BETAMYCIN LINCOMYCIN CAPSULES

1. Name of the medicinal product
Lincomycin Capsules, 500mg

2. Qualitative and quantitative composition
Each capsule contains 500mg Lincomycin

3. Pharmaceutical form
Tablet
White, round and flat caplets with bevelled edges.

4. Clinical particulars
4.1 Therapeutic indications

- Lincomycin has been shown to be effective in the treatment of the following infections when caused by susceptible strains of gram positive aerobes such as streptococci, pneumococci, and staphylococci, or by susceptible anaerobic bacteria.

- Upper respiratory infections including tonsillitis, pharyngitis, otitis media, sinusitis, scarlet fever and as adjuvant therapy for diphtheria. Effectiveness in the treatment of mastoiditis would be anticipated.

- Lower respiratory infections including acute and chronic bronchitis and pneumonia.

- Skin and soft tissue infections including cellulitis, furuncles, abscesses, impetigo, acne and wound infections. Conditions like erysipelas, lymphadenitis, paronychia (panaritium), mastitis and cutaneous gangrene, should, if caused by susceptible organisms, respond to lincomycin therapy.

- Bone and joint infections including osteomyelitis and septic arthritis.

- Septicemia and endocarditis. Selected cases of septicemia and/or endocarditis due to susceptible organisms have responded well to lincomycin. However, bactericidal drugs are often preferred for these infections.

- Bacillary dysentery Although *Shigella* is resistant to lincomycin *in vitro* (MIC approximately 200-400 mcg/mL), lincomycin has been effective in its treatment due to the very high levels of lincomycin attained in the bowel (approximately 3000-7000 mcg/gram of stool).

4.2 Posology and method of administration
Oral Administration

- Infections due to susceptible organisms, 500 mg t.i.d. (q8h).
- More severe infections: 500 mg q.i.d. (q6h).
- For optimal absorption, it is recommended that nothing be given by mouth for a period of 1 to 2 hours before or after oral administration of lincomycin.

Dosage in Children (over 1 month of age)
Oral Administration
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.
For optimal absorption, it is recommended that nothing be given by mouth for a period of 1 to 2 hours before or 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

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.

Beta-hemolytic Streptococcal Infections

Treatment should be continued for at least 10 days.

Incompatibilities

See section 6.2

4.3 Contraindications

Lincomycin is contraindicated in patients previously found sensitive to lincomycin or clindamycin or to any other component of the product.

4.4 Special warnings and precautions for use

The lincomycin injection formulation contains benzyl alcohol. The preservative benzyl alcohol has been associated with serious adverse events, including the "gasping syndrome", and death in pediatric patients. 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. The risk of benzyl alcohol toxicity depends on the quantity administered and the liver and kidneys capacity to detoxify the chemical. Premature and low-birth weight infants may be more likely to develop toxicity.

Pseudomembranous 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 agent.

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.

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.

Although lincomycin appears to diffuse into cerebrospinal fluid, levels of lincomycin in the CSF may be inadequate for the treatment of meningitis.[44,45] Thus, the drug should not be used in the treatment of meningitis.

If lincomycin antibiotic therapy is prolonged, liver and kidney function tests should be performed.

The use of antibiotics may result in overgrowth of non-susceptible organisms, particularly yeasts.

4.5 Interaction with other medicinal products and other forms of interaction

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.

FERTILITY, PREGNANCY AND LACTATION

Benzyl alcohol can cross the placenta. See Section **4.4. Special Warnings and Precautions for Use**.

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.[57] 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.

UNDESIRABLE EFFECTS

Adverse Drug Reactions

Adverse Drug Reaction Table[74,75]

System Organ Class	Adverse Drug Reactions
Infections and infestations	Pseudomembranous colitis, *Clostridium difficile* colitis, vaginal infection
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]
Vascular disorders	Hypotension,[b] thrombophlebitis[c]
Gastrointestinal disorders	Oesophagitis,[d] diarrhoea, nausea, vomiting, abdominal discomfort
Hepatobiliary disorders	Jaundice, liver function test abnormal
Skin and subcutaneous tissue disorders	Toxic epidermal necrolysis, Stevens-Johnson syndrome, acute generalised exanthematous pustulosis, dermatitis bullous, dermatitis exfoliative, erythema multiforme, rash, urticaria, pruritus
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.

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

5. Pharmacological properties
5.1 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.[94]

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.[94]

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

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.[94]

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*.

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.[78] Urinary excretion after this dose ranges from 1.8 to 24.8 percent (mean: 10.3 percent).[44,78]

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.[78] 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. 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.

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.[55] No effects on fertility were observed in rats administered lincomycin at 1.2x the MRH

6. Pharmaceutical particulars

6.1 List of excipients

Not available

6.2 Incompatibilities

None known.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Store below 30°C protected from light.

KEEP MEDICINES OUT OF REACH OF CHILDREN.

6.5 Nature and contents of container

4Capsules/Blister of PVC-ALU, 3Blisters/Box.

6.6 Special precautions for disposal and other handling

No special requirements.

7. Manufacturer:

Shandong Xier Kangtai Pharmaceutical Co., Ltd.
Private Economy Garden, Xinyan Town, Yanzhou City, Shandong Province, China