SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

KLINDAVER 600 mg/4 mL Injectable Solution

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active Substance: Each ampoule contains clindamycin phosphate equivalent to 600 mg clindamycin.
Excipients:
Benzyl alcohol……37,8 mg
Disodium edetate……2 mg

See section 6.1 for excipients.

3. PHARMACEUTICAL FORM

Sterile solution for intramuscular and intravenous use
Clear, colorless solution.

4. CLINICAL PARTICULARS

4.1. Therapeutical indications

KLINDAVER ampoule is indicated for the treatment of the following infections caused by susceptible strains of anaerobic bacteria, Gram-positive aerobic bacteria such as *streptococci, staphylococci and pneumococci*, susceptible strains of *Chlamydia trachomatis*.

• Upper respiratory tract infections including tonsillitis, pharyngitis, sinusitis, otitis media, and scarlet fever.
• Lower respiratory tract infections including bronchitis, pneumonia, empyema and lung abscess.
• Skin and soft tissue infections, including acne, furuncle, cellulite, impetigo, abscess and wound infections. Specific skin and soft tissue infections such as erysipelas and paronychia.
• Bone and joint infections, including osteomyelitis and septic arthritis.
• Gynecological infections including endometritis, pelvic cellulitis, vaginal dome infection and tubo-ovarial abscess, salpingitis, and inflammatory pelvic disease (in combination with an appropriate antibiotic with a Gram-negative aerobic spectrum of action).
• Intra-abdominal infections including peritonitis and abdominal abscess (in combination with an appropriate antibiotic with a Gram-negative aerobic spectrum of action).
•Septicemia and endocarditis. Clindamycin is effective in endocarditis cases whose *in vitro* bactericidal effect on the organism causing the infection in the serum concentrations reached is shown by tests.
• Dental infections such as periodontal abscess and periodontitis.
• Toxoplasmic encephalitis in AIDS patients. Clindamycin used in combination with pyrimethamine is effective in patients who cannot tolerate conventional therapy.

• *Pneumocystis jiroveci* (Previously classified as *Pneumocystis carinii*) pneumonia in AIDS patients. Clindamycin can be used in combination with primaquine in patients who cannot tolerate conventional therapy or do not respond adequately.

When KLINDAVER ampoule is used in combination with an antibiotic of the aminoglycoside group such as gentamicin or tobramycin, it is effective in preventing peritonitis and abdominal abscesses that may occur as a result of bacterial contamination secondary to intestinal perforation or trauma.
When used alone or in combination with quinine or chlorokinin, it is effective in the treatment of multidrug-resistant malaria, including *Plasmodium falciparum*.
The following microorganisms have been shown to be susceptible to clindamycin in vitro: *B melaninogenicus, B disiens, B bivius, Peptostreptococcus spp., G vaginalis, M mulieris, M curtissi and Mycoplasma hominis.*

4.2. Posology and method of administration

Posology/Frequency and Duration of administration:

The dosage should be determined according to the severity of the infection, the condition of the patient and the susceptibility of the bacteria causing the infection.
When the patient's condition improves, treatment can be continued with clindamycin pediatric granules or clindamycin capsules.

Adults

In severe infections, 600 mg to 1.2 g per day are administered in 2, 3 or 4 equal doses, either intramuscularly or intravenously. In more severe infections, 1.2-2.7 g per day is administered in 2, 3 or 4 doses.
Doses of up to 4800 mg per day have been successfully applied in life-threatening situations.
Doses over 600 mg are not recommended to be administered as a single intramuscular injection.

Treatment of inflammatory pelvic disease

KLINDAVER ampoule 900 mg intravenously every eight hours and an antibiotic with a Gram-negative aerobic spectrum (e.g. 2.0 mg / kg in those with normal renal function, then 1.5 mg / kg gentamicin every eight hours) are used together. It should be at least 48 hours after the patient's recovery, provided that it is not shorter than 4 days to intravenous treatment. Then, clindamycin treatment is continued with 450 mg clindamycin capsule 6 hours apart until a total treatment period of 10-14 days is completed.

Toxoplasmic encephalitis treatment in AIDS patients

Intravenously, KLINDAVER ampoule or orally clindamycin capsule is administered at a dose of 600-1200 mg per day for 2 weeks at 6-hour intervals, and then the treatment is continued with 300-600 mg clindamycin capsule 6 hours apart. Treatment should generally be continued for 8-10 weeks. Oral pyrimethamine dosage is 25-75 mg per day for 8-10 weeks. If primetamine is used in high

doses, 10-20 mg of folinic acid should be added daily.

Treatment of *Pneumocystis carinii* pneumonia in AIDS patients

KLINDAVER ampoule 600-900 mg every 6 hours for 21 days or 900 mg clindamycin capsule every 6 hours orally for 21 days and 15-30 mg primaquine orally once a day for 21 days.

Malaria treatment

There is no information available on parenteral administration. In oral administration (capsules or oral solution) 10-20 mg / kg / day in adults and 10 mg / kg / day in children in equal doses every 12 hours for 7 days or quinine (12 mg / kg every 12 hours) or with chloroquine (15-25 mg every 24 hours) for 3-5 days.

Method of administration:

It is administered intramuscularly or intravenously.

Dilution and infusion rate

KLINDAVER ampoule must be diluted before intravenous administration. The clindamycin concentration in the solution prepared by dilution for infusion should not exceed 18 mg / mL and the infusion rate should not exceed 30 mg per minute. Infusion rates are given in the table below.

Dosage	Dilute	Infusion time
300 mg	50 mL	10 min
600 mg	50 mL	20 min
900 mg	50-100 mL	30 min
1200 mg	100 mL	40 min

Administration of more than 1200 mg of KLINDAVER in one hour infusion period should be avoided.

Alternatively, treatment can be continued as a continuous infusion after the first dose of KLINDAVER ampoule is administered in adults as a rapid infusion as indicated in the table below.

Serum clindamycin levels to be achieved	Rate of first infusion	Infusion rate in maintenance therapy
Above 4 µg/mL	30 min 10 mg/min	0.75 mg/min
Above 5 µg/mL	30 min 15 mg/min	1.00 mg/min
Above 6 µg/mL	30 min 20 mg/min	1.25 mg/min

KLINDAVER is physically and chemically stable for at least 24 hours in 5% dextrose and sodium chloride solutions containing the following antibiotics at the concentrations used in clinics: Amikacin sulfate, aztreonam, cefamandole naphtha, cefazolin sodium, cefotaxime sodium, cefoxitin sodium,

ceftazidime sodium, ceftizoxime sodium, gentamicin. sulfate, netilmicin sulfate, piperacillin and tobramycin.
The compatibility and stability times of drug mixtures vary depending on concentration and other conditions (see Section 6.2 Incompatibilities).

Additional information on special populations:

Renal impairment:
No dose adjustment is required in patients with renal impairment (see Section 4.5 Interaction with other medicinal products and other forms of interaction and 5.2 Pharmacokinetic properties).

Hepatic impairment:
No dose adjustment is required in patients with hepatic impairment (see Section 4.5 Interaction with other medicinal products and other forms of interaction and 5.2 Pharmacokinetic properties).

Pediatric population:
Children over a month old
20-40 mg / kg per day to be given intramuscularly or intravenously in 3 or 4 equal doses.

More serious infections:
25-40 mg / kg per day to be given in 3 or 4 equal doses. In severe infections, it is recommended to administer not less than 300 mg per day, regardless of body weight.

Geriatric population:
No dosage adjustment is necessary in elderly patients with normal kidney and liver function. Doses used in adults are used.

Other issues to consider when using
In beta-hemolytic streptococcal infections, treatment should be continued for at least 10 days.

Parenterally administered drugs should be visually checked for particles and discoloration to the extent permitted by the packaging and solution.

4.3. Contraindications

KLINDAVER Ampoule is contraindicated in those known to be sensitive to clindamycin or lincomycin or any ingredient in the formulation.

4.4. Special warnings and precautions for use

Clindamycin should be used to treat serious infections. It has been reported that, starting from a mild watery diarrhea, severe persistent diarrhea, leukocytosis, fever, severe abdominal cramps accompanied by bloody and mucous excretion and, if left untreated, can progress to peritonitis, shock and toxic megacolon, causing pseudomembranous colitis, which can be fatal. Colitis due to antibiotic

use may begin during treatment or even 2-3 weeks after antibiotic treatment.

One of the most important known causes of antibiotic-related colitis is toxins produced by Clostridium difficile. The diagnosis of antibiotic-induced colitis is usually based on clinical symptoms. Demonstration of pseudomembranous colitis endoscopically confirms the diagnosis. Detection of Clostridium difficile in stool culture and C difficile toxin in stool samples in selective culture medium also proves the diagnosis.

In cases with mild colitis due to antibiotic use, it may be sufficient to discontinue antibiotic treatment. If necessary, colestipol (5 grams three times a day) or cholestyramine (4 grams three times a day) can be administered to bind toxins. In severe cases, an appropriate antibiotic treatment effective against Clostridium difficile should be initiated with fluid-electrolyte and protein supplementation. Vancomycin, used orally at doses of 125-500 mg four times a day for 7-10 days, is effective against Clostridium difficile. Since cholestyramine may reduce its effect by binding vancomycin, care should be taken to take them at least in two hours. Alternatively, 25,000 U bacitracin orally four times a day for 7-10 days can be used instead of oral vancomycin. The use of drugs that may cause intestinal stasis should be avoided in antibiotic-induced colitis.

Care should be taken when administering clindamycin therapy to patients with gastrointestinal disease, especially colitis.

Studies show that colitis and diarrhea caused by Clostridium difficile due to antibiotic use occur more in debilitated and / or elderly patients (> 60 years of age) and may have a more severe course.

Clindamycin should not be used in the treatment of meningitis as it does not pass into the cerebrospinal fluid adequately.

Liver and kidney functions should be checked in long-term treatments.

Safety and appropriate dosage have not been established in infants younger than 1 month.

KLINDAVER Ampoule treatment may cause excessive growth (superinfection) of non-susceptible organisms, especially yeast fungi.

KLINDAVER Ampoule should not be injected as a bolus into the vein without dilution, it should be administered as an infusion of at least 10-60 minutes as stated in the "Method and dosage" section.

Care should be taken when applying KLINDAVER Ampoule to atopic (allergic) persons.

It is not necessary to adjust the dose of clindamycin in patients with kidney disease. Although the half-life of clindamycin is prolonged in patients with moderate and severe liver disease, pharmacokinetic studies have shown that clindamycin accumulation may rarely occur when administered every 8 hours. Therefore, it is accepted that the dose does not need to be reduced in liver disease.

This product contains 9.45 mg benzyl alcohol per mL. It should not be administered to premature babies and newborns. It may cause toxic reactions and anaphylactoid reactions in infants and children up to the age of 3 years. It has been reported that benzyl alcohol can cause fatal gasping syndrome in premature babies.

This medicinal product contains less than 1 mmol sodium per mL; so essentially "does not contain sodium".

4.5. Interactions with other medical products and other forms of interaction

Erythromycin:

In vitro antagonism has been demonstrated between clindamycin and erythromycin. These two drugs should not be used together as they may be clinically important.

There is cross resistance between clindamycin and lincomycin.

Neuromuscular blocking drugs:

Clindamycin has a neuromuscular blocking effect that can strengthen the effect of other neuromuscular blocking drugs. Therefore, caution should be exercised in patients using such drugs.

During treatment with KLINDAVER and 7 days after treatment, patients should use other contraceptive measures (eg condom) in addition to oral contraceptives.

Additional information on special populations

Pediatric population:

No interaction studies in the pediatric population have been identified.

4.6. Pregnancy and lactation

General advice

Pregnancy category: B

Women with childbearing potential/Contraception

Since the safety of clindamycin in pregnant women has not been proven, KLINDAVER Ampoule should be used with caution in women who do not use a contraceptive method. Women using KLINDAVER ampoules should use an appropriate method of contraception.

Pregnancy

There are no adequate and controlled studies regarding the use of KLINDAVER Ampoule in pregnant women.

Caution should be exercised when administered to pregnant women.

The safety of clindamycin use during pregnancy has not yet been demonstrated. Therefore, KLINDAVER Ampoule should be used in pregnancy only if absolutely necessary.

Lactation

Clindamycin has been reported to pass into breast milk at concentrations of 0.7-3.8 μg / mL.

It should be decided whether breastfeeding or KLINDAVER Ampoule treatment should be stopped or not / whether to avoid the treatment.

The reproductive capability/Fertility

Fertility tests in rats treated orally up to a dose of 300 mg / kg / day (approximately 1.1 times the highest recommended dose in adult human on a mg/m^2 basis) showed no effect on fertility and mating ability.

4.7. Effects on ability to drive and use machines

No study has been conducted to determine the effect of clindamycin on driving and using machines.

4.8. Undesirable effects

The frequency of undesirable effects, including reactions reported in patients treated with clindamycin ampoule, are listed below. The effects observed with clindamycin are generally dependent on dose or concentration.

The incidence of undesirable effects has not been defined for clindamycin.

Very common (≥ 1/10), common (≥ 1/100 and < 1/10), uncommon (≥1/1000 and <1/100), rare (≥1/10.000 and <1/1000), very rare (<1/10.000) and unknown (estimation based on the existing data is impossible).

Infections and infestations

Not known: Vaginitis

Blood and Lymphatic System Disorders:

Not known: Transient neutropenia (leucopenia), eosinophilia, agranulocytosis and thrombocytopenia

No direct etiological link could be established with clindamycin treatment in any of these.

Immune system disorders

Not known: anaphylactoid reactions

Nervous system disorders

Uncommon: Few (uncommon) cases of dysgeusia with serious side effects have been observed with systemic administration of clindamycin using injection (IM or IV) or oral granulate solution.

Cardiac diseases

Uncommon: Cardiovascular arrest and hypotension (following rapid intravenous administration in rare cases)

Gastrointestinal diseases

Common: Abdominal pain, diarrhea

Uncommon: Nausea and vomiting

Not known: Esophagitis, esophageal ulcer

Hepato-biliary diseases

Common: abnormal liver function tests

Not known: Jaundice

Skin and subcutaneous tissue disorders

Uncommon: Maculopapular eruptions, urticaria

Unknown: Steven Johnson Syndrome, toxic epidermal necrolysis, exfoliative dermatitis, morbilliform-like skin rash, vaginitis, vesiculobullous dermatitis, pruritus, erythema multiforme, severe cutaneous adverse reaction (SCAR)

Musculoskeletal, connective tissue and bone disorders

Rare: Polyarthritis

Kidney and urinary disorders

An association between clindamycin and renal damage has not been established.

Rare: Azotemia, oliguria and / or proteinuria

General disorders and administration site conditions

Uncommon: Pain, sterile abscess (after intramuscular administration).

Common: Thrombophlebitis (after intravenous injection)

Not known: local irritation (after intramuscular administration)

These reactions can be prevented by giving intramuscular injections deeply into the muscle and avoiding prolonged use of the same intravenous catheter.

Reporting of the side effects:

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 and treatment

In case of overdose, specific treatment is not required.

The biological half-life of clindamycin in serum is 2.4 hours. Clindamycin cannot be easily removed from the blood by hemodialysis or peritoneal dialysis.

If an allergic reaction occurs, immediate treatment measures, including corticosteroids, adrenaline and antihistamines, should be administered.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: Systemic antibacterial, lincosamides

ATC Code: J01FF01

Clindamycin is a semi-synthetic antibiotic created using 7 (S) -chloro instead of the 7 (R) -hydroxyl group of the underlying compound lincomycin.

Mechanism of Action

Although clindamycin palmitate hydrochloride is not effective in vitro, it turns into antibacterial clindamycin at the end of in vivo hydrolysis. Clindamycin, similar to macrolides, binds to the 50S subunit of bacterial ribosomes, inhibiting the first stage of protein synthesis. Although basically bacteriostatic, it acts bactericidal against susceptible strains in high concentrations.

Clindamycin is effective in vitro against the following microorganisms.

Aerobe Gram-positive cocci: *Staphylococcus aureus* (penicillinase-producing and non-penicillinase strains), *Staphylococcus epidermidis* (some staphylococci resistant to erythromycin rapidly develop resistance to clindamycin), streptococci (except *Streptococcus faecalis*), pneumococci.

Anaerobe Gram negative bacilli: *Bacteroides* species (including Bacteroides fragilis group and Bacteroides melaninogenicus group), *Fusobacterium* species.

Anaerobe Gram-positive non-sporulating bacilli: *Propionibacterium, Eubacterium,Actinomyces* species.

Anaerobic and microaerophilic Gram-positive cocci: *Pepto coccus* species, *Pepto streptococcus* species, microaerophilic streptococci.

Clostridiums: While most strains of *Clostridium perfringens* are susceptible to clindamycin, other species such as *Clostridium sporogeneses* and *Clostridium tertium* are generally resistant. In these cases, bacterial susceptibility tests should be done.

5.2. Pharmacokinetic properties

General Particulars:

Absorption**:**

At the end of the short-term intravenous infusion, the highest active clindamycin concentrations in serum are reached.

When clindamycin phosphate is administered intramuscularly, the highest active clindamycin concentrations in serum are reached within 3 hours in adults and 1 hour in children. The highest serum concentrations of active clindamycin after parenteral administration of clindamycin phosphate and concentrations just before the next dose is given in Table 1 below.

Table 1: Active clindamycin concentrations in serum after clindamycin phosphate administration

Dosage	**Max Serum concentration (C_{max}) micrograms/mL**	**Serum concentration at the end of the dosage range micrograms/mL**
Healthy adults (after steady state is reached)		
600 mg intravenously every 30 minutes every 6 hours	10.9	2.0
600 mg intravenously every 30 minutes every 8 hours	10.8	1.1
900 mg intravenously every 30 minutes every 8 hours	14.1	1.7
600 mg intramuscularly every 30 minutes every 12 hours *	9	
Children (first dose) *		
5-7 mg / kg intravenously in one hour	10	
5-7 mg / kg intramuscularly	8	
3-5 mg / kg intramuscularly	4	

* Information on these groups was obtained from patients treated for infection.

Distribution:

By administering clindamycin phosphate to adults every 8-12 hours, to children every 6-8 hours, or by continuous intravenous infusion, serum clindamycin levels are maintained above the lowest inhibition concentrations of a large number of microorganisms in vitro. Steady serum levels are reached after the third dose.

Clindamycin does not show a significant penetration into the cerebrospinal fluid even in cases of inflammation of the meninges. Pharmacokinetic studies in elderly and young adult volunteers have shown that when clindamycin phosphate is administered intravenously, the pharmacokinetic properties of clindamycin (clearance, breakthrough half-life, volume of distribution and area under the curve) do not change with age.

Clindamycin is distributed in body fluids and tissues including bone and cannot reach the cerebrospinal fluid in effective concentration. It passes through the placenta into the fetal circulation and into milk during lactation. It is found in high concentration in bile.

Biotransformation:
Clindamycin is metabolized, presumably in the liver, to active N-dimethyl and sulfoxide metabolites and some inactive metabolites.

Elimination:
Approximately 10% of the taken dose is excreted in urine, 4% in faeces as active drug or active metabolites, and the remainder as inactive metabolites. In patients with reduced renal function, the half-life of clindamycin in serum is slightly prolonged.
Clindamycin accumulates in leukocytes and macrophages. More than 90% of clindamycin binds to plasma in the circulation. Breakthrough is slow and takes several days.
Clindamycin phosphate, which is biologically inactive, rapidly disappears from the serum; The half-life is on average 6 minutes. The half-life of active clindamycin in serum is approximately 3 hours in adults and 2.5 hours in children.
The elimination half-life of clindamycin is slightly prolonged in patients with significantly reduced kidney or liver function. Dose adjustment is not required for patients with mild or moderate kidney or liver disease. Pharmacokinetic studies in elderly and young adult volunteers have shown that when clindamycin phosphate is administered intravenously, the pharmacokinetic properties of clindamycin (clearance, breakthrough half-life, volume of distribution and area under the curve) do not change with age.

Linearity / nonlinear case:
Serum concentration of clindamycin increases in direct proportion to dose.

Characteristics in patients
Pharmacokinetic studies in elderly and young adults have shown that when clindamycin phosphate is administered intravenously, the pharmacokinetic properties of clindamycin (clearance, breakthrough half-life, distribution volume and area under the curve) do not change with age.

5.3. Preclinical safety data

Carcinogenicity

Long-term animal studies have not been conducted to evaluate the carcinogenic potential of clindamycin.

Mutagenicity

Genotoxicity tests were performed, including a rat microkernel test and an Ames Salmonella reversion test. Both tests are negative.

Reproductive toxicity

In fertility studies conducted in rats at doses up to 300 mg / kg per day (approximately 1.1 times the highest recommended dose for humans on mg / m^2 basis), no effect on reproduction was observed.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Benzyl alcohol
Disodium edetate
Water for injection
When necessary, pH adjustment was made with hydrochloric acid or sodium hydroxide.

6.2. Incompatibilities

Due to the low pH values of clindamycin salt solutions, incompatibilities can be expected with alkaline preparations or unstable drugs at low pH. KLINDAVER is physically incompatible with the following drugs:
Ampicillin sodium, phenytoin sodium, barbiturates, aminophylline, calcium gluconate, ceftriaxone sodium, ciprofloxacin, diphenylhydantoin, idarubicin hydrochloride, ranitidine hydrochloride and magnesium sulfate.

6.3. Shelf life

24 months

6.4. Special precautions for storage

It should be stored at room temperature between 15-30 ° C.
Keep in its package and out of the reach and sight of children.

6.5. Nature and contents of container

Packages containing 4 ml type I glass ampoules containing clindamycin phosphate equivalent to 150 mg of clindamycin in each mL.

6.6. Special precautions for disposal and other handling

Clindamycin Phosphate has been shown to be physically and chemically compatible for at least 24 hours in 5% dextrose and sodium chloride injection solutions containing the following antibiotics: Amikacin sulphate, aztreonam, cefamandole naphtha, cefazolin sodium, cefotaxime sodium, cefoxitin sodium, ceftazidime sodium, ceftizoxime sodium, gentamicin sulfate, netilmicin sulfate, piperacillin and tobramycin.

Compatibility and stability times of drug mixtures depend on concentration and other conditions.

Unused products or waste materials should be disposed of in accordance with the "Medical Waste Control Regulation" and "Packaging and Packaging Waste Control Regulations".

7. MARKETING AUTHORIZATION HOLDER

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8. MARKETING AUTHORIZATION NUMBER

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10. DATE OF REVISION OF THE TEXT