PRODUCT MONOGRAPH

LINCOCIN*

lincomycin injection USP

300 mg/mL sterile solution

lincomycin hydrochloride capsules USP

500 mg capsules

Antibiotic

Pfizer Canada Inc
17,300 Trans-Canada Highway
Kirkland, Quebec H9J 2M5

Date of Preparation:
17 September 2003

Control No. 086679

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Pfizer Canada Inc, Licensee

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THERAPEUTIC CLASSIFICATION

Antibiotic

ACTION, CLINICAL PHARMACOLOGY

The mode of action of lincomycin hydrochloride is the inhibition of protein synthesis by the inhibition of the binding of aminoacyl sRNA to the messenger ribosome complex at the 50S ribosomal unit.

INDICATIONS AND CLINICAL USES

Lincocin* (lincomycin hydrochloride) is indicated in the treatment of 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 resistant to other appropriate antibiotics.

Lincocin* is indicated in the treatment of osteomyelitis, when the causative organism has been found to be sensitive to this antibiotic.

CONTRAINDICATIONS

As with all drugs, the use of Lincocin* (lincomycin hydrochloride) is contraindicated in patients previously found to be hypersensitive to the drug or patients who have previously been found hypersensitive to clindamycin (Dalacin C) or to any other component of the product.

Lincocin* should not be given to persons with known pre-existing monilial infections.

Until further clinical experience is obtained, Lincocin* is not indicated in the newborn.

WARNINGS

Use of Lincocin* (lincomycin hydrochloride) has been associated with severe colitis which may be fatal. The major cause of this condition is a toxin produced by *Clostridium difficile*. The condition manifests as a spectrum of symptoms from watery to severe diarrhoea, fever, abdominal cramps and leucocytosis. This may be accompanied by the passage of blood and mucous which may result in peritonitis, shock and toxic megacolon if the drug is not discontinued and/or the condition treated.

Positive diagnosis can be made by performing an endoscopy, culture of the stool for *Clostridium difficile* and performing a selective assay for the toxin(s) produced by *C. difficile*.

Antibiotic associated colitis may occur 2-3 weeks after Lincocin® Administration and is more likely to be severe in elderly or debilitated patients.

Pseudomembraneous colitis has been reported with nearly all antibacterial agents, including lincomycin, and may range in severity from mild to life-threatening. Therefore, it is important to consider the diagnosis in patients who present with diarrhea subsequent to the administration of antibacterial agents.

Treatment with antibacterial agents alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by *Clostridium difficile* is a primary cause of "antibiotic-associated colitis". After the primary diagnosis of pseudomembranous colitis has been established, therapeutic measures should be initiated. Mild cases of pseudomembranous colitis usually respond to drug discontinuation alone. In moderate-to-severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation, and treatment with an antibacterial drug clinically effective against *Clostridium difficile* colitis

Anticholinergics and antiperistaltic agents may worsen the condition. Other causes of colitis should be considered.

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

Lincocin* should not be administered undiluted intravenously. All intravenous doses of Lincocin* should be given by infusion over a period of 30 to 120 minutes. Cases of cardiopulmonary arrest have been reported during the treatment of severe endocarditis when large intravenous doses (over 4 grams) were given rapidly without dilution. These reactions do not occur when the drug is diluted as noted under DOSAGE AND ADMINISTRATION.

This product contains benzyl alcohol. Benzyl alcohol has been reported to be associated with a fatal "Gasping Syndrome" in premature infants.

PRECAUTIONS

GENERAL:

Lincocin* (lincomycin hydrochloride) should be used with caution in those patients with a history of gastro-intestinal disease, specifically colitis.

Lincocin* is not indicated for use in the treatment of meningitis as the levels within the cerebral spinal fluid do not reach an adequate concentration to combat this infection.

No serious renal or neurologic abnormalities have been reported to date. No ototoxicity has been demonstrated in any of a large number of patients treated with Lincocin*.

USE IN OBSTETRICS AND NURSING MOTHERS:

No adverse effects on survival of offspring from birth to weaning were seen in studies performed in rates using oral doses of lincomycin you to 1000mg/kg (7.5 times the maximum human dose of 8g/day). No teratogenic effects were seen in a study conducted in rats treated with more than 55 times the highest recommended adult human dose of 8g/day.

In humans, lincomycin crosses the placenta and results in cord serum levels about 25% of the maternal serum levels. No significant accumulation occurs in the amniotic fluid.

Limited experience with 322 women receiving Lincocin orally at a dosage of 500 mg four times per day for seven days during pregnancy revealed no ill effect in the mother or the fetus. One hundred and ten of these patients were treated in the first trimester of pregnancy, 105 in the second trimester and 107 in the third trimester. All were suffering from cervicitis and/or vaginitis of bacterial origin in conjunction with their pregnancy.

One hundred and twelve of the children, ages 6½ to 7½ years, from these patients have been examined and compared with a control group of 65 children born at the same time in the same hospital. Lincocin* treatment did not result in any drug related abnormalities (physical, dental or developmental) when compared with the control group.

Lincocin* has been reported in breast milk at concentrations of 0.5 - 2.4 ug/mL. However, the use of lincomycin in pregnant and/or breast-feeding women should involve careful consideration of expected benefits and possible risks.

PATIENTS WITH SPECIAL DISEASES AND CONDITIONS:

The serum half-life of Lincocin* is increased in those patients with impaired renal or hepatic function. Therefore, consideration should be given to reducing the frequency of administration in these patients.

Since adequate data are not yet available in patients with pre-existing endocrine or metabolic diseases, its use in such patients is not recommended at this time unless special clinical circumstances so indicate. Efficacy of Lincocin* in the prophylactic treatment of rheumatic fever has not been established.

DRUG INTERACTIONS:

In vitro studies have shown antagonistic activity between Lincocin* and erythromycin; therefore, these agents should not be used concurrently.
Because Lincocin* has been shown to have neuromuscular blocking properties which may enhance the action of other neuromuscular blocking agents, it should be used with caution in patients receiving such agents.

LABORATORY TESTS:

The use of antibiotics occasionally results in overgrowth of non-susceptible organisms -- particularly yeasts. Should superinfections occur, appropriate measures should be taken. No direct relationship of the drug to liver disease has been established. However, it is recommended that all patients receiving treatment for longer than one or two weeks have liver and kidney function tests performed. If abnormal tests appear, the drug should be discontinued unless, in the opinion of the physician, the drug should be continued for the treatment of a serious infection.

During clinical studies of Lincocin* in the therapy of infectious disease, a few cases of neutropenia and/or leukopenia were reported. No cases of irreversible toxicity to the hematopoietic system have been reported; however, it is recommended that blood counts be obtained early and repeated periodically during the course of Lincocin* therapy.

ADVERSE REACTIONS

The following adverse reactions have been reported with the use of Lincocin* (lincomycin hydrochloride):

1. Gastrointestinal - Nausea, vomiting, abdominal distress, persistent diarrhea (See Warning Statement) and esophagitis.

2. Hematopoietic - Neutropenia, leukopenia, agranulocytosis, and thrombocytopenic purpura have been reported. There have been rare reports of aplastic anemia and pancytopenia in which lincomycin could not be ruled out as the causative agent.

3. Hypersensitivity Reactions - Hypersensitivity reactions such as angioneurotic edema, serum sickness and anaphylaxis have been reported, some of these in patients sensitive to penicillin. Rare instances of erythema multiforme, some resembling Stevens-Johnson syndrome, have been associated with Lincocin* administration.

4. Skin and Mucous Membranes - Pruritus, skin rashes, urticaria, vaginitis, and rare instances of exfoliative and vesiculobullous dermatitis have been reported.

5. Liver - Jaundice and abnormal liver function tests (particularly elevation of serum transaminase) have been observed during lincomycin therapy.

6. Cardiovascular - Instances of hypotension following parenteral administration have been reported, particularly after too rapid administration.

   Rare instances of cardiopulmonary arrest have been reported after too rapid intravenous administration. (See Dosage and Administration section).

7. Local Reactions - Local irritation, pain, induration, and sterile abscess formation have been seen with IM injection. Thrombophlebitis has been reported with IV injection. These reactions can be minimized by deep IM injection and avoidance of indwelling intravenous catheters.

SYMPTOMS AND TREATMENT OF OVERDOSAGE:

No cases of large 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.

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

Hemodialysis or peritoneal dialysis does not effectively remove lincomycin from the blood.

DOSAGE AND ADMINISTRATION

	INTRMUSCULAR (Sterile Solution)	**INTRAVENOUS (Sterile Solution)**
Adults	600 mg (2mL) every 24 hours	600 mg (2mL) every 8 to 12** hours. Administer as infusion in 250 mL or more of 5% glucose in water or normal saline over a period of 30 to 120 mins.
Severe	600 mg (2mL) every 12 hours	
Children*	10 mg/kg every 24 hours	10 to 20 mg/kg/day in two or three doses at 8 to 12 hour intervals. Administer as infusion diluted as for adults.
Severe	10 mg/kg every 12 hours	

* Over one month of age

** All doses may be increased in more severe infections. Doses as high as 8.4 grams per day, for seven days, in four divided doses of 2100 mg in an infusion of 250 mL, of normal saline, over a period of 120 minutes, were well tolerated in normal volunteers.

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

When therapy with lincomycin is required in individuals with severe impairment of renal function, an appropriate dose is 25% to 30% of that recommended for patients with normally functioning kidneys.

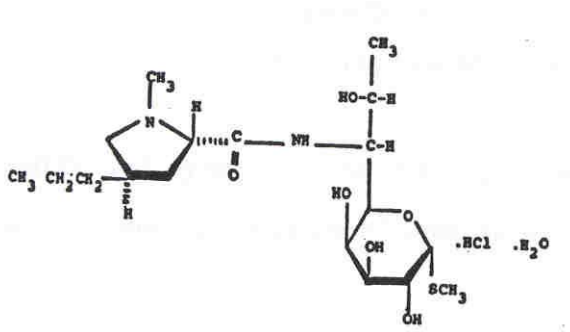
PHARMACEUTICAL INFORMATION

DRUG SUBSTANCE:

Proper Name: Lincomycin hydrochloride monohydrate

Chemical Name: D-erythro--galacto-Octopyranoside, methyl 6, 8-dideoxy-6-[[(1-methyl-4-propyl-2-pyrrolidinyl) carbonyl] amino]-1-thio-monohydrochloride, monohydrate, (2S-trans).

Structural Formula:



Molecular Formula: $C_{18}H_{34}N_2O_6S.HCl.H_2O$

Molecular Weight: 461.01

443.00 (anhydrous)

DESCRIPTION:

Lincomycin, an antibiotic produced by *Streptomyces lincolnensis* var. *lincolnensis*, is chemically distinct from other clinically available antibiotics except its semi-synthetic derivative clindamycin (Dalacin C) and is isolated as a white crystalline solid.

Lincomycin hydrochloride is stable in the dry state and in aqueous solution for at least 24 months. It is readily soluble in water at room temperature in concentrations up to 500 mg/mL. Physical stability of aqueous solutions can be maintained at drug concentrations up to 345 mg/mL at temperatures as low as 4 ºC. The solubility in 95 percent ethanol is 80 mg/mL.

RECONSTITUTED SOLUTIONS:

Lincocin* (600 mg - 2 mL and 1800 mg - 6 mL) was found to be compatible with 500 mL of the following solutions for a period of 24 hours at room temperature:

5% Dextrose in Water	10% Dextrose in Saline
5% Dextrose in Saline	Invert sugar 10%
10% Dextrose in Water	Polysal M with 5% dextrose
Ringer's Solution	Sodium lactate 1/6 molar

Compatibility was determined by a study which indicated no appreciable change in the pH of the resultant mixture and no loss of potency of the Lincocin* when diluted as indicated above.

Incompatibilities

When combined with lincomycin in an infusion solution, novobiocin, kanamycin, and phenytoin are each physically incompatible with lincomycin. This list may not be all-inclusive due to the multiple factors influencing drug compatibility data.

Stability and Storage recommendations:

Store at room temperature (15 -30 ºC), protect from light.

AVAILABILITY OF DOSAGE FORM

Lincocin* (lincomycin hydrochloride) is available as:

Sterile Solution - Each mL containing Lincocin* (lincomycin hydrochloride monohydrate) equivalent to lincomycin base 300 mg; also Benzyl Alcohol, 5 mg; Water for Injection, q.s. - supplied in 2 mL.

Capsules - 500 mg, each capsule containing Lincocin® (lincomycin hydrochloride monohydrate) equivalent to lincomycin base 500 mg, supplied in bottles of 100 capsules.

MICROBIOLOGY

In vitro studies indicate that the spectrum of activity includes *Micrococcus (Staphylococcus) aureus, Staphylococcus albus, 8-hemolytic Streptococcus, Streptococcus viridans, Streptococcus pneumoniae, Clostridium tetani, Clostridium perfringens and Corynebacterium diphtheriae*. Minimum inhibitory concentrations for these organisms are listed in Table I.

TABLE I
Minimum Inhibitory Concentrations (M.I.C.'s) *In Vitro* of Organisms Sensitive to Lincocin* (lincomycin hydrochloride)

ORGANISM	M.I.C. (mcg/mL)	Reference
Staphylococcus aureus	0.12 - 2.0	(16)
Staphylococcus albus	0.8 - 1.5	(9)
8-Hemolytic streptococcus	0.12 - 2.0	(16)
Streptococcus viridans	0.12 - 0.5	(16)
Streptococcus pneumoniae	0.12 - 1.0	(16)
Clostridium tetani & perfringens	0.36 - 1.4	(15)
Corynebacterium diphtheriae	0.4	(9)

This drug is not active against most strains of *Streptococcus faecalis, nor against Neisseria gonorrhoea, Hemophilus influenzae* (with the 2 mcg disk), or other gram-negative organisms or yeasts.

Lincocin* may or may not be bactericidal depending on the serum level attained and the sensitivity of the organism present.

Lincocin* resistance development by staphylococci is slow and stepwise rather than rapid and streptomycin-like. Lincocin* participates in the dissociated cross-resistance phenomenon with

erythromycin. Lincocin* is not cross-resistant with penicillin, ampicillin, erythromycin, tetracycline, or streptomycin. It is however cross-resistant with clindamycin.

Animal studies on the etiology of antibiotic-associated colitis and the protective effect of vancomycin has 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 the 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 mcg/mL (Table II).

TABLE II
Minimum Inhibitory Concentrations (M.I.C.)
of Vancomycin vs *C. difficile*.

# Strains	M.I.C. (mcg/mL)	Reference
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 MIC's for *C. difficile*.

PHARMACOLOGY

Clinical Absorption

Lincomycin is absorbed rapidly after oral administration, reaching peak levels in two to four hours. Levels above the minimum inhibitory concentration for most gram-positive organisms are maintained for six to eight hours. Intramuscular administration of lincomycin produces peak serum levels in 30 minutes with detectable levels persisting for 24 hours after a 600 mg dose.

Intravenous infusions of lincomycin over a two hour interval yield therapeutic levels for 14 hours (see TABLE III)

TABLE III
Average Serum Levels in mcg/mL of Lincomycin After Single Dose Administration in Normal Volunteers

			Time After Medication In Hours					
DOSAGE	**ROUTE**	**0.5**	**2**	**4**	**6**	**8**	**12**	**24**
500 mg	Oral	-	5.3	2.4	1.7	1.3	0.3	-
1000 mg	Oral	-	6.72	3.01	2.19	1.61	0.84	-
300 mg	I.M.	15.0	10.2	7.4	4.1	2.1	0.7	0
600 mg	I.M.	18.5	10.5	5.5	4.9	4.2	1.3	0.3
600 mg	I.V.	20.9	11.2	6.4	3.7	2.2	1.1	0

The biological half-life after oral, intramuscular or intravenous administration is 5.4 ± 1.0 hours.

Urinary Excretion

The urinary excretion of lincomycin varies depending on the dosage used and the route of administration (SeeTableIV).

TABLE IV
Range and Average 24-hour Urinary Recovery of Lincomycin After a Single Dose in Normal Volunteers

DOSAGE	ROUTE	RANGE*	AVERAGE*
500 mg	Oral	1.8 to 13.7	6.17
1000 mg	Oral	1.7 to 27.0	9.49
300 mg	I.M.	5.57 to 16.89	10.48
600 mg	I.M.	1.82 to 24.80	10.30
600 mg	I.V.	4.9 to 23.3	15.1

*Expressed as a percentage of the administration dose, 10 patients in each group.

Biliary Excretion

The bile is an important route of excretion of lincomycin as can be seen in the results tabulated in Table V.

TABLE V
Serum and Biliary Levels After Single Oral and I.V. Doses of Lincomycin

	SINGLE I.V. DOSE 600 mg		SINGLE ORAL DOSE 1000 mg	
TIME AFTER MEDICATION	**SERUM***	**BILE****	**SERUM***	**BILE****
0.5 hours	8.8	-	-	-
1 hour	-	67.0	-	-
2 hours	5.2	8.0	2.8	-
3 hours	-	-	-	1.0
4 hours	3.8	3.8	1.8	1.15
5 hours	-	7.0	-	-
6 hours	3.8	2.8	1.1	2.1
7 hours	-	1.2	-	-
8 hours	3.8	1.5	1.1	-
9 hours	-	2.4	-	-
10 hours	-	1.3	-	-
12 hours	0.9	-	0	17.0
14 hours	-	-	-	42.0
24 hours	0	0	0	0

* mcg/mL of serum
** mcg/mL of bile

Lincomycin Levels in Tissues and Body Fluids

Lincomycin penetrates most body tissues and fluids to a varying degree, depending on the dosage and route of administration. Table VI represents a compilation of data available in this regard.

TABLE VI
Tissue and Body Fluid Levels of Lincomycin in Humans

TISSUE OR BODY FLUID	LINCOMYCIN DOSAGE AND ROUTE OF ADMINISTRATION	RANGE OF VALUES*
Appendix	500 mg q6h for 3 days orally	0.9-13.5
Bile	500 mg q6h for 3 days orally	5.2-44.7
Breast	500 mg q6h for 3 days orally	<0.4- 1.7
Bronchus	500 mg q6h for 3 days orally	1.7
Gall Bladder	500 mg q6h for 3 days orally	0.9- 5.9
Lung	500 mg q6h for 3 days orally	1.5- 1.8
Muscle	500 mg q6h for 3 days orally	<0.6- 3.4
Omentum	500 mg q6h for 3 days orally	<0.4- 1.9
Pleural Fluid	500 mg q6h for 3 days orally	1.9- 3.6
Tonsil	500 mg q6h for 3 days orally	0.9-11.0
Amniotic Fluid	600 mg I.M. Single Dose	1.5- 6.9
Human Milk	500 mg q6h for 12 Doses	0.5- 1.8
Spinal Fluid (normal volunteers)	600 mg I.M. Single Dose	0.7- 1.15
Spinal Fluid (pneumococcal meningitis)	1200 mg I.V. q4h	20.0**
Joint Fluid	600 mg I.M. q6h	4.3-20.0
Aqueous Humor (non-inflamed eyes)	600 mg I.M. q4h	<0.5- 2.0
Aqueous Humor (inflamed eye)	600 mg I.M. q4h	21.0**
Bone	600 mg I.M. q6h	2.2- 6.6

* in mcg/mL of body fluids or mcg/gram of tissue homogenates
** only one specimen available.

The absorption of lincomycin administered orally is somewhat suppressed when given in the presence of cyclamates or cyclamate-containing foods or beverage.

TOXICOLOGY

The acute LD_{50} intraperitoneally in mice is 1000 mg/kg and orally in rats is >4000 mg/kg. Lincomycin was well tolerated orally in rats and dogs at doses up to 300 mg/kg/day for periods up to one year. Parenteral dosages of up to 60 mg/kg/day for 30 days subcutaneously in the rat and intramuscularly in the dog produced no significant systemic effects or pathological findings at necropsy.

Lincomycin at a daily dose level of 75 mg/kg subcutaneously was injected into mature male and female rats during a prebreeding period of 60 days and throughout two mating cycles (84 days). No evidence was obtained that lincomycin exerted any effect on breeding performance and no drug-induced anomalies were discovered in the young. Similarly no evidence was obtained that lincomycin, when given in sustained parenteral dosage of 50 mg/kg daily to pregnant bitches, produced a teratogenic effect of the canine embryo.

The subcutaneous LD_{50} value in the newborn rat was determined to be 783 mg/kg. Newborn rats and canine pups have tolerated multiple doses of 30 - 90 mg/kg/day of the drug without evidence of ill effects.

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