is further indicated for the treatment of cutaneous infections. In emergency cases where the causative organism is not yet identified, therapy may be initiated with AURO-AMOXICILLIN on the basis of clinical judgement, while awaiting the results of bacteriologic studies to determine its antimicrobial sensitivity.

CONTRAINDICATIONS

AURO-AMOXICILLIN is contraindicated in patients with a history of sensitivity to the penicillins or cephalosporins. Amoxicillin does not induce teratogenic effects in laboratory animals; however, its use in pregnancy is still undetermined.

WARNINGS

AURO-AMOXICILLIN is not effective against beta-lactamase-producing (penicillin-resistant) staphylococci.

Serious and occasionally fatal hypersensitivity (anaphylactoid) reactions have been reported in patients on parenteral and oral penicillin therapy. These reactions, however, are more apt to occur in individuals with a history of sensitivity to multiple allergens.

Therefore, before initiating therapy with AURO-AMOXICILLIN or any penicillin, careful inquiry should be made concerning previous hypersensitivity reactions to penicillins, cephalosporins or other allergens. If an allergic reaction occurs, AURO-AMOXICILLIN therapy should be discontinued and appropriate measures instituted. Serious anaphylactoid reactions require immediate emergency treatment with epinephrine, oxygen, intravenous steroids and airway management, as indicated.

PRECAUTIONS

AURO-AMOXICILLIN, as with all penicillins, should be administered with caution in the presence of renal or hepatic insufficiency.

Periodic assessment or renal, hepatic and hematopoietic functions should be made during prolonged AURO-AMOXICILLIN therapy. Since it is excreted mainly by the kidney, the dosage for patients with renal impairment should be reduced in proportion to the degree of loss of renal function.
The possibility of superinfections with mycotic organisms or bacterial pathogens should be kept in mind during AURO-AMOXICILLIN therapy. If superinfections occur (usually involving Aerobacter, Candida or Pseudomonas), the drug should be discontinued and appropriate measures instituted.

AURO-AMOXICILLIN should not be used if infectious mononucleosis is suspected since the occurrence of a morbilliform rash in patients with infectious mononucleosis following the use of amoxicillin is well documented.

The safety of amoxicillin in human pregnancy has not yet been established.

ADVERSE REACTIONS

As with other penicillins, the most common adverse reactions observed with amoxicillin are related to sensitization.

The following adverse reactions including moniliasis have been observed:

Hypersensitivity Reactions:
Urticaria, erythematous maculopapular rashes, angioneurotic edema, and rarely anaphylactoid reactions.

Liver:
A moderate rise in serum glutamic oxaloacetic transaminase (SGOT) has been noted, but the significance of this finding is unknown.

Gastrointestinal:
Nausea, loose stools and vomiting.

Hemic and Lymphatic Systems:
Anemia, thrombocytopenia, thrombocytopenic purpura, eosinophilia, leukopenia and agranulocytosis.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

In the treatment of overdosage, it is advisable to promote excretion by dialysis. In the case of hypersensitivity reactions, appropriate supportive measures and symptomatic treatment are recommended.

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

DOSAGE AND ADMINISTRATION

AURO-AMOXICILLIN (amoxicillin trihydrate) can be administered orally independent of meals. Therapy should be maintained for a minimum of 5 days.

Treatment should be continued for a minimum of 96 hours beyond the time the patient becomes asymptomatic or after evidence of bacterial eradication is observed. At least 10 days treatment is recommended for any infection caused by beta-hemolytic streptococci to prevent the occurrence of acute rheumatic fever or glomerulonephritis.

Infections of the upper respiratory or genitourinary tracts, skin and soft tissues, due to susceptible strains of the causative organism:

Adults	: 250 mg every 8 hours.
Children < 20 kg	: 20 mg/kg/day in divided doses every 8 hours.

In severe infections or infections associated with organisms where sensitivity determinations require higher blood concentrations:

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.

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

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.

Urethritis due to non-penicillinase producing N. gonorrhoea 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) of amoxicillin 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.

Before prescribing AURO-AMOXICILLIN, dark field examinations should be carried out in those cases where syphilis is also suspected and monthly serologic tests should be carried out for a minimum of 4 months.

For prevention of endocarditis: Adults: 3 g orally 1 hour before the procedure, then 1.5 g 6 hours after the initial dose. Children: 50 mg/kg (not to exceed adult dose) orally 1 hour before the procedure, then 25 mg/kg 6 hours after the initial dose.

In the treatment of chronic urinary tract infections, frequent bacteriologic and clinical evaluations are necessary. Doses smaller 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. 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.

Dosage In Renal Failure:

$$e = \frac{T}{t_{1/2}}$$

e - relative dosage interval
T - dosage interval
$t_{1/2}$ - serum half-life of the drug

The relative dose interval for amoxicillin is 4 hours; thus, in patients with renal failure in whom the $t_{1/2}$ is 6 hours the dosage interval is 24 hours.

PHARMACEUTICAL INFORMATION

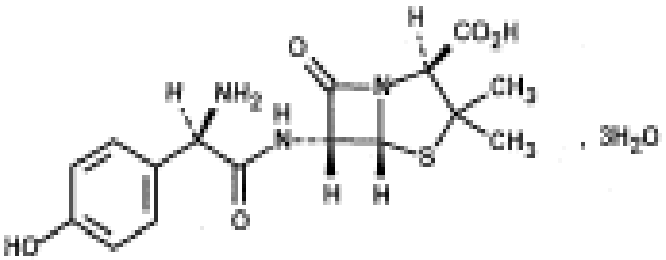
Drug Substance

Proper Name: Amoxicillin trihydrate

Chemical Name: (2*S*,5*R*,6*R*)-6-[[(2*R*)-2-amino-2-(4-hydroxyphenyl)acetyl]amino]-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: 419.4 g/mol

Description: Amoxicillin trihydrate is a white or almost white, crystalline powder. It is slightly soluble in water, very slightly soluble in alcohol, practically insoluble in fatty oils. It dissolves in dilute acids and dilute solutions of alkali hydroxides.

Other Properties:

pH	Between 3.5 and 5.5
Dissociation Constant (pKa)	pKa 2.4 (carboxyl), 7.4 (aromatic hydroxyl), 9.6 (α-ammonium) values of pKa of 2.63, 7.16 and 9.55 were determined at 350 by T suji et al.l
Partition Coefficients [Log p (octanol)]	0.87
Polymorphism	Amoxicillin Trihydrate manufactured by Aurobindo Pharma Limited is Trihydrate form.

AVAILABILITY OF DOSAGE FORMS

Dosage form	**Powder for Oral Suspension**
Strength	**125 mg / 5 mL and 250 mg / 5 mL**
Description	***For dry powder:*** White to off-white Granular Powder. ***For Reconstituted suspension:*** Pink suspension with bubble gum flavour.
Composition	**Non-medicinal Ingredients:** Sucrose, sodium citrate, sodium benzoate, edetate disodium, xanthan gum, bubble gum flavour, colloidal silicon dioxide, silicon dioxide and FD&C Red No.3.
Packaging	100 mL and 150 mL

Reconstituted Solution

Instructions for Reconstitution: At the time of dispensing, SHAKE BOTTLE TO LOOSEN THE POWDER. To reconstitute, add the following quantities of water:

Package Size	125 mg / 5 mL	250 mg / 5 mL
100 mL	72	72
150 mL	106	106

Shake thoroughly to obtain a uniform suspension.

Dry Powder: Store at room temperature (15ºC to 30ºC).
Reconstitution Suspension: The reconstituted suspension is stable for 7 days at room temperature (15ºC to 30ºC) and 14 days if refrigerated (2ºC to 8ºC).
Discard unused suspension after 7/14 days.

COMPARATIVE BIOAVAILABILITY STUDIES

A double blind, randomized, two-treatment, two-sequence, two-period, crossover, single-dose comparative oral bioavailability study of AURO-AMOXICILLIN (amoxicillin trihydrate) 250 mg/5 mL powder for oral suspension (Auro Pharma Inc.) versus APO-AMOXI (amoxicillin trihydrate) 250 mg/5 mL powder for oral suspension (Apotex Inc.) was conducted in 28 healthy, adult human male subjects under fasting conditions. A summary of the bioavailability data of 27 subjects who completed the study is presented in the following table.

SUMMARY TABLE OF THE COMPARATIVE BIOAVAILABILITY DATA

Amoxicillin (5 mL x 250 mg/5 mL) From measured data Geometric Mean Arithmetic Mean (CV %)				
Parameter	**Test***	**Reference†**	**% Ratio of Geometric Means**	**90% Confidence Interval**
$AUC_{0\rightarrow t}$ (hr.ng/mL)	17625.3 17906.5 (18.5)	18064.7 18322.7 (17.2)	97.6	94.5-100.8
$AUC_{0\rightarrow \infty}$ (hr.ng/mL)	17785.2 18066.1 (18.4)	18232.6 18486.8 (17.0)	97.6	94.5-100.7
C_{max} (ng/mL)	6558.9 6846.2 (29.0)	7114.4 7345.2 (24.6)	92.2	85.8-99.1
T_{max}§ (hr)	1.25 (0.75-2.75)	1.00 (0.75-2.75)		
$T_{½}$$ (hr)	1.4 (17.6)	1.4 (23.1)		

*AURO-AMOXICILLIN (amoxicillin trihydrate) 250 mg/5 mL powder for oral suspension (Auro Pharma Inc.).
† APO-AMOXI (amoxicillin trihydrate) 250 mg/5 mL powder for oral suspension (Apotex Inc.) was purchased from Canada.
§ Expressed as the median (range) only.
$ Expressed as arithmetic mean (CV%) only.

A double blind, randomized, two-treatment, two-sequence, two-period, crossover, single-dose comparative oral bioavailability study of AURO-AMOXICILLIN (amoxicillin trihydrate) 125 mg/5 mL powder for oral suspension (Auro Pharma Inc.) versus APO-AMOXI (amoxicillin trihydrate) 125 mg/5 mL powder for oral suspension (Apotex Inc.) was conducted in 28 healthy, adult human male subjects under fasting conditions. A summary of the bioavailability data of 25 subjects who completed the study is presented in the following table.

SUMMARY TABLE OF THE COMPARATIVE BIOAVAILABILITY DATA

Amoxicillin (10 mL x 125 mg/5 mL) From measured data Geometric Mean Arithmetic Mean (CV %)				
Parameter	**Test***	**Reference†**	**% Ratio of Geometric Means**	**90% Confidence Interval**
$AUC_{0\rightarrow t}$ (hr.µg/mL)	22.8 23.1 (15.1)	20.3 20.5 (14.0)	112.5	109.5-115.6
$AUC_{0\rightarrow \infty}$ (hr.µg/mL)	23.0 23.3 (15.1)	20.4 20.6 (14.0)	112.6	109.6-115.7
C_{max} (µg/mL)	7.9 8.2 (24.5)	7.2 7.4 (22.3)	111.0	103.7-118.8
T_{max}§ (hr)	1.25 (0.75-2.25)	1.00 (0.75-3.00)		
$T_{½}$$ (hr)	1.5 (20.0)	1.4 (23.0)		

*AURO-AMOXICILLIN (amoxicillin trihydrate) 125 mg/5 mL powder for oral suspension (Auro Pharma Inc.).
† APO-AMOXI (amoxicillin trihydrate) 125 mg/5 mL powder for oral suspension (Apotex Inc.) was purchased from Canada.
§ Expressed as the median (range) only.
$ Expressed as arithmetic mean (CV%) only.

MICROBIOLOGY

The investigation was conducted by assessment of the minimum inhibiting concentration (MIC), carried out by the serial dilution technique in Tryptose Phosphate Broth test tubes to determine the lowest concentrations of amoxicillin and ampicillin that induce inhibition of the visible growth of the test organisms (Table 1). Tubes, suitably seeded with 0.1 mL/tube of an 18 hour

broth culture of the test organisms were read after 24 hours of incubation at 37°C (28°C only in the case of Pseudomonas f1uorescens).

Comparative evaluation of the in vitro data show that amoxicillin has both a spectrum of action and a bacterial efficacy equivalent to that of ampicillin.
AURO-AMOXICILLIN is not effective against beta-Iactamase-producing organisms particularly resistant staphylococci (i.e., penicillin-resistant).

Pseudomonas-aeruginosa, Pseudomonas f1uorescens and all indole-positive Proteus species, i.e., Proteus morganii, Proteus rettgeri, Proteus vulgaris, are resistant to both amoxicillin and ampicillin, evidence which indicates complete cross-resistance between these two synthetic penicillins.

TABLE 1: Comparative in vitro antibacterial activity of amoxicillin and ampicillin on various microorganisms (single strains).

	MIC (µg/mL)	
Microorganism	Amoxicillin	Ampicillin
Micrococcus f1avus (ISM)	≤0.0015	≤0.0015
Sarcina lutea ATCC 9341	0.003	0.0015
Bacillus subtilis (ISM)	0.012	0.012
Staphylococcus aureus ATCC 6538P	0.024	0.024
Streptococcus haemolyticus (ISM)	0.39	0.78
Salmonella typhi (ISM)	0.39	0.39
Streptococcus faecalis (ISM)	0.78	1.56
Salmonella paratyphi A (ISM)	0.78	1.56
Salmonella paratyphi B (ISM)	0.78	0.39
Salmonella typhimurium 779/C (ISM)	0.78	1.56
Salmonella abortiva equina (ISM)	0.78	0.78
Escherichia coli 113/3	1.56	0.78
Proteus mirabilis (ISM)	1.56	1.56
Diplococcus pneumoniae (ISM)	6.25	6.25

The following organisms have been found relatively resistant:

Shigella sonnei (ISM)	12.50	6.25
Proteus vulgaris (ISM)	25.00	6.25
Klebsiella pneumoniae (ISM)	50.00	25.00
Aerobacter aerogenes ATCC 9724	50.00	25.00
Proteus vulgaris ATCC 6380	100.00	25.00
Proteus rettgeri (ISM)	>100.00	>100.00
Proteus morganii (ISM)	>100.00	>100.00
Pseudomonas aeruginosa (ISM)	>100.00	>100.00
Pseudomonas f1uorescens (ISM)	>100.00	>100.00
Staphylococcus aureus		

penicillin resistant (ISM)	>100.00	>100.00

"In vivo" Antibacterial Activity of Amoxicillin in Mice With Experimentally Induced Klebsiella Pneumoniae Infection (100% lethal) as Compared With Ampicillin

Six groups of 20 male albino mice (Swiss strain, weight 18-22 g) were infected intramuscularly with a broth-culture of Klebsiella pneumoniae (LD_{100}). Six hours post-challenge, each group of 20 mice were treated respectively with (i) amoxicillin 10, 50 and 250 mg/kg/twice/day orally as a suspension in 10% gum arabic at a constant volume of 0.5 mL/mouse and (ii) ampicillin at the same dose levels for 4 days.

The investigation was terminated 30 days post-challenge when the survivors were apparently healthy and exhibited body weight gains.

Oral Treatment: 4-day Duration

Chemotherapeutic Agent	Dose (mg/kg) 2x Daily; p.o.	% of Surviving Animals at the 30th Day After the Intramuscular inoculation of the *Klebsiella Pneumoniae* Broth Culture
Amoxicillin	10	70%
Amoxicillin	50	100%
Amoxicillin	250	100%
Ampicillin	10	20%
Ampicillin	50	70%
Ampicillin	250	90%

Comparative evaluation of the data show that amoxicillin has a greater antibacterial activity (Le., therapeutic activity) than ampicillin at all doses tested, possibly reflecting the more satisfactory oral absorption and markedly higher drug concentration in the blood.

PHARMACOLOGY

Amoxicillin is stable at gastric pH. It is completely absorbed in the upper gastrointestinal tract. Peak serum levels averaging 8 µg/mL are attained 2.0 hours after a 500 mg oral dose of amoxicillin by capsule. Serum levels of 0.19 µg/mL were detectable after 8 hours. Absorption is independent of meals.

In crossover studies in healthy fasting adults subjects, mean peak serum levels of 5 µg/mL were obtained following a single 250 mg capsule and levels of 6.6 to 10.8 µg/mL were obtained following a single capsule of 500 mg amoxicillin. Ampicillin in the same subjects and at the same dose levels exhibited mean peak serum levels of 2.7 µg/mL and 3.10 to 6.3 µg/mL, respectively.

Administration of a single oral dose of 500 mg amoxicillin by capsule to a group of 12 adult male volunteers gave observed peak blood levels of 6.75 µg/mL at 90 minutes; when the

suspension was administered to the same volunteers at a dosage of 500 mg, average peak blood levels of 8.46 µg/mL were observed at 60 minutes (Tables 2 and 3).

Following absorption from the gastrointestinal tract, amoxicillin is widely distributed and diffuses into most tissues and body fluids with the exception of brain and spinal fluid.

Amoxicillin is primarily excreted by the renal system and approximately 60-70% of a single 250 or 500 mg oral dose is excreted within 6 hours. The serum half-life of amoxicillin is 61.3 minutes.

TABLE 2
AMOXICILLIN CAPSULES - 500 mg

Serum Levels (µg/mL)								
20	40	60	90	150	240	300	360	480 min.
0.60	3.65	6.39	6.75	4.53	1.39	0.75	0.30	0.06

TABLE 3
AMOXICILLIN SUSPENSION - 500 mg/10 mL

Serum Levels (µg/mL)								
20	40	60	90	150	240	300	360	480 min.
3.64	6.10	8.46	7.94	2.84	1.07	0.44	0.25	0.08

TOXICOLOGY

Acute Toxicity

All of the laboratory animals tested tolerated the high dose of amoxicillin administered. The LD_{50} values were calculated on the basis of mortality recorded during 7 days following drug administration and are expressed in mg/kg body weight as follows:

Animals		LD_{50}	Route of Administration
Mice	(M & F)	5000 mg/kg	oral*, intramuscular and subcutaneous
Rats	(M & F)	5000 mg/kg	oral*, intramuscular and subcutaneous
Dogs	(M & F)	5000 mg/kg	oral*

*Oral dose to mice & rats was administered as a suspension by gastric intubation and dogs were administered capsules.

In all animals acutely treated with amoxicillin no mortality was observed at the doses administered (625, 1250, 2500, 5000 mg/kg/day). There was no change in behaviour or general health and symptoms of toxicity were absent. In only the dog, some vomiting was observed 2-4 hours following drug administration.

Subacute Toxicity

Rat Studies

Five groups of Wistar albino rats (males 10 and females 10, pregnant rats excluded) with an initial average body weight of 130-140 grams received oral doses of amoxicillin capsules (as a suspension in 5% gum arabic solution) and amoxicillin suspension at doses of 500 mg and 1000 mg/kg/day for 3 weeks, six days a week. The control group of rats received 10 mL/kg/day of a 5% solution of gum arabic.

Amoxicillin was tolerated by the rats of all doses. There were no changes in behaviour or food consumption and body weight gains were comparable to the control group. There were no effects on hematologic parameters, blood chemistry and urinalysis.

Post-mortem examinations conducted at the end of the 21-day treatment showed no pathologic evidence attributable to the administration of amoxicillin. The organ weights of lungs, heart, liver, kidneys, spleen, adrenals, testes and ovaries were normal and uniform for all groups of rats.

Dog Studies

Six beagle dogs (average initial body weight 11 kg) were divided into 3 groups of 2 dogs each (1 male and 1 female) and administered orally amoxicillin capsules, amoxicillin suspension and amoxicillin trihydrate at a dose equivalent to 250 mg/kg/day for 21 days (treatment administered 7 days a week). Each dog served as its own control, with baseline values established on day zero. No behaviour changes attributable to amoxicillin capsules or suspension treatment were exhibited; vomiting was observed in some dogs during the initial 3-4 days of treatment.

Food consumption throughout the investigation remained normal and uniform (average food consumed 300 g/dog/day). Body weight gain was comparable to the rate of body weight gain established for 9 days prior to treatment.

The results of hematological and blood chemistry examinations conducted at day 0,7, 14 and 21 showed no changes attributable to treatment. Urinalysis conducted on a 24 hour urine sample at the end of 21 days showed that amoxicillin produced no apparent toxic effects on the renal function of these dogs.

Chronic Toxicity

Rat Studies

Five groups of Wistar albino rats (males 10 and females 10, per group) with an initial average body weight of 70-75 g were administered daily for 6 consecutive months (7 days a week) as a suspension, amoxicillin capsules and amoxicillin suspension at doses of 50 and 250 mg/kg/day, respectively. The fifth group served as the control and received 5 mLlkg/day of the suspending vehicle.

The rats did not show any behavioural changes or toxic symptoms. All treated rats showed weight gains comparable to the control group.

Results of monthly hematological examinations made during the treatment period showed no changes attributable to the chronic administration of amoxicillin. Blood chemistry values at the end of 6 months of treatment were within the normal range and showed no significant differences as compared to the control group.

Chronic administration of amoxicillin did not apparently affect renal function, since urinalysis (pH, specific gravity, glucose, and sediment) were negative; however, albumin, blood and acetone were found in some urine samples from treated as well as control rats.

Gross and microscopic examinations of internal organs showed no changes. Some inflammatory foci of congestion were found in the lung of control and treated rats. No histopathologic changes attributable to the chronic administration of amoxicillin were evident in the various organs tested.

TERATOLOGICAL STUDIES IN ANIMALS

Rat: Gestation Terminated on 21st Day
Sixty pregnant Wistar albino rats (having an initial average weight of 250-260 g) were divided randomly into 7 groups; 10 rats each in groups 1-5 and 5 rats each in the teratogenic control groups 6 and 7. Amoxicillin capsules (as suspension) and amoxicillin suspension were administered orally from the 1st to the 20th day of gestation of doses of 100 and 1000 mg/kg/day. The control group received 10 mLlkg/day of a 5% solution of gum arabic orally. The teratogenic control groups (groups 6 and 7) received on the 8th and 13th day, respectively, a 150 mg/kg dose of Trypan Blue. On the 21 st day of gestation, delivery was induced by cesarean section.

The pattern of gestation, the behaviour of the pregnant rats and the body weight gains were comparable to the control animals. The results showed that amoxicillin capsules or suspension had no adverse effects on gestation, embryo development, numbers of viable newborn and on the skeletal structures. In the group receiving Trypan Blue (teratogenic control), pregnant rats showed significantly lower body weight gains and adverse effects such as marked reductions in the number of implants, increased resorption sites, reduction in viable fetuses and reductions in average body weight of live fetuses.

Rat: Full Term Delivery
The experimental conditions were similar to the above study, except that the rats were allowed to deliver spontaneously.

No adverse effects on the gestation, general behaviour and physical health of the females were observed. Deliveries occurred at the end of the normal term of gestation. There were no effects on embryo or fetal development, the number of viable newborns and on the structure and development of the newborn rats throughout the duration of the weaning period. The post-natal

mortality of the newborn rats was followed for the entire period of weaning and no deaths were attributable to amoxicillin capsules or amoxicillin suspension.

Rabbit: Full Term Delivery
Fifty pregnant Burgundy blonde rabbits with an initial mean weight of 3.0-3.5 kg were divided into 5 groups of 10 rabbits each and administered amoxicillin capsules and amoxicillin suspension at doses of 100 and 1000 mg/kg/day, mixed in the feed. The control group was untreated.

The behaviour and the general health of the pregnant rabbits were normal for the overall period of gestation, with delivery occurring at full-term and no incidence of abortion or intolerance to treatment.

The numbers and mean body weights of newborns from the rabbits treated with amoxicillin capsules or amoxicillin suspension were comparable to those of the newborns from the untreated control rabbits. There were no stillbirths or skeletal malformations.

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42. Product monograph – APO-AMOXI, Apotex Inc., Date of Revision: October 21, 1996. Control No. 023896