Lincocin 500 mg, **Hard capsule**
Lincomycin hydrochloride hydrate

Date: 03/2021. Version 02

Reference market: Belgium

West Africa

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

LINCOCIN 500 mg, hard capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

The capsules are dark blue (upper part) and blue (lower part), filled with white powder and marked "P&U 500" on both the upper and lower parts.
One capsule contains 500 mg of lincomycin as lincomycin hydrochloride.

Excipients with known effect:

The hard capsules contain lactose (see section 4.4).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Hard capsules

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Lincomycin is indicated in the treatment of serious infections caused by aerobic Gram-positive bacteria sensitive to lincomycin, such as streptococci, pneumococci, and staphylococci, or susceptible anaerobic bacteria:

1. Infections of the upper respiratory tract: chronic sinusitis caused by anaerobic bacteria.
   Lincomycin can be used in some cases of chronic suppurative otitis media or as adjunctive therapy with an antibiotic active against aerobic gram-negative organisms. Infections caused by *H. influenzae* do not constitute an indication (see section 5.1).
2. Lower respiratory tract infections such as infectious episodes of chronic bronchitis and pneumonia.
3. Severe infections of the skin and soft tissues caused by susceptible organisms when penicillins are not indicated.
4. Bone and joint infections including osteomyelitis and septic arthritis.
5. Septicaemia and endocarditis.
   Certain selected cases of sepsis and/or endocarditis caused by susceptible organisms respond well to treatment with lincomycin. However, to treat these infections, it is often necessary to choose bactericidal medicines.

4.2 Posology and method of administration

The dose and method of administration should be determined by the severity of the infection, the patient's condition and susceptibility of the pathogen.

Posology

Adults
Oral route
500 mg 3 or 4 times per day, preferably 1–2 hours before or after a meal. The capsules should be taken with a sufficient quantity of water.

Paediatric population
Oral route
30 to 60 mg/kg/day, divided into 3–4 equal doses, preferably 1 to 2 hours before or after a meal. The capsules should be taken with a sufficient quantity of water.

POSOLOGY IN CASES OF RENAL AND/OR LIVER DYSFUNCTION
If treatment with lincomycin is necessary in patients with severe renal and/or hepatic dysfunction, the appropriate dose is 25–30% of the recommended dose for patients with normal kidney or liver function.

Method of administration

Oral use

4.3 Contraindications

- Hypersensitivity to the active substance, one of the excipients listed in section 6.1, or clindamycin.
- In case of meningitis (see sections 4.4 and 5.2).

4.4 Special warnings and precautions for use

Severe hypersensitivity reactions, including anaphylactic reactions and serious cutaneous undesirable effects such as Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), acute generalised exanthemous pustulosis (AGEP) and erythema multiforme (EM) have been reported in patients receiving treatment with lincomycin. In the event of an anaphylactic reaction or severe skin reaction, lincomycin should be discontinued and appropriate treatment initiated (see section 4.8).

Clostridium difficile-associated diarrhoea (CDAD) has been reported with the use of nearly all antibacterial agents, including lincomycin, and its severity can range from mild diarrhoea to fatal colitis. Antibacterial therapy alters the normal flora of the colon, resulting in proliferation of *C. difficile* which produces toxins A and B. CDAD may manifest as mild and watery diarrhoea but can progress to severe and persistent diarrhoea, leukocytosis, fever, severe abdominal cramps, and mucus or blood in the stool. Without treatment, the patient may develop potentially fatal peritonitis, shock, and toxic megacolon. Medicines known to inhibit peristalsis are contraindicated in these clinical circumstances.

CDAD may be more common and more severe in elderly or debilitated persons. Toxin hyperproductive strains of *C. difficile* may also be associated with increased morbidity and mortality.

The potential for CDAD must be considered in all patients who exhibit diarrhoea following antibiotic use. A thorough medical history should be taken as CDAD has been reported to occur up to two months after administration of antibacterial agents. Diagnosis is generally based on clinical symptoms, but may also be confirmed by endoscopy or identification of *Clostridium difficile* and its associated toxins in the stool (see section 4.8).

Lincomycin should be prescribed with caution in patients with a history of gastrointestinal disease, particularly colitis.

Excipients with known effect:
The capsules contain lactose. Patients with galactose intolerance, Lapp lactase deficiency or glucose-galactose malabsorption syndrome (rare inherited diseases) should not take this medicine.
The hard capsules contain sodium. This medicine contains less than 1 mmol sodium (23 mg) per capsule, that is to say essentially 'sodium-free'.

Because lincomycin does not adequately diffuse into the cerebrospinal fluid, this medicinal product cannot be used in the treatment of meningitis (see sections 4.3 and 5.2).

Antagonism between lincomycin and erythromycin and chemically related macrolides has been demonstrated *in vitro*. As this phenomenon may be of clinical significance, these two types of medicines cannot be used simultaneously.

Liver and kidney function should be checked during prolonged treatment.

The use of lincomycin may cause overproliferation of non-susceptible organisms, particularly yeasts.

It has been shown that lincomycin has neuromuscular blocking properties which may enhance the activity of other neuromuscular blockers. Lincomycin should therefore be used with caution in patients treated with these medications.

Lincomycin should be administered with caution in hypersensitive patients.

In patients with renal and/or severe hepatic impairment associated with severe metabolic abnormalities, lincomycin should be used with caution and the dose should be adjusted (see section 4.2). During treatment at high doses, blood levels should be monitored, as the serum half-life may be 2 to 3 times longer in these patients.

Given the possibility of severe reactions to lincomycin in breast-fed infants, a decision must be taken whether to discontinue either breast-feeding or treatment with this medicinal product, taking into account the importance of treatment for the mother (see section 4.6).

4.5 Interaction with other medicinal products and other forms of interaction

The activity of neuromuscular blockers may be enhanced (see section 4.4).

During simultaneous oral administration of a mixture of kaolin and pectin, lincomycin absorption is inhibited by at least 90%. These mixtures should be administered at

least 2 hours before or 3–4 hours after administration of lincomycin, in order to avoid this interaction.

Antagonism between lincomycin, erythromycin and chemically related macrolides has been demonstrated *in vitro*. This interaction may be clinically significant; these two types of medicines cannot be administered simultaneously.

Lincomycin may interfere with alkaline phosphatase levels in the plasma. Values obtained can be erroneously high.

4.6 Fertility, pregnancy and lactation

Pregnancy

Animal studies do not indicate reproductive toxicity (see section 5.3).

Data on the use of lincomycin in pregnant women are limited. Infants born to 302 patients treated with lincomycin at different stages of pregnancy exhibited no more neonatal abnormalities or growth retardation than children a control group between birth and 7 years of age.

Lincomycin crosses the placental barrier in humans and results in serum levels corresponding to 25% of those measured in maternal serum. There is no significant accumulation in amniotic fluid.

As a precaution, it is preferable to avoid the use of lincomycin during pregnancy unless treatment is clearly necessary.

Breast-feeding

Given the possibility of severe reactions to lincomycin in breast-fed children, a decision must be made either to discontinue breast-feeding or to discontinue treatment with this medicinal product, taking into account the benefit of breast-feeding for the child and the benefit of treatment for the mother (see section 4.4).

Fertility

Animal studies have shown no effect on fertility (see section 5.3). No clinical data are available regarding either male or female fertility.

4.7 Effects on ability to drive and use machines

No studies have been performed to determine the effect of lincomycin on the ability to drive or use machines. Although no specific effects have been observed on the ability to drive or operate machinery, occasional cases of vertigo have been reported.

4.8 Undesirable effects

Summary of the safety profile
The most common side effects are gastrointestinal in nature (diarrhoea, nausea and vomiting).

The table below lists undesirable effects identified in clinical trials and post-marketing surveillance by system organ class and by frequency. In each frequency group, the undesirable effects are presented in descending order of seriousness.

Table of undesirable effects

System organ class	**Very common (≥ 1/10)**	**Common (≥ 1/100, < 1/10)**	**Uncommon (≥ 1/1,000, < 1/100)**	**Rare (≥ 1/10,000, < 1/1,000)**	**Very rare (< 1/10,000)**	**Frequency unknown *(cannot be estimated from the available data)***
Infections and infestations			Vaginal infections			Pseudomembranous colitis, Colitis due to *Clostridium difficile*
Blood and lymphatic system disorders						Pancytopenia, Agranulocytosis, Aplastic anaemia, Neutropenia, Leukopenia, Thrombocytopenic purpura
Immune system disorders						Anaphylactic reaction, Angioedema, Serum sickness
Cardiac disorders						Heart failure [a] Arythmias[e]
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			Rash, Urticaria	Pruritus		Toxic epidermal necrolysis (TEN), Acute generalised exanthemous pustulosis (AGEP), Stevens-Johnson syndrome, Bullous dermatitis, Exfoliative dermatitis, Erythema multiforme

Table of undesirable effects

System organ class	Very common (≥ 1/10)	Common (≥ 1/100, < 1/10)	Uncommon (≥ 1/1,000, < 1/100)	Rare (≥ 1/10,000, < 1/1,000)	Very rare (< 1/10,000)	Frequency unknown *(cannot be estimated from the available data)*

a. Rare cases have been reported after intravenous administration was carried out too rapidly.
b. Following parenteral administration, especially when administration was carried out too rapidly.
c. Event reported in association with intravenous injection.
d. Event reported in association with oral preparations.
e. Rare cases have been reported after intravenous administration of high doses was carried out too rapidly.

Description of selected undesirable effects
Diarrhoea associated with *Clostridium difficile*: Almost all antibiotics, including penicillins, cephalosporins, and lincosamides, can give rise to severe diarrhoea (sometimes delayed), colitis or pseudomembranous colitis, induced by *Clostridium difficile* toxins. Treatment must be stopped if diarrhoea occurs. Colitis may also occur for up to 2–3 weeks after discontinuation of treatment. Medicines known to inhibit intestinal peristalsis should be avoided (see section 4.4).

Other special populations
Patients with severe renal and/or severe hepatic impairment: lincomycin should be used with caution in patients with severe renal impairment and/or severe hepatic impairment associated with severe metabolic abnormalities and the dose should be reduced in these populations (see sections 4.2 and 4.4).

Reporting of suspected undesirable effects
Reporting suspected undesirable effects after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Health professionals should report any suspected undesirable effects via the national reporting system.

4.9 Overdose

In cases of overdose, gastrointestinal disorders, including abdominal pain, nausea, vomiting and diarrhoea, have been reported. In case of overdose, vomiting or gastric lavage may be induced if necessary. No specific antidote is known. Haemodialysis and peritoneal dialysis are not effective in removing lincomycin from the serum.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Lincomycin is an antibiotic belonging to the Lincosamide family.
ATC code: J01FF02.

Mechanism of action

Lincomycin binds to the 50S subunit of the bacterial ribosome and inhibits protein synthesis. The action of lincomycin is primarily bacteriostatic.

Pharmacokinetic/pharmacodynamic relationships

Its efficacy is related to the period during which the antibiotic is maintained above the minimum inhibitory concentration (MIC) of the pathogen (%T/MIC).

Mechanism(s) of resistance

Cross resistance between lincomycin and clindamycin is complete. Resistance in staphylococci and streptococci is most commonly due to methylation of specific 23S RNA nucleotides of the 50S ribosomal subunit, which can cause cross resistance to macrolides and streptogramins B (MLS Phenotype B). Macrolide-resistant isolates of these organisms should be tested for inducible resistance to lincomycin/clindamycin using the "zone D" test.

Critical concentrations (*Breakpoints*)
As critical levels for lincomycin have not been established by the European Committee on Antimicrobial Susceptibility Testing (EUCAST), critical levels for clindamycin should be tested instead. Resistance to lincosamides can be induced by macrolides in macrolide-resistant staphylococci, *Streptococcus pneumoniae* and beta-haemolytic streptococci. Screening for induced resistance to clindamycin should be performed using the “zone D” test or other standard methodology in isolates of these macrolide-resistant organisms.

EUCAST Critical Levels for clindamycin

Pathogens	**Minimum inhibitory concentrations (MIC in mg/L)**	
	S	**R**
Staphylococcus sp.	≤ 0.25	> 0.5
Streptococcus groups A, B, C, G	≤ 0.5	> 0.5
Streptococcus pneumoniae	≤ 0.5	> 0.5
Streptococci, Viridans group	≤ 0.5	> 0.5
Gram-positive anaerobic bacteria (except *Clostridium difficile*)	≤ 4	> 4
Gram-negative anaerobic bacteria	≤ 4	> 4

Prevalence of acquired resistance

The prevalence of acquired resistance may vary depending on geographical area and time for certain species, and local information on resistance is desirable, especially when treating severe infections. Expert advice may be necessary and should be sought when the prevalence of local resistance is such that the usefulness of the antibiotic in at least some types of infections is debatable. Particularly in serious infections or in cases of treatment failure, a microbiological diagnosis with verification of the pathogen and its sensitivity to lincomycin/clindamycin is recommended.

The data below are available for clindamycin, and are based on European surveillance studies available in 2013.

Frequently susceptible organisms	Remarks
Gram-positive aerobic microorganisms	
Actinomyces israelii[a]	
Staphylococcus aureus (susceptible to methicillin)	
Streptococcus agalactiae	
Streptococci of the Viridans group	
Anaerobic microorganisms	
Bacteroides sp.[a] (except *B. fragilis*)	
Fusobacterium sp.[a]	
Peptococcus sp.[a]	
Prevotella sp.	
Veillonella sp.[a]	
Other microorganisms	
Chlamydia trachomatis[a]	
Clamydophila pneumoniae[a]	
Gardnerella vaginalis[a]	
Mycoplasma hominis[a]	

Organisms for which acquired resistance may be a problem	Remarks
Gram-positive aerobic microorganisms	
Staphylococcus aureus (resistant to methicillin)[b]	
Staphylococcus epidermidis[b]	
Staphylococcus haemolyticus	
Staphylococcus hominis	
Streptococcus pneumoniae	Resistance rate between > 20 and 49% in some European countries
Gram-negative aerobic microorganisms	
Moraxella catarrhalis[c]	
Anaerobic microorganisms	
Bacteroides fragilis	
Clostridium perfringens	Higher resistance rates in Spain (10–20%)
Peptostreptococcus sp.	Higher resistance rates in Spain (10–20%)
Propionibacterium sp.	

Naturally resistant organisms	Remarks
Gram-positive aerobic microorganisms	
Enterococcus sp.	
Listeria monocytogenes	
Gram-negative aerobic microorganisms	
Escherichia coli	
Klebsiella sp.	
Neisseria gonorrhoeae	
Pseudomonas aeruginosa	
Anaerobic microorganisms	
Clostridium difficile	
Other microorganisms	

Frequently susceptible organisms	Remarks
Mycoplasma pneumoniae	
Ureaplasma urealyticum	

[a] No updated information available.
[b] At least one European region has reported resistance rates above 50%.
[c] Most isolates show intermediate inherent resistance.

5.2 Pharmacokinetic properties

Absorption

Administration of a single 500 mg oral dose of lincomycin on an empty stomach results in mean peak serum concentrations of 2.8 to 5.3 µg/ml 2 to 4 hours after administration. Oral bioavailability is estimated to be 20–35% on an empty stomach. Administration immediately after a meal reduces oral absorption by approximately 50%.

Distribution

Lincomycin is approximately 72% bound to plasma proteins. Published studies have reported that plasma protein binding is saturable. Consequently, percentage of the medicinal product bound to proteins decreases when serum concentrations are higher.

Lincomycin is widely distributed and is not clearly concentrated in any particular organ. Diffusion into bone tissue is excellent.

Concentrations in foetal blood and in the peritoneal and pleural fluids up to 25–50% of blood levels can be achieved. This value is 50–100% in breast milk, approximately 40% in bone tissues and 75% in the soft tissues. Lincomycin passes into breast milk.

Lincomycin crosses the blood-brain barrier and the placental barrier. Although lincomycin appears to diffuse into the cerebrospinal fluid (CSF), concentrations of lincomycin in the CSF appear insufficient to treat meningitis (see sections 4.3 and 4.4).

Biotransformation

Metabolism of lincomycin takes place in the liver.

Elimination

The normal elimination half-life is 4 to 6 hours.

Lincomycin is excreted in the urine and the bile, and is found in the faeces. Biliary excretion is high, and the concentrations obtained are some 10 times higher than blood concentrations.

Urinary excretion varies depending on the method of administration. Following administration of a single oral dose of 500 mg,urinary excretion ranges from 1.8 to 13.7 percent (mean : 6.2 percent).

Elimination in the faeces represents approximately 33% of an oral dose.

Renal impairment

The serum half-life of lincomycin may be prolonged in patients with severe renal impairment compared to those with normal function. Neither haemodialysis nor peritoneal dialysis are effective in removing lincomycin from the plasma (see section 4.2).

Hepatic impairment
In patients with abnormal hepatic function, the serum half-life may be twice as long as in patients with normal hepatic function (see section 4.2).

5.3 Preclinical safety data

Non-clinical data based on conventional studies of pharmacological safety, repeated dose toxicity, genotoxicity, carcinogenicity, and reproductive and developmental functions, have revealed no particular hazard for humans. No developmental toxicity was observed when doses 6 times higher than the maximum recommended human dose (MRHD) were administered to pregnant female rats during the period of organogenesis. No effects on fertility were observed in rats administered lincomycin at 1.2 times the MRHD.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

500 mg capsules
Capsule contents: lactose, talc, magnesium stearate
Capsule: gelatine, disodium salt of indigotin sulfonic acid, titanium dioxide

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Hard capsules: 24 months.

6.4 Special precautions for storage

Capsules: Store at a temperature not exceeding 25 °C.
Solution for injection and syrup: store at room temperature (15–25 °C).

6.5 Nature and contents of container

Hard capsules:
- Packages of twelve 500 mg gel capsules.

6.6 Special precautions for disposal and other handling

No special requirements for disposal.

7. MARKETING AUTHORISATION HOLDER AND MANUFACTURER

Marketing Authorisation Holder:
Pfizer NV/SA,17 Boulevard de la Plaine,

1050 Brussels,
Belgium.

Manufacturer:
Pfizer Italia S.r.l.
Località Marino del Tronto, 63100 Ascoli Piceno (AP),
Italy

Nature and contents of container:
LINCOCIN 500 mg gel capsules, box of 12 capsules.

Local representative:
Pfizer West Africa

Administrative address:
PFIZER WEST AFRICA
REGUS PLATEAU 3RD FLOOR
AZUR 15 BUILDING
12 BOULEVARD DJILY MBAYE
DAKAR SÉNÉGAL BP 3857 DAKAR RP

8. GENERAL CONDITIONS OF PRESCRIPTION AND SUPPLY

Medicinal product subject to prescription.

9. DATE OF REVISION OF THE TEXT

01/2021