1. Name of the medicinal product
Lincomycin capsules 500mg
Brand name: Clamicin-500

2. Qualitative and quantitative composition
Each capsule contains Lincomycin hydrochloride equivalent to 500mg Lincomycin.
For the full list of excipients, see section 6.1.

3. Pharmaceutical form
Hard capsules

4. Clinical particulars

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.
(1) 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.
(2) Lower respiratory infections including acute bronchitis and pneumonia.
(3) Skin and soft tissue infections including cellulitis, furuncles, abscesses, impetigo, acne and wound infections, conditions like erysipelas, lymphadenitis paronychia (panaritium), mastitis and cutaneous gangerene should, if caused by susceptible organisms, respond to lincomycin therapy.
(4) Bone and joint infections including osteomyelitis and septic arthritis.
(5)Septicemia and endocarditis: Selected cases of speticamia and/or endocarditis due to susceptible organisms have responded well to lincomycin. However, bactericidal drugs are often preferred for these infections.
(6) Baciliary dysentery – although Shigella is resistant to lincomycin in vitro (MIC approximately 200-400µg/ml), lincomycin has been effective in its treatment due to the very high levels of lincomycin attained in the bowel (approximately 3000-7000µg/gram of stool).

Posology and method of administration

For ORAL use only

Administration
Adults
1 Serious infections due to susceptible organisms: 500mg t.i.d.(q9h).
2 More severe infections 500mg q6h or q.i.d.
Children (over 1 month of age)
Oral
1 Serious infections: 30 mg/kg/day divided into 3 or 4 equal doses.
2 More severe infections: 60mg/kg/day divided into 3 or 4 equal doses.

Contraindications

Lincomycin is contraindicated in patients previously found sensitive to lincomycin or cindamycin.

Special warnings and precautions for use

As is the case for almost all antibiotic therapies the lincomycin therapy has been associated with severe colitis, which may end fatally. The clinical spectrum varies from mild, watery diarrhea to severe, persistent diarrhea, leukocytosis, fever, severe abdominal cramps which may be associated with the passage of blood and mucus which, if allowed to progress, may produce peritonitis, shock and toxic megacolon. The diagnosis of antibiotic-associated colitis is usually made by the recognition of the clinical symptoms. It can be substantiated by endoscopic demonstration of pseudomembranous colitis and may be further confirmed by culture of the stool for Clostridium difficile on selective media and assay of the stool specimen for the toxin(s) of the C. difficile.

Onset of antibiotic-associated colitis has occurred during the administration or even two or three weeks following administration of the antibiotic. The disease is likely to take a more severe course in older patients or in patients who are debilitated.

In case of occurrence of mild associated colitis discontinuance of lincomycin is recommended. Treatment with cholestyramine-and colestipol resins is recommended as these products have been shown to bind the toxin in vitro. The recommended dosage for cholestyramine is 4 grams given 3 to 4 times daily and for colestipol, 5 grams given 3 times daily.

When severe antibiotic-associated colitis occurs, this has to be treated with appropriate fluid electrolyte and protein supplementation.

Studies have also indicated that a toxin(s) produced by Clostridia (especially C. difficile) is (are) the principal direct cause of antibiotic-associated colitis. These studies also indicate that this toxigenic Clostridium is usually sensitive in vitro to vancomycin. When 125 to 500 mg vancomycin 4 times daily is administered for 7 to 10 days, there is a rapid observed disappearance of the toxin from faecal samples and a coincident clinical recovery from the diarrhea. In some cases colitis may reoccur after cessation of vencomycin treatment. 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. As an alternative therapy oral bacitracin 25.000 units q.i.d, for 7-10 days could he considered.

Drugs which cause bowel stasis should be avoided.

Caution should be exercised in prescribing lincomycin doses in patients with a history of GI disease, particularly colitis.

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.

Antagonism has been demonstrated between lincomycin and erythromycin in vitro. Because of possible clinical significance, these two drugs should not be administered concurrently.

If lincomycin antibiotic therapy is prolonged, liver and kidney function tests should be performed.
The use of lincomycin may result in overgrowth of non-susceptible organisms, particularly yeasts.
Lincomycin should not be injected intravenously undiluted as a bolus, but should be infused over at least 10-60 minutes as directed in the DOSAGE AND ADMINISTRATION section.
Lincomycin has been shown to have neuromuscular blocking properties that may enhance the action of other neuromuscular blocking agents. Therefore, it should be used with caution in patients receiving such agents.
Lincomycin should be administered with caution in atopic individuals. Patients with very severe renal disease and/or very severe hepatic disease accompanied by severe metabolic aberrations should be dosed with caution, and serum lincomycin levels monitored during night-dose therapy.

Interaction with other medicinal products and other forms of interaction
It enhances muscle relaxation caused by muscle relaxants. Antidiarrheal agents, chloramphenicol, erythromycin decreases the effect. In combination with narcotic analgesic agents possible respiratory diseases.

Fertility, pregnancy and lactation
Safety for use in pregnancy has not been established.
Lincomycin has been reported to appear in breast milk in ranges from 0.5 to 2.4µg/ml.

Effects on ability to drive and use machines
No studies on the effects on the ability to drive and use machines have been performed.

Undesirable effects
(1) Gastrointestinal – Nausea, vomiting, abdominal disorder and persistent diarrhea (see SPECIAL PRECAUTIONS) and, with oral preparations esophagitis.
(2) Hematopoletic – Neutropenia, leukopenia, agranulocytosis and thrombocytopenic purpura have been reported. There have been rare reports of aplastic anemia and pancytopenia in which Iincomycin could not be ruled out as the causative agent.
(3) Hypersensitivity reactions – Hypersensitivity reactions such as angioeurotic edema, serum sickness and an aphylaxis have been reported, some of these in patients sensitive to penicillin. Rare instance of erythema multiforme, some resembling Stevens -Johnnon syndrome have been associated with lincomycin administration.
(4) Skin and mucous membranes – Pruritus, skin rashes, urticaria, vaginitis and rare instances of exfoliative and vasiculobullous dermatitis have been reported.
(5) Liver – Jaundice and abnormal liver function tests (particularly elevation of serum transaminase) have been observed during lincomycin thereapy.
(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).

Overdose

When overdose, it is mainly symptomatic therapy and supportive therapy, such as gastric lavage, emetic and rehydration.

5. Pharmacological properties

Pharmacodynamic properties

Pharmacotherapeutic group: antibacterials for system use, lincomycin combinations.
ATC code: J01FF02

Depending on the sensitivity of the micro-organism and the concentration of the antibiotic, lincomycin may be either bactericidal or bacteriostatic. The in vitro spectrum includes following micro-organisms:

(1) Sensitive micro-organisms (MIC ≤ 2µg/ml)
– Anaerobic non-sporulating gram-positive bacteria a.o. Actinomyces spp., Propionibacterium spp. and Eubacterium spp.
– Anaerobic and micro-aerofilic gram-positive cocci a.o. Peptococcus spp., Peptostreptococcus spp. and micro-aerofilic streptococci.
– Aerobic gram-positive micro-organisms a.o. staphylococci, streptococci (except S. faecalis) and pneumococci.

(2) Moderately sensitive micro-organisms (MIC between 2 and 4 µg/ml) which are likely to respond to higher dosages.
– Anaerobic non-sporufating gram-negative bacteria a.o. Bacteroides spp. and Fusobacterium spp.
– Anaerobic sporulating gram-positive bacteria a.o. Clostridium spp.

(3) Resistant micro-organisms or micro-organisms showing low sensitivity (MIC ≥ 8 µg/ml) a.o. Streptococcus faecalis, Neisseria most Haemophilus influenza starins, Pseudomonas and other gram-negative micro-organisms. Cross resistance of the dissociated type has been observed in vitro between oleandomycin and lincomycin on the one side and the macrolides (erythromycin, oleandomycin and spiramycin) on the other side. Absolute cross resistance exists between lincomycin and cindemycin. Micro-organisms have not developed resistance to Lincocin rapidly when tested by in vitro or in vivo methods. Staphylococcus develop in vitro resitance to lincomycin or cindamycin in a slow, stepwise manner.

Pharmacokinetic properties

Absorption

Absorption of orally on empty stomach, administered lincomycin is 20-35%. After an oral 500mg dose peak levels of circa 3µg/ml are reached in 2 to 4 hours. This value is diminished with about 50% in case the drug is administered with meals. For most

gram-posistive micro-organisms serum levels are maintained above the MIC (between 1 and 2 µg/ml) for 6 to 8 hours. Intramuscular administration of a single dose of 600 mg produces a peak serum level of 12-20µg/ml at ½ 1hour with detectable concentration as long as 24 hours. The intravenous infusion over a 2-hour interval of 600mg of Lincocin results in a maximum serum concentrations of 20µg/ml at 30 minutes, yielding concentrations of 1 to 2µg/ml at 14 hours.

Distribution

Direct and indirect evidence suggests that protein binding decreases with higher serum concentration 5.471 (saturable plasma protein binding) in the foetal blood, the peritoneal and the pleural liquid concentrations of 25-50% of the blood levels can be reached in the mother milk 50-100% in the bone tissues about 40% and in surrounding softer tissues 75%.

However lincomycin penetrates slowly in the cerebrospinal fluid (1-18% of the blood level); in case of meningitis, liquor levels up to 40% of the blood levels have been observed.

Excretion

The relatively strong metabolism is mainly taking place through the liver. The normal serum half-life time is 5.4 ± 1 hour. However, this time can be prolonged in case of disturbed liver and/or renal function. Therefore consideration should be given to decreasing the frequency of administration of lincomycin in patients with impaired hepatic or renal function.

After a single oral dose of 500mg the excretion in microbiologically active form in the urine varies from 1 to 31% (average 4%) and in the faeces amounts to about 33%.

Apparently the bile is an important route of excretion after oral administration, giving bile levels which are about 10 times higher than blood levels. After a 600mg intramuscular dose the excretion of microbiologically active product in the urine is 1.8 to 24.8% (average 17.3%), in the faeces 4 to 14%. After intravenous administration of 600mg over a 2 hours period, the excretion in microbiologically active product in the urine is 4.9 to 30.3% (average 13.8%). The remainder is being excreted as microbiologically non-active metabolites. There is no influence of haemodialysis and peritoneal dialysis on the excretion of lincomycin from the blood.

5.3 Preclinical safety data

The carcinogenic potential of lincomycin has not been evaluated. Lincomycin was not found to be mutagenic in the Ames Salmonella reversion assay or the V79 Chinese hamster lung cells at the HGPRT locus. It did not induce DNA strand breaks in V79 Chinese hamster lung cells as measured by alkaline elution or chromosomal abnormalities in cultured human lymphocytes. In vivo, lincomycin was negative in both the rat and mouse micronucleus assays and it did not induce sex-linked recessive lethal mutations in the offspring of male Drosophila. However, lincomycin did cause unscheduled DNA syntheses in freshly isolated rat hepatocytes. Impairment of

fertility was not observed in male or female rats given oral 300 mg/kg doses of lincomycin (0.36 times the highest recommended human dose based on mg/m2).

6. Pharmaceutical particulars

List of excipients

Magnesium stearate, capsule shell

Incompatibilities

The following drugs are physically incompatible with lincomycin: novobiccin, kanamycin.

Shelf life

3 years.

Special precautions for storage

Store below 30°C. Protect from moisture.
Keep out of the reach of children.

Nature and contents of container

PVC/aluminum foil blister.

Special precautions for disposal and other handling

No special requirements. Any unused product or waste material should be disposed of in accordance with local requirements.

7. APPLICANT/MANUFACTURER

Manufacturer: YANGZHOU NO.3 PHARMACEUTICAL CO., LTD
Address: NO.51 Guotai Road, Yiling Town, JiangDu City, Jiangsu Province, China