PT. PFIZER INDONESIA
Local Product Document

Generic Name: Lincomycin
Trade Name: LINCOCIN®
CDS Effective Date: February 13, 2018
Supersedes: October 28, 2014

Pada proses pembuatannya bersinggungan dengan bahan bersumber babi

DESCRIPTION

LINCOCIN® Capsules contain lincomycin hydrochloride which is the monohydrated salt of lincomycin, a substance produced by the growth of a member of the *lincolnensis* group of *Streptomyces lincolnensis* (Fam. *Streptomycetaceae*). It is a white or practically white, crystalline powder and is odorless or has a faint odor. Its solutions are acid and are dextrorotatory. Lincomycin hydrochloride is freely soluble in water; soluble in dimethyl-formamide, and very slightly soluble in acetone.

CLINICAL PHARMACOLOGY

Microbiology - Lincomycin has been shown to be effective against most of the common gram-positive pathogens. Depending on the sensitivity of organism and concentration of the antibiotic, it may be either bactericidal or bacteriostatic. Cross resistance has not been demonstrated with penicillin, chloramphenicol, ampicillin, cephalosporins or the tetracyclines. Despite chemical differences, lincomycin exhibits antibacterial activity similar but not identical to the macrolide antibiotics (e.g., erythromycin). Some cross resistance (with erythromycin) including a phenomenon known as dissociated cross resistance or macrolide effect has been reported. Microorganisms have not developed resistance to lincomycin rapidly when tested *in vitro* or *in vivo* methods. Staphylococci developed resistance to lincomycin in a slow, stepwise manner based on *in vitro*, serial subculture experiments. This pattern of resistance development is unlike that shown for streptomycin.

Studies indicate that lincomycin does not share antigenicity with penicillin compounds.

Biological Studies - *In vitro* studies indicate that the spectrum of activity includes *Staphylococcus aureus*, *Staphylococcus albus*, *β-hemolytic Streptococcus*, *Streptococcus viridans*, *Diplococcus pneumoniae*, *Clostridium tetani*, *Clostridium perfringens*, *Corynebacterium diphteriae* and *Corynebacterium acnes*.

NOTE: this drug is not active against most strains of *Streptococcus faecalis*, nor against *Neisseria gonorrhoeae*, *Neisseria meningitidis*, *Hemophilus influenzae*, or other gram-negative organism of yeasts.

Human Pharmacology - Lincomycin is absorbed rapidly after a 500 mg oral dose, reaching peak levels in 2 to 4 hours. Levels are maintained above the Minimum Inhibitory Concentration (MIC) for most gram-positive organisms for 6 to 8 hours. Urinary recovery of drug in a 24-hour period ranges from 1.0 to 31 percent (mean: 4.0) after a single oral dose of 500 mg of lincomycin. Tissue level studies indicate that bile is an important route of excretion. Significant levels have been demonstrated in the majority of body tissues. Although the drug is not present in significant amounts in the spinal fluid of normal volunteers, it has been demonstrated in the spinal fluid of one patient with pneumococcal meningitis.

Intramuscular administration of a single dose of 600 mg of lincomycin produces a peak serum level at 30 minutes with detectable levels persisting for 24 hours. Urinary excretion after this dose ranges from 1.8 to 24.8 percent (mean: 17.3)

The intravenous infusion over a 2-hour interval of 600 mg of lincomycin in 500 ml of 5 percent glucose in distilled water yields therapeutic levels for 14 hours. Urinary excretion ranges from 4.9 to 30.3 percent (mean 13.8)

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

Hemodialysis and peritoneal dialysis do not effectively remove lincomycin from the blood.

Pharmacodynamic Properties

Mode of Action:

Lincomycin is an antibiotic produced by fermentation of *Streptomyces lincolnensis*. Lincomycin inhibits bacterial protein synthesis by binding to the 50S subunit of the bacterial ribosome. Lincomycin is predominantly bacteriostatic *in vitro*. The antibacterial activity of lincomycin appears to best correlate with the length of time the concentration of active ingredient remains above the MIC of the infecting organism.

Mechanism of Resistance

Cross resistance between lincomycin and clindamycin is complete. Resistance in staphylococci and streptococci is most often due to methylation of specific nucleotides in the 23S RNA of the 50S ribosomal subunit, which can determine cross resistance to macrolides and streptogramins B (MLS_B phenotype). Macrolide-resistant isolates of these organisms should be tested for inducible resistance to lincomycin/clindamycin using the D-zone test.

Antibacterial Spectrum

The prevalence of acquired resistance may vary geographically and with time for selected species and local information on resistance is desirable, particularly when treating severe infections. As necessary, expert advice should be sought when the local prevalence of resistance is such that the utility of the agent in at least some types of infections is questionable.

Lincomycin is cross-resistant with clindamycin. A decrease in clindamycin/lincomycin susceptibility over time has been noted in particular among methicillin-resistant *Staphylococcus aureus*.

Antimicrobial Activity
Lincomycin has been shown to be active against most strains of the following bacteria **both *in vitro* and in clinical infections:** (see Section **INDICATIONS AND USAGE**).

Staphylococcus aureus
Streptococcus pneumoniae

The following *in vitro* data are available, but their clinical significance is unknown.

Lincomycin has been shown to be active *in vitro* against the following microorganisms; however, the safety and efficacy of LINCOCIN® in treating clinical infections due to these organisms have not been established in adequate and well controlled trials.

Gram-positive bacteria:
Corynebacterium diphtheriae
Streptococcus pyogenes
Viridans group streptococci

Anaerobic bacteria:
Clostridium tetani
Clostridium perfringens

Pharmacokinetic Properties
Oral administration of a single 500 mg dose of lincomycin in the fasting state produces an average peak serum level of 5.3 µg/mL at 2 hours post-dose. Administration immediately after a meal reduces oral absorption.

Tissue level studies indicate that bile is an important route of excretion. Significant levels have been demonstrated in the majority of body tissues. Although lincomycin appears to diffuse into cerebrospinal fluid (CSF), levels of lincomycin in the CSF appear inadequate for the treatment of meningitis.

Preclinical Safety Data
Nonclinical data from conventional studies on repeated administration toxicity, genotoxicity, carcinogenesis, and reproductive and developmental toxicity have not identified any particular risks to humans. No developmental toxicity was observed when doses greater than 6x the maximum recommended human dose (MRHD) were administered to pregnant rats during the organogenesis period. No effects on fertility were observed in rats administered lincomycin at 1.2x the MRHD.

INDICATION AND USAGE
LINCOCIN® is indicated in the treatment of serious infections due to susceptible strains of streptococci, pneumococci and staphylococci. Its use should be reserved for penicillin-allergic patients or where therapy with penicillin is inappropriate. Because of

the risk of severe colitis, the nature of infection and the suitability of less toxic alternatives (e.g., erythromycin) should be considered before selecting lincomycin.

CONTRAINDICATIONS

LINCOCIN® is contraindicated in patients previously found sensitive to lincomycin or clindamycin or to any other component of the product. It is not indicated in the treatment of minor bacterial infections or viral infections.

WARNINGS

Lincomycin therapy, like therapy with other broad spectrum antibiotics, has been associated with pseudomembranous colitis which may end fatally. Therefore it should be reserved for serious infections where less toxic antimicrobial agents are inappropriate, as described in INDICATIONS AND USAGE section. Diarrhea, colitis, and pseudomembranous colitis have been observed to begin up to several weeks following cessation of therapy with lincomycin. Consequently, it is important to consider this diagnosis in patients who present with diarrhea subsequent to the administration of lincomycin.

Severe hypersensitivity reactions, including anaphylactic reactions and severe cutaneous adverse reactions (SCAR) such as Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), acute generalised exanthematous pustulosis (AGEP), and erythema multiforme (EM) have been reported in patients receiving lincomycin therapy. If an anaphylactic reaction or severe skin reaction occurs, lincomycin should be discontinued and appropriate therapy should be initiated (see Section **ADVERSE REACTIONS**).

Treatment with antibiotics alters the normal flora of the colon and may permit the overgrowth of clostridia. Studies indicate a toxin produced by *Clostridium difficile* is the primary cause of “antibiotic-associated colitis”.

Clostridium difficile associated diarrhea (CDAD) has been reported with use of nearly all antibacterial agents, including lincomycin, and may range in severity from mild diarrhea to fatal colitis. Treatment with antibacterial agents alters the normal flora of the colon leading to overgrowth of *C. difficile.*

C. difficile produces toxins A and B which contribute to the development of CDAD. Hypertoxin producing strains of *C. difficile* cause increased morbidity and mortality, as these infections can be refractory to antimicrobial therapy and may require colectomy. CDAD must be considered in all patients who present with diarrhea following antibiotic use. Careful medical history is necessary since CDAD has been reported to occur over two months after the administration of antibacterial agents.

After the diagnosis of pseudomembranous colitis has been established, therapeutic measures should be initiated.

Mild cases of colitis may respond to drug discontinuance alone. Moderate to severe cases should be managed promptly with fluids, electrolytes and protein supplementation as indicated and be treated with an antibacterial drug clinically effective against *Clostridium difficile* colitis. Vancomycin has been found to be

effective in the treatment of antibiotic associated pseudomembranous colitis produced by *Clostridium difficile*. The usual adult dose is 500 mg to 2 g of vancomycin orally per day in three to four divided doses administered for 7 to 10 days. Cholestyramine or colestipol resins bind vancomycin *in vitro*. If both a resin and vancomycin are to be administered concurrently, it may be advisable to separate the time of administration of each drug. Systemic corticoids and corticoid retention enemas may help relieve the colitis. Other causes of colitis should also be considered.

Although lincomycin appears to diffuse into cerebrospinal fluid, levels of lincomycin in the CSF may be inadequate for the treatment of meningitis. Thus, the drug should not be used in the treatment of meningitis.

A careful inquiry should be made concerning previous sensitivities to drugs and other allergens.

Usage in Pregnancy - Safety for use in pregnancy has not been established.

Usage in Newborn - Until further clinical experience is obtained, LINCOCIN® preparations (lincomycin) are not indicated in the newborn.

Nursing Mothers - Lincomycin has been reported to appear in breast milk in ranges of 0.5 to 2.4 mcg/ml.

PRECAUTIONS

Review of experience to date suggests that a subgroup of older patients with associated severe illness may tolerate diarrhea less well. When LINCOCIN® preparations (lincomycin) are indicated in these patients, they should be carefully monitored for change in bowel frequency.

LINCOCIN® should be prescribed with caution in individuals with a history of gastrointestinal disease particularly colitis.

LINCOCIN® like any drug, should be used with caution in patients with a history of asthma or significant allergies.

The use of antibiotics occasionally results in overgrowth of non-susceptible organisms, particularly yeasts. Should superinfections occur, appropriate measures should be taken. When patients with pre-existing monilial infections require therapy with LINCOCIN®, concomitant antimonilial treatment should be given.

During prolonged therapy with LINCOCIN®, periodic liver and renal function studies and blood counts should be performed.

Since adequate data are not yet available in patients with pre-existing liver disease, its use in such patients is not recommended at this time unless special clinical circumstances so indicate.

Lincomycin has been shown to have neuromuscular blocking properties that may enhance the actions of other neuromuscular blocking agents. Therefore, it should be used with caution in patients receiving such agents.

Indicated surgical procedures should be performed in conjunction with antibiotic therapy.

FERTILITY, PREGNANCY AND LACTATION
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. There are limited data on the use of lincomycin in pregnant women. The progeny of 302 patients treated with lincomycin at various stages of pregnancy showed no increases in congenital anomalies or delayed development compared to a control group for up to 7 years after birth. Lincomycin should be used during pregnancy only if clearly needed.

Lincomycin has been reported to appear in human breast milk in concentrations of 0.5 to 2.4 mcg/ml.

EFFECTS ON ABILITY TO DRIVE AND USE MACHINES
No studies were conducted to determine the effect of lincomycin on ability to drive and use machines.

ADVERSE REACTIONS
Gastrointestinal - Glossitis, stomatitis, enterocolitis, and pruritus ani.

Renal - Renal dysfunction as evidenced by azotemia, oliguria, and/or proteinuria has been observed in rare instances.

Adverse Reactions Table: ADRs by SOC and CIOMS frequency category listed in order of decreasing medical seriousness or clinical importance within each frequency category and SOC

System Organ Class	**Very Common (≥1/10)**	**Common (≥1/100 to <1/10)**	**Uncommon (≥1/1000 to <1/100)**	**Rare (≥1/10,000 to <1/1000)**	**Very Rare (<1/10,000)**	**Frequency Not Known *(Cannot be Estimated from the Available Data)***
Infections and infestations			Vaginal infection			Pseudomembranous colitis, *Clostridium difficile* colitis
Blood and lymphatic system disorders						Pancytopenia, Agranulocytosis, Aplastic anaemia, Neutropenia, Leukopenia, Thrombocytopenic purpura
Immune system disorders						Anaphylactic reaction, Angioedema, Serum sickness
Cardiac disorders						Cardio-respiratory arrest[a]

Adverse Reactions Table: ADRs by SOC and CIOMS frequency category listed in order of decreasing medical seriousness or clinical importance within each frequency category and SOC

System Organ Class	Very Common (≥1/10)	Common (≥1/100 to <1/10)	Uncommon (≥1/1000 to <1/100)	Rare (≥1/10,000 to <1/1000)	Very Rare (<1/10,000)	Frequency Not Known *(Cannot be Estimated from the Available Data)*
Vascular disorders						Hypotension[b], Thrombophlebitis[c]
Gastrointestinal disorders		Diarrhoea, Nausea, Vomiting				Oesophagitis[d], Abdominal discomfort
Hepatobiliary disorders						Jaundice, Liver function test abnormal
Skin and subcutaneous tissue disorders			Rash, Urticaria	Pruritus		Toxic epidermal necrolysis Stevens-Johnson syndrome, Acute generalised exanthematous pustulosis Dermatitis bullous, Dermatitis exfoliative, Erythema multiforme
General disorders and administration site conditions						Injection site abscess sterile[e], Injection site induration[e], Injection site pain[e], Injection site irritation[e]

a. Rare instances have been reported after too rapid intravenous administration.
b. Following parenteral administration, particularly after too rapid administration.
c. Event has been reported with intravenous injection.
d. Event has been reported with oral preparations.
e. Reported with intramuscular injection.

INTERACTIONS

Lincomycin has been shown to have neuromuscular blocking properties that may enhance the action of other neuromuscular blocking agents. Therefore, lincomycin should be used with caution in patients receiving such agents.

OVERDOSE

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

DOSAGE AND ADMINISTRATION

If significant diarrhea occurs during therapy, this antibiotic should be discontinued (see **WARNING** section).

ORAL - Adults: Serious infections due to susceptible organisms, 500 mg 3 times per day (every 8 hours). More severe infections, 500 mg 4 times per day (every 6 hours).
Children over 1 month of age: Serious infections, 30 mg/kg/day divided into 3 or 4 equal doses. More severe infections, 60 mg/kg/day divided into 3 or 4 equal doses.

In cases of β-hemolytic streptococcal infections, treatment should be continued for at least 10 days.

Note: For optimal absorption, it is recommended that nothing be given by mouth for a period of 1 to 2 hours before and after oral administration of lincomycin.

Dosage in Patients with Diminished Hepatic or Renal Function
In patients with impaired hepatic function or impaired renal function, lincomycin's serum half-life is increased. Consideration should be given to decreasing the frequency of administration of lincomycin in patients with impaired hepatic or renal function.

Patients with diminished renal function: When therapy with LINCOCIN® 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.

ANIMAL PHARMACOLOGY
In vivo experimental animal studies demonstrated the effectiveness of LINCOCIN® preparations (lincomycin) in protecting animals infected with *Streptococcus viridans*, *β-hemolytic-Streptococcus*, *Staphylococcus aureus*, *Diplococcus pneumoniae*, and *Leptospira pomona*. It was ineffective in *Klebsiella*, *Pasteurella*, *Pseudomonas*, *Salmonella*, and *Shigella* infections.

CLINICAL STUDIES
Experience with 345 obstetrical patients receiving this drug revealed no ill effects related to pregnancy.

PHARMACEUTICAL PARTICULARS
List of excipients:
Lactose, talc, magnesium stearate and hard gelatin capsule shells.

The opaque dark blue color cap capsule shell components contain gelatin, FD&C blue 1, ponceau 4R, and titanium dioxide.

The opaque light blue body capsule shell components contain gelatin, FD&C blue 1, FD&C Red 40, and titanium dioxide.

HOW SUPPLIED
LINCOCIN® Capsules contain lincomycin hydrochloride equivalent to 500 mg of lincomycin.

LINCOCIN® 500 mg; Box, 3 blisters @ 10 capsules; Reg No.: DKL7219808601A1

Store at maximum temperature 30°C.

HARUS DENGAN RESEP DOKTER

Manufactured by

PT. Pfizer Indonesia
Jakarta, Indonesia