LINCOCIN® capsules, syrup, injection
(Lincomycin)

1. NAME OF THE MEDICINAL PRODUCT

LINCOCIN®

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

LINCOCIN® is available as:

- LINCOCIN® Injection 300 mg/mL
- LINCOCIN® Injection 600 mg/2 mL
- LINCOCIN® Capsules 500 mg
- LINCOCIN® Syrup 250 mg/5ml

3. PHARMACEUTICAL FORM

Capsules, syrup
FOR ORAL USE

Solution for injection
FOR INTRAVENOUS AND INTRAMUSCULAR USE

4. CLINICAL PARTICULARS

4.1. THERAPEUTIC INDICATIONS

LINCOCIN® is indicated in severe infections due to strains of staphylococci, pneumococci and streptococci susceptible to its action.
Its use should be reserved to penicillin-allergic patients or to other patients for whom, in the physician's opinion, penicillin is inappropriate.
Because of the possible risk of developing a severe colitis (see section 4.4. SPECIAL WARNINGS AND PRECAUTIONS FOR USE), before starting treatment with LINCOCIN®, the physician should carefully evaluate, also depending on the nature of the infection to be treated, the suitability of less toxic alternatives.
LINCOCIN® has been found to be effective in the treatment of infections due to staphylococci resistant to other antibiotics: however, since strains of staphylococci resistant to LINCOCIN® have been isolated, susceptibility tests should be performed during the treatment with LINCOCIN®.
The drug may be administered in concomitance with other antimicrobial agents when indicated.

4.2. POSOLOGY AND METHOD OF ADMINISTRATION

Posology

Oral route
Adults

- Severe infections: 500 mg every 8 hours

- Very severe infections: 500 mg every 6 hours
  To achieve an optimal absorption, it is recommended to ingest nothing save water for a period of one to two hours before and after administration of LINCOCIN®.

Intramuscular route
Adults
- Severe infections: 600 mg (2 ml) every 24 hours.
- Very severe infections: 600 mg (2 ml) every 12 hours or more frequently, depending on the severity of the infection.

Paediatric population

Children over 2 years of age
- Severe infections: 10 mg/kg/daily by intramuscular injection.
- Very severe infections: 10 mg/kg/ every 12 hours or more frequently.

Intravenous route
Adults
600 mg (2 ml) by intravenous route every 8-12 hours.
In case of very severe infections, the dose may be increased.

Paediatric population

Children (over 2 years of age)
10-20 mg/kg/daily divided into 2-3 infusions every 12-8 hours.

Method of administration

LINCOCIN® injectable solution should be diluted at concentrations no higher than 600 mg/100ml (see "Compatibilities" section below) and administered by slow infusion lasting not less than 1 hour. Severe cardiopulmonary reactions have occurred following administration at concentrations and administration rates higher than those recommended.
In case of beta-hemolytic streptococcal infection, treatment should be prolonged for at least 10 days to reduce the likelihood of occurrence of rheumatic disease and glomerulonephritis.

Patients with impaired renal function: if treatment with lincomycin is required in patients with severely reduced renal function, the appropriate recommended dose is equivalent to 25-30% of those normally recommended in patients with normal renal function.

Compatibilities
Lincomycin is physically compatible for 24 hours at room temperature, unless otherwise indicated, with:

- **Infusion solutions:** Dextrose in water, 5% and 10% solutions; dextrose in saline solution, 5% and 10% solutions; Ringer solution; 1/6 M Sodium lactate; Travert 10%-Electrolyte No. 1; Dextran in 6% saline solution w/v.

- **Vitamins in infusion solutions:** B complex vitamins; B complex vitamins with ascorbic acid.

- **Antibiotics in infusion solutions:** Penicillin G sodium (satisfactory for 4 hours); cephalothin; cephaloridine; tetracycline HCl; colistimethate (satisfactory for 4 hours); ampicillin, methicillin; cloramphenicol; polymixin B sulfate.

Incompatibilities
Lincomycin is physically incompatible with novobiocin and kanamycin.

It should be stressed that the determinations of compatibility and incompatibility are only physical observations not chemical determinations. No adequate clinical evaluations of the safety and efficacy of these combinations have been performed so far.

4.3. CONTRAINDICATIONS

Hypersensitivity to lincomycin, to clindamycin, or to any of the excipients listed in section 6.1.
The drug is not indicated in the treatment of minor bacterial or viral infections.
LINCOCIN® injectable solution must not be given to premature babies, neonates or children younger than 2 years (see section 4.4. Special WARNINGS AND PRECAUTIONS for Use).

4.4. SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Serious hypersensitivity reactions, including anaphylactic reactions and severe cutaneous adverse reactions (SCAR), e.g., Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), acute generalized exanthematous pustulosis (AGEP) and erythema multiforme (EM), have been reported in patients receiving lincomycin therapy. If anaphylactic reactions or severe skin reactions occur, lincomycin administration should be discontinued and an appropriate therapy should be initiated (see section **4.8. UNDESIRABLE EFFECTS**).

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.

Cases of mild colitis may subside following discontinuation of treatment with lincomycin. Moderate to severe cases should promptly be managed with the administration of fluids, electrolyte solutions and proteins (if indicated).

Antiperistaltic drugs, such as opioids and diphenoxylate with atropine, could prolong and/or worsen the situation. Vancomycin has been shown to be effective in the treatment of pseudomembranous colitis caused by *Clostridium difficile*. The usual adult dose is 0.5–2 g daily of oral vancomycin, divided into three to four administrations for 7-10 days.

Cholestyramine and colestipol resins bind vancomycin *in vitro*. If both a resin and vancomycin are to be administered concurrently, it is advisable to separate the time of administration of each drug. However, all the other causes responsible for colitis should also be considered.

Currently available data show that elderly or weakened patients may tolerate less well diarrhea; if these patients need to be treated with LINCOCIN®, they should be carefully monitored for any changes in bowel frequency.
LINCOCIN® should be prescribed with caution in patients with history of gastrointestinal disorders, especially colitis and in atopic individuals.

During a long-term therapy, periodical checks of liver and kidney functions and complete blood count should be performed. The serum half-life of lincomycin increases in patients with impaired liver or renal function. In such patients, a reduced frequency of administration of lincomycin should be considered. In particular, since adequate clinical data are not yet available, it should be advisable to avoid the use of LINCOCIN® in patients with pre-existing liver disease, unless special clinical circumstances indicate so.

Though it seems that lincomycin passes into the cephalorachidian fluid, its levels in cephalorachidian fluid may be inadequate for the treatment of meningitis. Therefore, the drug should not be used in the management of this condition.

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

Lincomycin should not be administered as intravenous bolus, but in infusions, as described in section **4.2. POSOLOGY AND METHOD OF ADMINISTRATION.**

The use of antibiotics may occasionally result in growth of non-susceptible organisms, particularly yeasts. If a superinfection occurs, adequate measures should be taken. If a patient with pre-existing monilial infections needs treatment with LINCOCIN®, concomitant antimonilial therapy should be given.

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

Excipient information

Lincocin injectable solution contains **benzyl alcohol**.
The preservative benzyl alcohol may cause allergic reactions.
Intravenous administration of benzyl alcohol has been associated with serious adverse events and death in paediatric patients including neonates (“gasping syndrome”). Although normal therapeutic doses of this product ordinarily deliver amounts of benzyl alcohol that are substantially lower than those reported in association with the “gasping syndrome”, the minimum amount of benzyl alcohol at which toxicity may occur is not known.

Premature and low-birth weight infants may be more likely to develop toxicity.

Benzyl alcohol containing formulations should not be used for more than 1 week in children under 3 years of age unless necessary. If use of a benzyl alcohol-containing formulation of Lincocin is necessary, it is important to consider the combined daily metabolic load of benzyl alcohol from all sources, especially in patients with liver or kidney impairment, as well as in pregnant or breast-feeding women, because of the risk of accumulation and toxicity (metabolic acidosis).

The capsules contain **lactose**. Patients with rare hereditary problems of galactose intolerance, the total lactase deficiency, or glucose-galactose malabsorption should not take this medicine.

4.5. INTERACTION WITH OTHER MEDICAMENTS AND OTHER FORMS OF INTERACTION

Lincomycin could enhance the neuromuscular blocking effect of drugs with such specific action. There is a known cross reactivity between clindamycin and lincomycin.

4.6. FERTILITY, PREGNANCY AND LACTATION

Pregnancy
There are limited data on the use of lincomycin in pregnant women. In woman, lincomycin crosses the placenta reaching, at cord level, serum levels of 25% with respect to maternal serum levels. There is no significant accumulation at amniotic fluid level. The progeny of 302 patients treated with lincomycin at different stages of pregnancy did not show an increase in congenital anomalies or developmental delays compared to a control group up to 7 years after birth.

Lincomycin should only be used during pregnancy if strictly necessary.

Lincocin contains benzyl alcohol as a preservative. Benzyl alcohol can cross the placenta (see section 4.4. SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Breastfeeding
Lincomycin is excreted into the mother's milk in concentrations of 0.5 to 2.4 mcg/mL.

4.7. 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.

4.8. UNDESIRABLE EFFECTS

Table of adverse reactions

System organ class	**Very common (≥1/10)**	**Common (≥1/100 to <1/10)**	**Uncommon (≥1/1,000 to <1/100)**	**Rare (≥1/10,000 to <1/1,000)**	**Very rare (<1/10,000)**	**Frequency not known *(cannot be estimated from the available data)***
Infections and infestations			Vaginal infection			Pseudomembranous colitis, colitis from *Clostridium difficile* (see section 4.4)
Blood and lymphatic system disorders						Pancytopoenia, agranulocytosis, aplastic anaemia, neutropoenia, leukopoenia, thrombocytopoenic purpura
Immune system disorders						Anaphylactic reactions, angio-oedema, serum

						sickness
Cardiac disorders						Cardiopulmonary arrest[a]
Vascular disorders						Hypotension[b], thrombophlebitis[c]
Gastrointestinal disorders		Diarrhoea, nausea, vomiting				Oesophagitis[d], abdominal discomfort
Hepatobiliary disorders						Jaundice, abnormal liver function tests
Skin and subcutaneous tissue disorders			Skin rash, urticaria	Itching		Toxic epidermal necrolysis, Steven-Johnson syndrome, acute generalized exanthematous pustulosis, bullous dermatitis, exfoliative dermatitis, erythema multiforme
General disorders and administration site conditions						Sterile injection-site abscess[e], injection-site induration[e], injection-site pain[e], injection-site irritation[e]

a Rare cases have been reported after excessively rapid intravenous administration.
b After parenteral administration, particularly after excessively rapid administration.
c Event reported with intravenous injection.
d Event reported with preparation for oral use.
e Reported with intramuscular injection.

Other adverse events:

Gastrointestinal disorders: Glossitis, stomatitis, enterocolitis, *pruritus ani*.

Renal and urinary disorders: Although no direct relationship between treatment with lincomycin and renal damage has been established, renal dysfunction as evidenced by elevation of blood urea levels, oliguria and/or proteinuria has been observed in a few cases.

Ear and labyrinth disorders: Instances of vertigo and tinnitus have occasionally been reported.

If allergic reactions should occur, therapy should be discontinued and standard emergency treatment (adrenaline, corticosteroids, antihistamines) should be started.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorization of the medicinal product is important, as it allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions.

4.9. OVERDOSE

No data are known so far.

5. PHARMACOLOGICAL PROPERTIES

5.1. PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic group: Antibacterial agents for systemic use. Lincosamides.
ATC code: J01FF02.

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.

Methodology for determining in vitro susceptibility to lincomycin
Susceptibility testing should be conducted using standardized laboratory methods, such as those described by the Clinical and Laboratory Standards Institute (CLSI) or the European Committee on Antimicrobial Susceptibility Testing (EUCAST). Because CLSI and EUCAST have not established susceptibility breakpoints for lincomycin, clindamycin should be tested instead. Resistance to lincosamides may be inducible by macrolides in macrolide-resistant staphylococci, Streptococcus pneumoniae, and beta-hemolytic streptococci. Macrolide-resistant isolates of these organisms should be screened for inducible clindamycin resistance using the D-zone test or other standard methodology.

CLSI dilution and disk diffusion susceptibility interpretive criteria for clindamycin

Organism	Susceptibility Interpretive Criteria					
	Minimal Inhibitory Concentrations (MIC in µg/mL)			Disk Diffusion (Zone Diameters in mm)		
	S	I	R	S	I	R
Staphylococcus spp.	≤0.5	1–2	≥4	≥21	15–20	≤14
Streptococcus pneumoniae, β-hemolytic streptococci and viridans group streptococci	≤0.25	0.5	≥1	≥19	16–18	≤15
Anaerobic Bacteria	≤2	4	≥8	NA	NA	NA
Disk content 2 µg. MIC interpretive criteria for anaerobes are based on agar dilution. NA=not applicable.						

The validity of both the dilution and disk diffusion test methods should be verified using quality control (QC) strains, as indicated by CLSI. Acceptable limits when testing clindamycin against these organisms are listed in the table below.

Quality control ranges for clindamycin susceptibility tests (CLSI)

Organism	Minimum Inhibitory Concentration Range (MIC in µg/mL)	Disk Diffusion Range (Zone Diameters in mm)
Staphylococcus aureus ATCC 29213	0.06–0.25	NA
Staphylococcus aureus ATCC 25923	NA	24–30
Streptococcus pneumoniae ATCC 49619	0.03–0.12	19–25
Bacteroides fragilis ATCC 25285	0.5–2	NA
Bacteroides thetaiotaomicron ATCC 29741	2–8	NA
Eggerthella lenta ATCC 43055	0.06–0.25	NA
MIC ranges for anaerobic bacteria are based on agar dilution.		
NA=Not applicable		
ATCC® is a registered trademark of the American Type Culture Collection		

EUCAST dilution and disk diffusion susceptibility interpretive criteria for clindamycin[94]

Organism	Minimal Inhibitory Concentrations (MIC in µg/mL)		Disk Diffusion (Zone Diameters in mm)	
	S	R	S	R
Staphylococcus spp.	≤0.25	>0.5	≥22	<19
Streptococcus groups A, B, C, G	≤0.5	>0.5	≥17	<17
Streptococcus pneumoniae	≤0.5	>0.5	≥19	<19
Viridans group streptococci	≤0.5	>0.5	≥19	<19
Gram-positive anaerobes (except *Clostridium difficile*)	≤4	--	NA	NA
Gram-negative anaerobes	≤4	--	NA	NA
Disk content 2 µg. MIC interpretive criteria for anaerobes are based on agar dilution. NA=not applicable.				

Quality control ranges for clindamycin susceptibility tests (EUCAST)

Organism	Minimum Inhibitory Concentration Range (MIC in µg/mL)	Disk Diffusion Range (Zone Diameters in mm)
Staphylococcus aureus ATCC 29213	0.06–0.25	23-29
Streptococcus pneumoniae ATCC 49619	0.03–0.12	22-28
NA=Not applicable		
ATCC® is a registered trademark of the American Type Culture Collection		

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* and in some species of *Clostridium*.

Organisms that are commonly susceptible to lincomycin include:

Aerobic and facultative gram-positive bacteria:

- *Staphylococcus aureus* (methicillin-susceptible strains only); *Streptococcus pneumoniae*; Streptococcus pyogenes; viridans group streptococci; *Corynebacterium diphtheria*e.

Anaerobic and microaerophilic bacteria:

- *Clostridium perfringens*; *Clostridium tetani*; *Propionibacterium acnes*.

5.2. 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.

Intramuscular administration of a single dose of 600 mg of lincomycin produces average peak serum levels of 11.6 µg/mL at 60 minutes and maintains therapeutic levels for 17 to 20 hours for most susceptible gram-positive organisms. Urinary excretion after this dose ranges from 1.8 to 24.8 percent (mean: 10.3 percent).

A two hour intravenous infusion of 600 mg of lincomycin achieves average peak serum levels of 15.9 µg/mL and yields therapeutic levels for 14 hours for most susceptible gram-positive organisms. Urinary excretion ranges from 4.9 to 23.3 percent (mean: 15.1 percent).

The biological half-life after intramuscular administration is approximately 5 hours. The serum half-life of lincomycin may be prolonged in patients with severe impairment of renal function compared to patients with normal renal function.[79] In patients with abnormal hepatic function, serum half-life may be two-fold longer than in patients with normal hepatic function.[80] Hemodialysis and peritoneal dialysis are not effective in removing lincomycin from the serum.

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.

5.3. 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.

6. PHARMACEUTICAL PARTICULARS

6.1. LIST OF EXCIPIENTS

Information not available

6.2. INCOMPATIBILITIES

When combined with lincomycin in an infusion solution, novobiocin, kanamycin, and phenytoin are each physically incompatible with lincomycin.

6.3. SHELF LIFE

Please see pack for expiry of product.

6.4. SPECIAL PRECAUTIONS FOR STORAGE

Store at controlled room temperature 15°C-30°C.

6.5. NATURE AND CONTENTS OF CONTAINER

LINCOCIN® is available as:

- LINCOCIN® Injection 300 mg/mL in 5's (vials)
- LINCOCIN® Injection 600 mg/2 mL in 5's (vials)
- LINCOCIN® Capsules 500 mg in 12’s blister pack
- LINCOCIN® Syrup 250 mg/5 mL in 60 mL bottle

Not all pack sizes may be marketed.

Lincocin/LPD/PK-01
According to Italy approved SPC dated: 19 May 2022 & approved information in Pakistan

Marketed by:
Pfizer Pakistan Limited

*Please visit our website **www.pfizerpro.com.pk** for latest version of Product leaflet.*