Lincocin™
(lincomycin hydrochloride)

Upjohn

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Composition

LINCOCIN™ Capsules 500mg
Each capsule contains:
Lincomycin (lincomycin hydrochloride monohydrate) 500mg - Lactose - Talc - Magnesium stearate - Indigotindisulfonate sodium - Titanium dioxide - Gelatin.
LINCOCIN™ Syrup 250mg/5ml
Each ml contains:
Lincomycin (lincomycin hydrochloride monohydrate) 50mg - Propylparaben - Methylparaben - Sorbic acid - Saccharin sodium - Sucrose - Imitation raspberry flavor - Imitation guarana flavor - Purified water.
LINCOCIN™ Sterile solution 300mg/ml
Each ml contains:
Lincomycin (lincomycin hydrochloride monohydrate) 300mg - Benzyl alcohol - Water for injection.

Forms, ways of administration and packages

ORAL ADMINISTRATION
- **Capsules**:
  Package of 12 and 100 capsules at a dose of 500mg.
- **Syrup**:
  Bottle of 60ml at a dose of 250mg/5ml.

INTRAMUSCULAR OR INTRAVENOUS ADMINISTRATION AFTER DISSOLUTION
- **Sterile solution**:
  Single dose 2ml disposable syringe, 2ml vial and 10ml vial at a dose of 300mg/ml.

Properties

MICROBIOLOGY
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 $\leq 2\mu g/ml$)
   - 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 $4\mu g/ml$) which are likely to respond to higher dosages
   - anaerobic non-sporulating 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 $\geq 8\mu g/ml$) a.o. **Streptococcus faecalis**, **Neisseria**, most **Haemophilus influenzae** strains, **Pseudomonas** and other gram-negative micro-organisms.

Cross resistance of the dissociated type has been observed in vitro between clindamycin and lincomycin on the one side and the macrolides (erythromycin, oleandomycin and spiramycin) on the other side. Absolute cross resistance exists between lincomycin and clindamycin. Micro-organisms have not developed resistance to LINCOCIN™ rapidly when tested by in vitro or in vivo methods. Staphylococci develop in vitro resistance to lincomycin or clindamycin in a slow, stepwise manner.

PHARMACOKINETICS
- Absorption
  Resorption of orally, on an empty stomach, administered lincomycin is 20-35%. After an oral 500mg dose peak levels of circa $3\mu g/ml$ 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-positive micro-organisms serum levels are maintained above the MIC (between 1 and $2\mu g/ml$) for 6 to 8 hours. Intramuscular administration of a single dose of 600mg produces a peak serum level of 12-20$\mu g/ml$ at 1/2 to 1 hour with detectable concentration as long as 24 hours. The intravenous infusion over a 2-hours interval of 600mg of LINCOCIN™ results in a maximum serum concentration of $20\mu g/ml$ at 30 minutes, yielding concentrations of 1 to $2\mu g/ml$ at 14 hours.
- Distribution

Direct and indirect evidence suggests that protein binding decreases with higher serum concentrations (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 microbiological non-active metabolites. There is no influence of hemodialysis and peritoneal dialysis on the excretion of lincomycin from the blood.

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 gangrene 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 septicemia and/or endocarditis due to susceptible organisms have responded well to lincomycin. However, bactericidal drugs are often preferred for these infections.
6. Bacillary 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).

Dosage and administration

ADULTS

A. **Oral**
   1. Serious infections due to susceptible organisms: 500mg t.i.d. (q8h).
   2. More severe infections: 500mg q6h or q.i.d.

B. **Intramuscular injection**
   1. Serious infections: 600mg I.M. every 24 hours.
   2. More severe infections: 600mg I.M. every 12 hours (or more often) as determined by the severity of the infection.

C. **Intravenous injection** (see dilution and infusion rates)
   1. Serious infections: 600mg to 1 gram every 8 to 12 hours.
   2. For more severe infections these doses may have to be increased.
   3. In life threatening situations, daily intravenous doses of as much as 8 grams have been given.

CHILDREN (over 1 month of age)

A. **Oral**
   1. Serious infections: 30mg/kg/day divided into 3 or 4 equal doses.
   2. More severe infections: 60mg/kg/day divided into 3 or 4 equal doses.

B. **Intramuscular injection**
   1. Serious infections: 10mg/kg/day as 1 intramuscular injection.
   2. More severe infections: 10mg/kg given every 12 hours or more often.

C. **Intravenous injection**

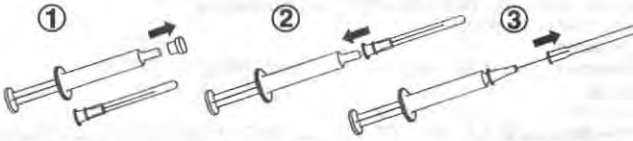
10 to 20mg/kg/day depending on the severity of the infection may be infused in divided doses as described in the section on dilution and infusion rates.

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.
In cases of beta-hemolytic streptococcal infections, treatment should be continued for at least 10 days.
For optimal absorption it is recommended that nothing be given by mouth for a period of one to two hours before and after oral administration of lincomycin.
DILUTION AND INFUSION RATES
Intravenous doses are given on the basis of 1 gram of lincomycin diluted in not less than 100ml of appropriate solution and infused over a period of not less than one hour.

Dose	Volume diluent	Time
600mg	100ml	1hr
1 gram	100ml	1hr
2 grams	200ml	2hr
3 grams	300ml	3hr
4 grams	400ml	4hr

These doses may be repeated as often as required to the limit of the maximum recommended daily dose of 8 grams of lincomycin.
Note:
Severe cardiopulmonary reactions have occurred when this drug has been given at greater than the recommended concentration and rate.
DIRECTIONS FOR USING SYRINGE FOR SINGLE USE
1. Remove tip cap.
2. In a sterile way position needle.
3. Remove needle shield. The syringe is now ready for use.



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

Adverse reactions
1. **Gastrointestinal** - Nausea, vomiting, abdominal distress and persistent diarrhea (see SPECIAL PRECAUTIONS) and, with oral preparations, 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 lincomycin 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).
7. **Local reactions** - Local irritation, pain, induration and sterile abscess formation have been seen with I.M. injection. Thrombophlebitis has been reported with I.V. injection. These reactions can be minimized by deep I.M. injection and avoidance of indwelling I.V. catheters.

Special precautions

The injectable form of this product contains benzyl alcohol. Benzyl alcohol has been reported to be associated with a fatal "gasping syndrome" in premature infants.
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 500mg 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 vancomycin 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 be 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 high-dose therapy.

Incompatibilities

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

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.

Interactions

Cross resistance has been demonstrated between clindamycin and lincomycin.

Storage

Store at controlled room temperature (15°-30°C).
The expiry date (month/year) is mentioned on the package after "EXP.:" (EXP. = expiry date).
Upjohn s.a. - Puurs - Belgium

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