Drugfield PHARMACEUTICALS LIMITED

SUMMARY OF PRODUCT CHARACTERISTICS

(SmPC)

BIOCINE® SYRUP

(Lincomycin Hydrochloride 250mg/5ml)

1. NAME OF THE MEDICINALPRODUCT
BIOCINE® (LINCOMYCIN HYDROCHLORIDE **250mg/5ml**) SYRUP

2. QUALITATIVE AND QUANTITATIVECOMPOSITION
Each 5ml ml contains 250mg Lincomycin
For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM
Liquid

4. Clinical particulars
4.1 **Therapeutic indications**

Biocine® has been shown to be very effective in the treatment of the following conditions caused by gram-positive aerobes such as *Streptococci, Pneumococci and Staphylococci* (including penicillinase-producing *staphylococci*) or by susceptible anaerobic bacteria;

- Bone and joint infections including osteomyelitis and septic arthritis.
- Skin and soft tissue infections such as cellulitis, abscesses, furuncles, impetigo acne and wound infections.
- Upper respiratory infections including tonsillitis, pharyngitis, otitis media, finufitis, scarlet fever and as adjuvant therapy for diphtheria.
- Lower respiratory infections such as acute and chronic bronchitis and pneumonia.
- Septicaemia and endocarditis.
- Bacillary dysentery.
- Usage in Neonates. Biocine® is well tolerated in neonates and no adverse effects were reported.

4.2 Posology and method of administration

Posology

	Oral
Adults	500mg three times daily
Severe	500mg (or more) four times daily
Children	30mg/kg/day in 3 to 4 equal doses
Severe	60mg/kg/day in 3 or 4 equal doses

Biocine® should not be injected intravenously as a bolus.

Method of administration
Oral administration

4.3 **Contraindications**

Biocine® is contra-indicated in patients previously found sensitive to Lincomycin or Clindamycin.

4.4 **Special warnings and precautions for use**

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 gdaily 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 ofeach 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 Lincomycin Capsules, they should be carefully monitored for any changes in bowel frequency.

Lincomycin Capsules 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 Lincomycin Capsules 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.

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 (Especially clindamycin).

4.6 **Pregnancy and Lactation**

Biocine® should be used in pregnancy only if clearly needed.

A decision should be made to discontinue breastfeeding or discontinue the drug, taking into account the importance of the drug to the mother.

Lactation

Lincomycin Hydrochloride is being excreted into human milk. The effects in the nursing infants are unknown.

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

- Skin mucous membrane: purities, skin rashes, urticaria, vaginitis.
- Gastrointestinal: Nausea, vomiting, abdominal distress and persistent diarrhoea.
- Haematopoietic: Leucopenia, Neutropenia, agranulocytosis and thrombocytopenic purpura.
- Severe allergic reactions (rash; hives; itching; difficulty breathing; tightness in the chest; swelling of the mouth, face, lips, or tongue); bloody or watery stools; change in how much urine is passed; difficulty swallowing; dizziness; mouth irritation or mouth sores;

ringing in the ears; severe or persistent diarrhea; stomach pain or cramps; swelling of hands, eyes, or throat; yellowing of skin or eyes.

- In the event of over dosage, symptomatic and supportive therapy should be given as appropriate.

4.9 Overdose

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

5. PHARMACOLOGICALPROPERTIES

5.1 Pharmacodynamics 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 (MLSB 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	0.06–0.25	NA
ATCC 43055		
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 pneumonia	≤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 diphtheriae*.

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 aftera 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 1.8to 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 serumhalf-life of lincomycin may be prolonged in patients with severe impairment of renal functioncompared 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.80Hemodialysis 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 havebeen demonstrated in the majority of body tissues.

Although lincomycin appears to diffuse intocerebrospinal fluid (CSF), levels of lincomycin in the CSF appear inadequate for the treatmentof 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. PHARMACEUTICALPARTICULARS

6.1 **List of excipients**

Sodium Methyl Paraben
Sodium Propyl Paraben
Sorbitol
Sodium Saccharin
Sodium Carboxyl Methyl Cellulose
Banana Flavour
Rasberry Essence Flavour
Purified water

6.2 **Incompatibilities**

None have been reported or are known

6.3 **Shelf life**
36 Months

6.4 **Special precautions for storage**
Store below 30^{o}C in tight container protected from light and moisture.

6.5 **Nature and contents of container and special equipment for use, administration or implantation**
Each 5ml (teaspoonful) contains Lincomycin Hydrochloride equivalent to 250mg Lincomycin base, in 100ml bottles.

6.6 **Special precautions for disposal and other handling**
No special requirements.

7. APPLICANT/MANUFACTURER
Drugfield Pharmaceuticals Limited
Lynson Chemical Avenue Km38,
Lagos-Abeokuta Expressway
Sango-Otta, Ogun State, Nigeria
Tel: +2348033513989
Email:Info@drugfieldpharma.com