SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

LİNKOSOL 600mg/ 2ml Solution for Injection Ampoule

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active ingredients:

Each 2 ml ampoule contains; Lincomycin hydrochloride equivalent to 600 mg lincomycin.

Excipients:

Benzyl alcohol ..... 18.9 mg/ per ampoule (2 ml)

Water for injection..... q.s ..... 2.0 ml/ per ampoule (2 ml)

3. PHARMACEUTICAL FORM

Ampoule.

Sterile, clear, colourless solution for injection

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

LINKOSOL is indicated in the treatment of serious infections due to susceptible strains of gram positive aerobes such as streptococci, pneumococci, and staphylococci, or susceptible anaerobic bacteria:

Lincomycin has been shown to be effective in the treatment of infections caused by *Staphylococcus aureus* and *Streptococcus pneumoniae.*

Lincomycin has also been shown to be active *in vitro* against the following microorganisms;*Streptococcus pyogenes, Streptococcus* viridans, *Corynebacterium diphtheriae, Propionibacterium acnes, Clostridium tetani, Clostridium perfringens.*

1. Tonsillitis, pharyngitis, otitis media, sinusitis and other upper respiratory infections (and as adjuvant therapy for diphtheria.)
2. Acute bronchitis, infectious exacerbationperiods of chronic bronchitis, pneumonia and other lower respiratory infections

3. Skin and soft tissue infections including cellulitis, furuncles, abscesses, impetigo and wound infections. Conditions like erysipelas, lymphadenitis, paronychia, 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/or endocarditis.

4.2 Posology and method of administration

Posology:

Adults:

A. Intramuscular Injection:

1. 600 mg IM every 24 hours.
2. More severe infections, 600 mg intramuscularly every 12 hours (or more often).

B. Intravenous Infusion (see. Dilution and Infusion Rates)

1. 600 mg 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. Maximum daily dose of lincomycin is 8 grams.

Children (over 1 month of age):

A. Intramuscular Injection:

1. 10 mg/kg/day as 1 intramuscular injection.
2. More severe infections, 10 mg/kg given every 12 hours or more often.

B. Intravenous Infusion (see. Dilution and Infusion Rates)

10 to 20 mg/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.

Method of Administration

Dilution and infusion rates for intravenous infusion:

Intravenous doses are given on the basis of 1 gram of LINKOSOL diluted in not less than 100 mL of appropriate solution*(see. Section 6.2)* and infused over a period of not less than 1 hour.

Dose	**Volume of diluent**	**Infusion rates**
600 mg	100 mL	1 hr
1 g	100 mL	1 hr
2 g	200 mL	2 hr
3 g	300 mL	3 hr
4 g	400 mL	4 hr

These doses may be repeated as often as required to the limit of the maximum recommended daily dose of 8 grams of LINKOSOL

Severe cardiopulmonary reactions have occurred when LINKOSOL has been given at greater than the recommended concentration and rate.

Additional informationon special populations

Renal impairment:

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.

Consideration should be given to decreasing the frequency of administration of LINKOSOL in patients with impaired renal function due to prolonged half-life of lincomycin.

Monitoring of serum lincomycin levels is recommended during high-dose therapy in patients with severe impairment of renal function.

Hepatic impairment:

Consideration should be given to decreasing the frequency of administration of LINKOSOL in patients with impaired hepatic function due to prolonged half-life of lincomycin.

Monitoring of serum lincomycin levels is recommended during high-dose therapy in patients with severe impairment of renal function.

Pediatric populations:

LINKOSOL contains benzyl alcohol. Benzyl alcohol has been reported to be associated with fatal Gasping Syndrome which may cause multiple organ dysfunction, respiratory system disorders and severe metabolic acidosis in premature infants (see. 4.4 Special warnings and precautions for use).

Geriatric populations:

There are insufficient data regarding to use of this population.

Other warning should be considered when using:

Treatment with LINKOSOL should be continued for at least 10 days in Beta-hemolytic streptococcal infections

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

LINKOSOL contains 18.9 mg benzyl alcohol per 2 ml ampoule. The preservative benzyl alcohol has been associated with serious adverse events, including the "gasping syndrome" (may cause multiple organ dysfunction, respiratory system disorders, severe metabolicacidosis) and death in premature infants. Although normal therapeutic doses of this product ordinarily deliver amounts of benzyl alcohol that are substantially lower than those reported inassociation 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 hepatic capacity to detoxify the chemical. Premature and low-birth weight infants may be more likely to develop toxicity.

Must not be given to premature babies or neonates.

May cause toxic reactions and anaphylactoid reactions in infants and children up to 3 years old.

Pseudomembraneous 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 of pseudomembraneous colitis in patients who present with diarrhea subsequent to the administration of antibacterial agents.

Severe diarrhea and pseudomembraneous colitis has been reported with several antibiotics, including lincomycin.

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. Clinical manifestations may vary between mild watery diarrhea as a single symptom and bloody, mucoid severe diarrhea with leucocytosis, fever and abdominal cramps. Peritonitis, shock and megacolon may occur, if it is not treated. That case may occur during treatment or 2-3 weeks after the administration of antibiotic. Diagnosis of pseudomembranous colitis based on clinical findings and confirmed by endoscopic examination and detection of *Clostridium difficile* toxins in feces. 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**.**

Disease may be more severe in elderly and debilitated patients. In mild cases, discontinuation of drug and adminstartion of cholestyramine or colestipol resins is sufficient. In severe cases, oral vancomycin 125 – 500 mg every 6 hours may given for 7 to 10 days with fluids and electrolytes therapy.

Recurrences may treated with vancomycin. As ananother treatment option, bacitracin may given 25,000 units every 6 hours for 10 days.

Drugsshould be avoided which lead to intestinal stasis such as diphenoxylate.

LINKOSOL should be used with caution in patients with gastrointestinal system disorders, particularly colitis.

Levels of lincomycin in the cerebrospinal fluid may be inadequate for the treatment of meningitis. Thus, the drug should not be used in the treatment of meningitis.

LINKOSOL **should not be injected intravenously undiluted as a bolus**, but should be infused over at least 60 minutes as directed in the "Method of Administration" section. Lliver and kidney function should be monitored closely in prolonged therapy.

The use of LINKOSOL may result in overgrowth of nonsusceptible organisms, particularly yeasts.

LINKOSOL should be used with caution in patients with a history of asthma or significant allergies.

Certain infections may require incision and drainage or other indicated surgical procedures in additionto antibiotic therapy.

4.5 Interaction with other medicinal products and other forms of interaction

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

When administered concomitantly, kaolin reduces the gastrointestinal absorption oflincomycin by as much as 90%, resulting in decreased plasma concentrations of lincomycin. If administration of both drugs is necessary, patients should receive kaolin at least 2 hoursbefore lincomcyin.

Lincomycin has been shown to have neuromuscular blocking properties that may enhance the action of other neuromuscular blocking agents such as tubocurarine, pancuronium. Lincomycin should be used with caution in patients receiving such agents.

Additional information on special populations

There were no any clinically significant pharmacokinetic drug-drug interaction observed in studies performed with lincomycin 600 mg ampoules.

Pediatric populations:

There were no any interaction studies in this population.

4.6 Pregnancy and lactation

General advice

Pregnancy Category: C

Women of childbearing potential / Birth control (Contraception):

Data not avaliable.

Pregnancy:

LINKOSOL contains benzyl alcohol as a preservative. Benzyl alcohol can cross the placenta (see. 4.4 Special warnings and precautions for use).

There are no adequate and controlled studies in pregnant women.

Animal studies are insufficient with respect to effects on pregnancy /and-or/ embryonal/foetal development/ and-or/ parturition/ and-or/ postnatal development.

The potential risk for humans is unknown.

LINKOSOL should not be used during pregnancy unless clearly necessary

Lactation:

Lincomycin has been reported to appear in human milk, because of the potential for serious adverse reactions in nursing infants from LINKOSOL, a decision should be made whether to discontinue nursing, or to discontinue the drug

Reproductive ability/fertility:

Impairment of fertility was not observed in rats given oral 300 mg/kg doses oflincomycin (0.36 times the highest recommended human dose based on mg/m^2).

4.7 Effects on ability to drive and use machines

Not applicable.

4.8 Undesirable effects

Obeserved effects with lincomycin are usually related to dose or concentration of drug.

Adverse drug reactions are listed below by system organ class and frequency. Frequencies are defined as: 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 not known (cannot be estimated from the available data).

Blood and lymphatic system disorders

Rare : Aplastic anemia and pancytopenia

Not known : Neutropenia, leukopenia, agranulocytosis and thromboscytopenic purpura

Immune system disorders

Rare : Erythema multiforme, some resembling Stevens-Johnson syndrome

Not known : Angioneurotic edema, serum sickness and anaphylaxis

Cardiac disorders

Rare : Cardiopulmonary arrest, after rapid intravenous administration

Not known : Hypotension especially after rapid parenteral administration

Gastrointestinal disorders

Not known : Nausea, vomiting, abdominal pain and persistent diarrhea, glossitis, stomatitis colitis, pruritus ani.

On set of pseudomembranous colitis symptoms may occur during or after antibiotic treatment (see. 4.4 Special warnings and precautions for use).

Hepato-biliary disorders

Not known : Jaundice and abnormal liver function tests (particularly elevations of serum transaminase)

No direct relationship of lincomycin to liver dysfunction has been established.

Skin and subcutaneous tissue disorders

Rare : Exfoliative and vesiculobullous dermatitis

Not known : Skin rashes, urticaria and vaginitis

Renal and urinary disorders

Rare : Azotemia, oliguria, and/or proteinuria

No direct relationship of lincomycin to liver dysfunction has been established.

General disorders and administration site conditions

Not known : Tinnitus, vertigo.

Local irritation, pain, induration, and sterile abscess formation have been seen with IM injection. Thrombophlebitis has been reported with IV injection.

Reporting of suspected adverse reactions

If you get any side effects not listed in this leaflet, talk to your doctor or pharmacist. You can also report side effects directly to your doctor or pharmacist. You can also report side effects directly to your country's related health authority. By reporting side effects, you can help provide more information on the safety of this medicine.

4.9 Overdose

Experience with over dose is limited.

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antıbacterials for systemic use, Lincosamides

ATC Code: J01FF02

Lincomycin is an antibacterial agent which belongs to group of lincosamides. Lincomycin may be bacteriostatic or bactericidal in action, depending on the concentration of the drug attained at the site of infection and the susceptibility of the infecting organism.

Mechanism of action:

Lincomycin appears to inhibit protein synthesis by binding to 50S ribosomal subunits as macrolides.

In vitro spectrum of lincomycin:

Susceptible microorganisms:

- Gram-positive anaerobic non-sporeforming bacteria including *Actinomyces, Propionibacterium* and *Eubacterium*
- Gram-positive anaerobic and microaerophilic cocci including *Peptococcus, Peptostreptococcus* and microaerophilic streptococci
- Gram-positive aerobic bacteria including *Staphylococcus, Streptococcus, Pneumococcus* (except *Enterococcus faecalis*)

Moderately susceptible microorganisms:

- Gram-negative anaerobic non-sporeforming bacteria including *Bacteroides* and *Fusobacterium*
- Gram-positive anaerobic sporeforming bacteria including *Clostridium*

Less susceptible or resistant microorganisms:

- Most strains of *Streptococcus faecalis, Neisseria, Haemophilus influenzae* and *Pseudomonas and* other gram-negative bacteria.

5.2 Pharmacokinetic properties

General properties:

Absorption:

Following IM administration of 600 mg of lincomycin hydrochloride, peak plasma concentrations (12 – 20 mcg/ml) of the drug occur in 30 or 60 minutes. After 14 hours serum concentration decreased to 1-2 μg/ml and detectable concentrations may persist for up to 24 hours.

Following IV infusion of 600 mg of lincomycin hydrochloride over a period of 2 hours,peak serum concentrations (20 mcg/ml) of the drug occur in 30minutes. After 14 hours serum concentration decreased to 1-2 μg/ml

Distribution:

The concentration of lincomycin may reach 25-50% of concurrent plasma concentrations of the antibiotic in foetus blood, peritoneal fluid and pleural fluid; 50-100% in breast-milk, 40% in bone tissues and 75% in the soft tissues around the bone. Lincomycin diffuses poorly into the CSF (1-18% of concurrent plasma concentration); however, in the cases of inflamed meninges, concentrations of the drug may reached to 40% of plasma concentration.

Biotransformation:

Lincomycin is metabolized in the liver.

Elimination:

The biological half-life of lincomycin is 5.4 ± 1 hours. The serum half-life of lincomycin may be prolonged in patients with impairment of renal and/or hepatic function. Therefore, consideration should be given to decreasing the frequency of administration of LINKOSOL in patients with impaired hepatic or renal function.

Following intramuscular administration of 600 mg of lincomycin hydrochloride, 1.8-24.8%(mean: 17.3%) of the dose is excreted in urine and 4-14% of the dose is excreted in feces.Following a two hour intravenous infusion of 600 mg of lincomycin, amount of microbiologically active metabolite which detected in the urine is ranges from 4.9 to 30.3% of the dose (mean: 13.8%).The remaining portion of the antibiotic is excretedfrom the body as inactive metabolites.

Lincomycin is not effectively removedfrom the blood by haemodialysis or peritonealdialysis.

Linearity/non-linearity:

Data not available

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 Chinesehamster lung cells at the HGPRT locus. It did not induce DNA strand breaks in V79 Chinese hamsterlung cells as measured by alkaline elution or chromosomal abnormalities in cultured humanlymphocytes. *In vivo*, lincomycin was negative in both the rat and mouse micronucleus assays and it didnot 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/m^2).

Reproduction studies have been performed in rats using oral doses of lincomycin up to 1000 mg/kg (1.2 times the maximum daily human dose based on mg/m^2) and have revealed no adverse effects on survival of off spring from birth to weaning.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Benzyl alcohol

Water for injection

6.2 Incompatibilities

Lincomycin sterile solution is compatible with the following infusion solutions for at least 24 hours:

- 5% Dextrose Injection
- 10% Dextrose Injection
- 5% Dextrose and 0.9% Sodium Chloride Injection
- 10% Dextrose and 0.9% Sodium Chloride Injection
- Ringer's Injection
- 1/6 M Sodium Lactate Injection
- Dextran in Saline 6% w/v

Lincomycin sterile solution is compatible with the following infusion solutions which contains vitamins and antibiotics at concentrations of generally used in clinical practice for at least 24 hours:

- B-Complex or B-Complex with Ascorbic Acid
- Penicillin G Sodium (Satisfactory for 4 hours)
- Cephalothin

- Tetracycline HCl
- Cephaloridine
- Colistimethate (Satisfactory for 4 hours)
- Ampicillin
- Methicillin
- Chloramphenicol
- Polymyxin B Sulfate

Incompatibility and stability duration of drug mixtures may vary depending on the density and other conditions.

It should be emphasized that the compatible and incompatible determinations are physical observations only, not chemical determinations. adequate clinical evaluation of the safety and efficacy of these combinations has not been performed.

Lincomycin is physically incompatible with novobiocin, kanamycin and phenitoine.

6.3 Shelf life

36 months

6.4 Special precautions for storage

Store at room temperature below 30°C

6.5 Nature and contents of container

LINKOSOL: each 2 ml ampoule contains lincomycin hydrochloride equivalent to lincomycin 600 mg and cardboard box contains 1 or 100 ampoules

6.6 Special precautions for disposal and other handling

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

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8. MARKETING AUTHORISATION NUMBER(S)

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9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORİSATION

Date of first authorisation: 30 June 1999

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04/11/2014