PRODUCT MONOGRAPH

RIVA-CLINDAMYCIN
(Clindamycin Hydrochloride)

150mg and 300mg Capsules

Antibiotic

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Date of Preparation
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Control # 066886

PRODUCT MONOGRAPH

RIVA-CLINDAMYCIN

(clindamycin hydrochloride)

Capsules

USP

THERAPEUTIC CLASSIFICATION

Antibiotic

ACTION AND CLINICAL PHARMACOLOGY

Clindamycin exerts its antibacterial effect by causing cessation of protein synthesis and also causing a reduction in the rate of synthesis of nucleic acids.

The mechanism of action of clindamycin in combination with Primaquine on *Pneumocystis carinii* is not known.

Absorption:

Clindamycin is rapidly and almost completely absorbed from the gastrointestinal tract in man and peak serum levels are seen in about 45 minutes. The average peak serum level following a single 150 mg dose in adults is 2.74 µg/mL. Therapeutically effective average levels at 6 hours after a 150 mg dose of 0.73 µg/mL are found.

The absorption of clindamycin is not appreciably affected by food intake. Peak serum levels following a single 250 mg oral dose of clindamycin with the patient in the fasting state were 3.1 µg/mL at 45 minutes whereas the same dose administered with food gave a peak level of 2.4 µg/mL. A 250 mg dose administered one hour after food gave a peak level of 2.8 µg/mL but

this peak did not occur until two hours after administration of the medication. A 250 mg dose with the patient in a fasting state and with food administered one hour after the medication resulted in peak levels of 3.1 µg/mL at 1½ hours.

Excretion:

The 48 hour urinary excretion of clindamycin in adults following a single dose of 150 mg represented 10.9% of the administered dose (range 4.8% to 12.8%). These measurements were made by bioassay and both the percent recovered and the urinary concentration are quite variable. The urinary concentration following a single 50 mg dose of clindamycin in the first 24 hours ranged from 8 to 25 µg/mL of urine.

Fecal excretion of clindamycin has also been determined. Patients on a three week study when administered 1 gram of clindamycin per day had an average of 283 µg/gm of stool. Patients on lincomycin 2 grams per day under the same conditions showed 3980 µg/gm of stool. In single dose studies following administration of 250 mg of clindamycin, only 2.7% of the dose was excreted in the feces in 48-96 hours.

Tissue Penetration:

In three patients following the administration of 150 mg of clindamycin serum levels reached 2.25 µg/mL in 2 hours and declined to 1.5 µg/mL at 4 hours. During this period antibiotic synovial fluid levels were 1 µg/mL at 2 hours and remained unchanged for the next and last 2 hours of observation.

Various other body fluids and tissues were also assayed for clindamycin and the results of these assays and serum levels at the same time are recorded in Table 1.

TABLE I

Specimen	No. of Specimens	Average Serum Level	Average Fluid Level μg/mL	Tissue Level μg/mg
Pancreatic fluid (C6-264)	4	1.15	45.1	
Bile (C6-264)	19	3.35	52.45	
Gall Bladder (C6-24)	16	0.81		4.33
Liver (C6-265)	1	42.35		3.80
Kidney (C6-265)	1	1.50		9.07
Bone (C4-390)	2	2.44		9.91

A single dose, randomized, blinded, two-way, crossover bioavailability study was performed to compare the rate and extent of absorption and bioequivalence of Riva-Clindamycin 300 mg Capsules with Dalacin®C 300 mg capsules in fasting volunteers. The pharmacokinetic mean plasma data calculated for the two products are tabulated below:

TABLE II

	Geometric Mean Arithmetic Mean (C.V.)		
	Riva-Clindamycin (1 x 300 mg)	Dalacin®C** (1 x 300 mg)	Ratio (%) Geometric Mean
AUC_T (ng.h/mL)	11143.8 12394.3 (44)	11319.5 12733.9 (50)	98
AUC_I (ng.h/mL)	11695.7 13086.2 (46)	11879.7 13367.0 (49)	98
C_{MAX} (ng/mL)	3203.2 3425.6 (38)	3052.1 3257.0 (36)	105
T_{MAX}* (h)	0.86 (49)	0.89 (40)	--
T½* (h)	5.29*** (109)	2.89 (48)	--

* For T_{max} and $T_{1/2}$ parameters these are the arithmetic means (standard deviation).
** Dalacin® C manufactured by UpJohn Canada, Scarborough, ON, Canada.
*** For the calculation of the elimination phase, a manual selection of Kel begin and end points, was made for Subject No. 10 with treatment A (Riva), resulting in a $T_{1/2}$ of 24.33 hours for this subject. The $T_{1/2}$ value for Subject No. 10 skews the $T_{1/2}$ mean for treatment A (Riva), and therefore results in a larger than expected mean for this treatment.

INDICATIONS AND CLINICAL USE

RIVA-CLINDAMYCIN (clindamycin hydrochloride) is indicated in the treatment of serious infections due to sensitive anaerobic bacteria, such as *bacteroides* species, *peptostreptococcus*, anaerobic streptococci, *clostridium* species and microaerophilic streptococci.

RIVA-CLINDAMYCIN is also indicated in serious infections due to sensitive gram-positive organisms (staphylococci, including penicillinase-producing staphylococci, streptococci and pneumococci) when the patient is intolerant of, or the organism is resistant to other appropriate antibiotics.

RIVA-CLINDAMYCIN is indicated for the treatment of the *Pneumocystis carinii* pneumonia in patients with AIDS. Clindamycin in combination with primaquine may be used in patients who are intolerant to, or fail to respond to conventional therapy.

RIVA-CLINDAMYCIN is indicated for prophylaxis against alpha-hemolytic (viridans group) Streptococci before dental, oral and upper respiratory tract surgery.

1. The prophylaxis of bacterial endocarditis in patients allergic to penicillin with any of the following conditions: congenital cardiac malformations, rheumatic and other acquired valvular dysfunction, 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 regurgitation but associated with thickening and/or redundancy of the valve leaflets.

2. Patients taking oral penicillin for prevention or recurrence of rheumatic fever should be given another agent such as clindamycin, for prevention of bacterial endocarditis.

CONTRAINDICATIONS

As with all drugs, the use of RIVA-CLINDAMYCIN (clindamycin hydrochloride) is contraindicated in patients previously found to be hypersensitive to this compound. Although cross-sensitization with lincomycin hydrochloride has not been demonstrated, it is recommended that RIVA-CLINDAMYCIN not be used in patients who have demonstrated lincomycin sensitivity.

Until further clinical experience is obtained RIVA-CLINDAMYCIN is not indicated in the newborn (infants below 30 days of age), or in pregnant women.

WARNINGS

Some cases of severe and persistent diarrhea have been reported during or after therapy with RIVA-CLINDAMYCIN (clindamycin hydrochloride). This diarrhea has been occasionally associated with blood and mucus in the stools and has at times resulted in acute colitis. When endoscopy has been performed, some of these cases have shown pseudomembrane formation.

If significant diarrhea occurs during therapy, this drug should be discontinued or, if necessary, continued only with close observation. Significant diarrhea occurring up to several weeks post therapy should be managed as if antibiotic-associated.

If colitis is suspected, endoscopy is recommended. Mild cases showing minimal mucosal changes may respond to simple drug discontinuance. Moderate to severe cases, including those showing ulceration or pseudomembrane formation should be managed with fluid, electrolyte and protein supplementation as indicated. Corticoid retention enemas and systemic corticoids may be of help in persistent cases, anticholinergic and antiperistaltic agents may worsen the condition. Other causes of colitis should be considered.

Studies indicate a toxin(s) produced by Clostridia (especially *Clostridium difficile*) may be a principal cause of clindamycin and other antibiotic-associated colitis. These studies also indicate that this toxigenic Clostridium is usually sensitive *in vitro* to vancomycin. When 125 mg to 500 mg of vancomycin were administered orally 4 times a day for 5-10 or more days, there was a rapid observed disappearance of the toxin from fecal samples and a coincidental recovery from the diarrhea.

It should be noted that serious relapses have occurred up to 1 month after apparently successful treatment. A relatively prolonged period of continuing observation is therefore recommended.

In patients with G-6-PD deficiency, the combination of clindamycin with primaquine may cause hemolytic reactions; reference should also be made to the primaquine product monograph for other possible risk groups for other possible hematologic reactions.

PRECAUTIONS

RIVA-CLINDAMYCIN (clindamycin hydrochloride) like any drug, should be prescribed with caution in atopic individuals.

The use of antibiotics occasionally results in overgrowth of nonsusceptible organisms, particularly yeasts. Should superinfections occur, appropriate measures should be taken as dictated by the clinical situation.

As with all antibiotics, perform culture and sensitivity studies in conjunction with drug therapy.

Since abnormalities of liver function tests have been noted occasionally in animals and man, periodic liver function tests should be performed during prolonged therapy. Blood counts should also be monitored during extended therapy.

Routine blood examinations should be done during therapy with primaquine to monitor potential hematologic toxicities.

RIVA-CLINDAMYCIN may be used in anuretic patients. Since the serum half-life of clindamycin in patients with impaired hepatic function is greater than that found in normal patients, the dose of RIVA-CLINDAMYCIN should be appropriately decreased. Hemodialysis and peritoneal dialysis are not effective means of removing the compound from the blood. Periodic serum levels should be determined in patients with severe hepatic and renal insufficiency.

ADVERSE REACTIONS

Only 65 of the 851 patients treated for infections developed side effects representing 7.6% of the total study group or 8% of the 813 patients with follow-up. Only 22 of these patients' symptoms were considered due to clindamycin for an incidence of 2.7% among the 813 cases with follow-up.

Gastrointestinal

Abdominal pain occurred in 12 patients for an overall incidence of 1.4% in 851 patients and was considered drug related in 7 (0.8%).

Diarrhea occurred in 22 cases for an overall incidence of 2.6% and was drug related in 13 (1.5%). Vomiting occurred in 14 cases with an overall incidence of 1.6%. Seven patients (0.8%) had nausea which was drug related in 2 cases (0.2%). Side effects were severe in 10 instances. (see Warnings). Esophagitis, at times severe, has been reported.

Hemopoietic

Transient neutropenia (leukopenia) has been reported. Its relationship to therapy is unknown. No irreversible hematologic toxicity has been reported. However, in clindamycin/primaquine

combination studies, serious hematologic toxicities (grade III, grade IV neutropenia or anemia, platelet counts $<50 \times 10^9$/L, or methemoglobin levels of 15% or greater) have been observed.

Skin and Mucous Membranes

Skin rashes have been reported in 6 patients (0.7%), none of which could be determined as drug related. One case of urticaria was reported but its relationship to drug therapy could not be determined.

Liver

Although no direct relationship of clindamycin to liver dysfunction has been noted, transient abnormalities in liver function tests (elevations of alkaline phosphatase and serum transaminase) have been observed in a few instances.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

No cases of overdosage have been reported. It would be expected however, that should overdosage occur, gastrointestinal side effects including abdominal pain, nausea, vomiting and diarrhea might be seen. During clinical trials, one 3 year old child was given 100 mg/kg of clindamycin for 5 days and showed mild abdominal pain and diarrhea. One 13 year old patient was given 75 mg/kg for 5 days with no side effects. In both cases laboratory values remained normal.

Overdosage should be treated with simple gastric lavage. No specific antidote is known.

DOSAGE AND ADMINISTRATION

Adults: 150 mg every 6 hours

Moderately severe infections: 300 mg every 6 hours

Severe infections: 450 mg every 6 hours

Children (over 1 month of age):

One of the following two dosage ranges should be selected depending on the severity of the infection:

1. 8 to 16 mg/kg/day (4-8 mg/lb/day) divided into 3 or 4 equal doses.
2. 16 to 20 mg/kg/day (8-10 mg/lb/day) divided into 3 or 4 equal doses.

Pneumocystis carinii pneumonia in patients with AIDS:

RIVA-CLINDAMYCIN (clindamycin hydrochloride) 300-450 mg may be given orally every 6 hours in combination with 15-30 mg of primaquine for 21 days. Alternatively, clindamycin phosphate 600-900 mg (IV) may be given every 6 hours or 900 mg (IV) every 8 hours in combination with oral daily dose of 15-30 mg of primaquine. If patients should develop serious hematologic adverse effects, reducing the dosage regimen of primaquine and/or RIVA-CLINDAMYCIN capsule should be considered.

Absorption of RIVA-CLINDAMYCIN (clindamycin hydrochloride) is not appreciably modified by ingestion of food and may be taken with meals.

To avoid the possibility of esophageal irritation, RIVA-CLINDAMYCIN capsules should be taken with a full glass of water.

For prevention of endocarditis:

Adults: 300 mg orally 1 hour before procedure; then 150 mg 6 hours after initial dose.

Children: 10 mg/kg (not to exceed adult dose) orally 1 hour before procedure; then 5 mg/kg 6 hours after initial dose.

Note: With β-hemolytic streptococcal infections, treatment should continue for at least 10 days to diminish the likelihood of subsequent rheumatic fever or glomerulonephritis.

PHARMACEUTICAL INFORMATION

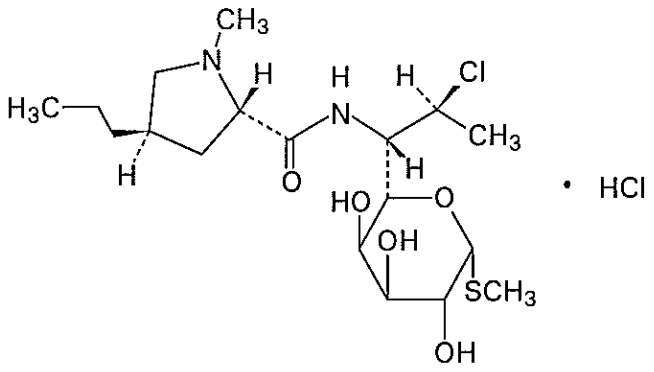
DRUG SUBSTANCE

Proper Name: Clindamycin hydrochloride

Chemical Name: 1. L-threo-α-D-galacto-Octopyranoside, methyl 7-chloro-6,7,8-trideoxy-6-[[(1-methyl-4-propyl-2-pyrrolidinyl)-carbonyl]-amino]-1-thio-, (2S-trans)-, monohydrochloride.

2. Methyl 7-chloro-6,7,8-trideoxy-6-(1-methyl-*trans*-4-propyl-L-2-pyrrolidinecarboxamino)-1-thio-L-*threo*-α-D-*galacto*- octopyranoside monohydrochloride.

Structural Formula:



Molecular Formula: $C_{18}H_{33}ClN_2O_6S \cdot HCl$ (anhydrous)

Molecular Weight: 461.45 (anhydrous) 479.47 (monohydrate)

Description: A white or almost white, hygroscopic, crystalline powder. It is freely soluble in water, in dimethylformamide, and in methanol; soluble in alcohol, practically insoluble in acetone. Clindamycin hydrochloride has a pH of 4.4, a pKa of 7.6, a partition coefficient of 185 and a melting point of 141-143°C.

COMPOSITION

RIVA-CLINDAMYCIN capsules are formulated to contain clindamycin hydrochloride equivalent to 150 mg or 300 mg of clindamycin base. The following excipients are used in the manufacturing of the capsules: corn starch, lactose monohydrate, magnesium stearate, talc and hard gelatin capsule shells. The capsule shells contain gelatin, sodium lauryl sulfate, silicon dioxide and titanium dioxide. The 150 mg capsules contain dyes FD&C Blue #1, FD&C Red #3, D&C Yellow #10, D&C Red #33 and FD&C Red #40. The 300 mg capsules contain FD&C Blue #1.

STABILITY AND STORAGE RECOMMENDATIONS:

Store bottles between 15-30°C.

Store unit dose packages between 15-25°C and protect from high humidity.

AVAILABILITY

RIVA-CLINDAMYCIN (clindamycin hydrochloride) is available as:

150 mg Capsule: Each hard gelatin capsule with opaque amethyst body and opaque maroon cap contains clindamycin hydrochloride equivalent to 150 mg of clindamycin base.

300 mg Capsule: Each hard gelatin capsule with opaque light blue body and opaque light blue cap contains clindamycin hydrochloride equivalent to 300 mg of clindamycin base.

Supplied: Bottles of 100, 500 and 1000 capsules.

MICROBIOLOGY

Table III lists minimum inhibitory concentrations (M.I.C.) of organisms demonstrated to be sensitive to the action of clindamycin, *in vitro* by the standard serial dilution procedure using brain heart infusion broth.

TABLE III

Organism	M.I.C. (µg/mL)
Staphylococcus aureus (coagulase positive)	0.05 - 1.5
Staphylococcus aureus (coagulase negative)	0.05 - 0.1
β-hemolytic streptococcus	0.025 - 0.05
Streptococcus viridans	0.025 - 0.05
Diplococcus pneumoniae	0.025 - 0.05
Bacteroides fragilis	0.05 - 3.1
Peptostreptococcus	<1.0 - 3.0
Peptococcus	<1.0 - 3.0

Table IV lists minimum inhibitory concentrations of organisms for which some strains may be sensitive to clindamycin. Individual M.I.C. determinations for these organisms are recommended before clindamycin is used.

TABLE IV

Organism	M.I.C. (µg/mL)
Neisseria gonorrhoeae	0.01 - 6.3
Hemophilus influenzae	1.6 - 50
Clostridium tetani	3.2
Clostridium perfringens	0.025 - 0.1
Corynebacterium diphtheriae	0.2
Corynebacterium acnes	0.1 - 50
Actinomyces israelii	0.05 - 0.2
Chlamydia trachomatis	0.25 - 2.0

Table V lists minimum inhibitory concentrations of organisms resistant to clindamycin *in vitro*. Clindamycin is not recommended in infections due to these organisms.

TABLE V

Organism	M.I.C. (µg/mL)
Streptococcus faecalis	0.8 - 64
Enterococcus	12.5 - >100
Neisseria meningitis	6.3 - 25
E. Coli	8.0 - 125
Aerobacter aerogenes	>500
Klebsiella pneumoniae	16.0 - 250
Proteus species	64 - 1000
Pseudomonas aeruginosa	1000
Salmonella species	32 - 250
Shigella species	36 - 64

Clindamycin activity was bactericidal in laboratory media for 19 of 20 hospital staphylococci isolates at 1.6 µg/mL or less. The twentieth isolate was killed at 3.2 µg/mL.

Clindamycin resistance development by staphylococci is slow and stepwise rather than rapid and streptomycin-like. Clindamycin, like lincomycin, participates in the dissociated cross-resistance phenomenon with erythromycin.

Clindamycin is not cross-resistant with penicillin, ampicillin, erythromycin, tetracycline or streptomycin. It is, however, cross-resistant with lincomycin.

When tested with commercial human serum, clindamycin at a concentration of 1 µg/mL of clindamycin free base is 92.8% protein bound.

When tested against over 7000 clinical isolates of staphylococci, streptococci and pneumococci from 11 Canadian hospitals and compared with other antibiotics, clindamycin showed the results seen in Table VI.

TABLE VI

Staphylococci (All Types)				
	No. Tested	Sensitive	Resistant	% Sensitive
Clindamycin 2 µg	4087	4548	259	94.6
Lincomycin 2 µg	4837	4555	282	94.2
Erythromycin 2 µg	4836	4233	603	88.5
Penicillin G, 2 I.U.	4836	2006	2830	41.5
Ampicillin 2 µg	3559	1955	1604	54.9
Streptococci (All Types except Strep. faecalis)				
Clindamycin 2 µg	1505	1467	38	97.5
Lincomycin 2 µg	1521	1485	36	97.6
Erythromycin 2 µg	1521	1515	6	99.6
Penicillin G, 2 I.U.	1517	1497	20	98.7
Ampicillin 2 µg	1498	1474	24	98.4
Pneumococci				
Clindamycin 2 µg	785	783	2	99.7
Lincomycin 2 µg	785	781	4	99.5
Erythromycin 2 µg	785	783	2	99.7
Penicillin G, 2 I.U.	785	783	2	99.7
Ampicillin 2 µg	664	662	2	99.7

Animal studies on the etiology of antibiotic-associated colitis and the protective effect of vancomycin have suggested a toxin(s) produced by Clostridia as the causative agent. Studies in

hamsters have shown that oral vancomycin was protective against clindamycin-induced enterocolitis when administered concurrently with or prior to the antibiotic challenge. Vancomycin produced a marked decrease in colonic clostridia counts suggesting that its antimicrobial action was responsible for its protective effect. This was supported by the finding that *in vitro*, vancomycin did not decrease the cytotoxic activity of an isolated toxin associated with antibiotic-induced enterocolitis in hamsters. In rabbits, vancomycin administered concurrently with clindamycin was protective against enterocolitis and resulted in a greatly lower fecal clostridia count. Extracts from the stools of these rabbits were not lethal to mice.

Analysis of the feces of patients with pseudomembranous colitis has shown the presence of a neutralizable toxin and clostridia species (most frequently C. difficile). Almost all strains of C. difficile tested were sensitive to vancomycin with minimum inhibitory concentrations ranging from 0.2 to 16 µg/mL (Table VII).

TABLE VII

Minimum Inhibitory Concentrations (M.I.C.'s) of Vancomycin vs. C. difficile.

# Strains	M.I.C. (µg/mL)	References
39	≤ 4	10
10	0.5 - 4	3
15	0.2 - 1.6	8
37	0.5 - 16	5
17	<1	6

When patients with pseudomembranous colitis were treated with oral vancomycin 125 to 500 mg four times daily, fecal vancomycin concentrations greatly exceeded the minimum inhibitory concentrations for C. difficile.

PHARMACOLOGY

Three large multiple dose tolerance studies were conducted in normal volunteers.

One group of 216 volunteers took 1 gram per day or 2 grams per day of clindamycin for 4 weeks. The most frequent side effect noted was diarrhea in some volunteers, particularly at the 2 gram per day dose which is more than 3 times the recommended daily dose. With the exception of one patient who developed infectious hepatitis during the study, laboratory tests showed no significant aberrations considered drug related. Occasional patients developed elevated serum transaminase and serum alkaline phosphatase.

A second group of 150 volunteers was similarly treated and laboratory determinations were essentially normal. Audiograms were performed before, during and up to 90 days after treatment and showed no drug related changes.

A third group of 172 volunteers was evaluated in a comparison of lincomycin 500 q.i.d., ampicillin 250 mg q.i.d., clindamycin 150 mg q.i.d., and placebo. Subjects receiving ampicillin showed a peak incidence of moderate to mild diarrhea second only to lincomycin and greater than clindamycin during the first week of therapy, then demonstrated a drop in the incidence to placebo levels or below during the second and third week. Meanwhile, the incidence of diarrhea in both the lincomycin and the clindamycin groups remained slightly above that reported for the placebo group during the second and third weeks of therapy. One patient on lincomycin and one on clindamycin developed a rash. No drug related laboratory test abnormalities were noted.

Five volunteers were evaluated before and after treatment with clindamycin 500 mg q.i.d., for 10 days with reference to true or pseudo-cholinesterase levels. No abnormalities in these levels were noted.

TOXICOLOGY

Animal

The results of acute toxicity studies in animals are shown in Table VIII.

TABLE VIII

Animal LD_{50} Results		
Species	Route	LD_{50} (mg/kg)
Adult Mouse	I.P.	262
Adult Mouse	I.V.	143
Adult Rat	Oral	2714
Adult Rat	S.C.	2618
Newborn Rat	S.C.	245

The following subacute and chronic animal toxicology was performed:

5 Day Oral Tolerance Study in Rats:

500 mg/kg was administered to rats with no drug related toxicity noted except that all rats developed diarrhea at this dose level.

5 Day Oral Tolerance Study in the Dog:

Doses of 113 mg/kg and 500 mg/kg were administered. The higher dose was vomited 1-2 hours after administration but otherwise no abnormalities of a drug related nature were noted.

6 Month Subacute Oral Toxicity in the Rat:

Clindamycin, at doses of 30, 100 and 300 mg/kg, was given to groups of 20 rats daily for 6 months. Data obtained after one month were normal. Similarly, data at the end of 6 months showed no drug related effects. A fourth group of 20 rats received a dose of 600 mg/kg for

3 months and also showed the drug to be well tolerated by male and female rats without any drug related effects.

1 Month Subacute Oral Toxicity in the Dog:

Clindamycin, at doses of 30, 100 and 300 mg/kg, was given to 3 groups of 6 dogs with a comparable group of 6 dogs as a control. All dogs were healthy and all dose levels well tolerated.

Fluctuations in the serum glutamic pyruvic transaminase values were seen in the 300 mg/kg group after 2 weeks therapy. Less fluctuation was seen in the SGOT levels and other tests of hepatic function did not reflect the adaptive metabolic change which these elevated transaminase values are believed to show. Two dogs in each group were sacrificed and no drug related lesions were found upon complete necropsy and microscopic observations on these dogs.

1 Year Chronic Oral Toxicity in the Rat:

Doses of 0, 30, 100 and 300 mg/kg were administered daily to rats for one year and 600 mg/kg to 6 months. As expected, mortality did occur due to coincidental disease and the group at 600 mg/kg had a higher mortality rate although no definitive drug related findings were noted.

1 Year Chronic Oral Toxicity in the Dog:

Dogs were administered clindamycin at doses of 0, 30, 100 and 300 mg/kg for 1 year. Some dose related elevations of serum glutamic pyruvic transaminase values were seen during the 7th to 9th month of this study, but periodic liver biopsies examined by light and electron microscopy did not disclose any hepatic cell damage. All other data noted no drug related changes.

Teratogenic and Reproductive Studies in the Rat:

Teratologic evaluation of 20-day foetuses was made and no evidence of teratogenic effect was noted. Treated rat dams gave birth to normal litters and no evidence was obtained that clindamycin affected the fecundity of the dam or the development of the offspring.

Teratogenic and Reproductive Studies in the Mouse:

Clindamycin, in doses of 20, 50 and 200 mg/kg, was administered to pregnant mice from day 6 through day 15 of gestation. At the 200 mg/kg level there was pronounced expected toxicity associated with a 40% mortality. Similarly, at this toxic level there was increased foetal loss. Litter size, litter weight and mean pup weight were significantly reduced. At the 200 mg/kg level there was an increased incidence of major malformations which is thought to be due to malnutrition of the dam as a result of this toxic dose of the drug.

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