Clindamycin phosphate

Klindex®

150mg/mL (600mg/4mL)
Solution for Injection (I.M./I.V.)
Antibacterial

℞

FORMULATION
Each mL contains 150 mg of clindamycin (as phosphate)

PHARMACEUTICAL FORM
Solution for Injection

CLINICAL PARTICULARS
Therapeutic indications
Acute and chronic bacterial infections caused by clindamycin-sensitive pathogens, such as
- Infections of bones and joints
- Infections of the ear, nose and throat area
- Infections of the dental and maxillary area
- Infections of the deep respiratory tract
- Infections of the pelvic and abdominal area
- Infections of female genitalia
- Infections of skin and soft tissues
- Scarlet fever
- Septicaemia
- Endocarditis

Dosage and administration
Adults and adolescents above 14 years of age
Receive in
- moderately severe infections: 8-12 mL of clindamycin daily (equivalent to 1.2-1.8 g clindamycin) in 2-4 single doses
- severe infections: 16-18 mL of clindamycin daily (equivalent to 2.4-2.7 g clindamycin) in 2-4 single doses.

The maximum daily dose for adults and adolescents above 14 years of age is 32 mL of clindamycin (equivalent to 4.8 g clindamycin) in 2-4 single doses.

Infants (over 4 weeks of age), children (up to 14 years of age)
Depending on the localisation and severity of the infection: 20-40 mg clindamycin per kg body weight in 3-4 single doses.

Dosage in hepatopathies
In patients with moderate to severe hepatopathies, the elimination half-life of clindamycin is prolonged. Dose reduction is usually not necessary when clindamycin is administered every 8 hours.

In patients with severe hepatic insufficiency, however, the plasma levels of clindamycin should be monitored. According to the results of this measure, dose reduction or prolonged dosage interval may become necessary.

Dosage in nephropathies
In case of nephropathy, the elimination half-life is prolonged. However, no dose reduction is necessary in mild to moderate impairment in renal function.

In patients with severe renal insufficiency or anuria, however, the plasma levels should be monitored. According to the results of this measure, dose reduction or alternatively prolonged dosage interval of 8 or even 12 hours may be necessary.

Dosage in haemodialysis
Clindamycin is not haemodialysable. No additional dose is therefore necessary prior to or after dialysis.

Mode of administration
Clindamycin is injected intramuscularly or infused intravenously.

Clindamycin must never be injected undiluted intravenously!

In case of intramuscular administration, a single dose of 600 mg clindamycin should not be exceeded.

Prior to intravenous infusion, the solution is to be diluted in such a way that the concentration is not more than 12 mg clindamycin per mL solution. The infusion rate shall not exceed 30 mg clindamycin per minute. Not more than 1.200 mg clindamycin per hour should be given as single infusion.

Contraindications
Clindamycin is contraindicated in patients previously found to be sensitive to clindamycin, lincomycin or, to any excipient of the medicinal product.

Clindamycin solution for injection must not be given to premature babies or neonates because of the benzyl alcohol content (see Special warnings and precautions for use and Pregnancy and lactation).

Special warnings and precautions for use
The clindamycin injectable formulation contains benzyl alcohol. Benzyl alcohol has been reported to be associated with a fatal "Gasping Syndrome" in premature infants. Benzyl alcohol may cause toxic reactions and anaphylactoid reactions in infants and children up to 3 years old. The amount of benzyl alcohol at which toxicity may occur is not known.

Treatment with antibacterial agents alters the normal flora of the colon leading to overgrowth of *Clostridium difficile*. This has been reported with use of nearly all antibacterial agents, including clindamycin. *Clostridium difficile* produces toxins A and B which contribute to the development of *Clostridium difficile* associated diarrhea (CDAD) and is a primary cause of "antibiotic-associated colitis".

It is important to consider the diagnosis of CDAD in patients who present with diarrhea subsequent to the administration of antibacterial agents. This may progress to colitis, including pseudomembranous colitis (see Undesirable effects), which may range from mild to fatal colitis. If antibiotic-associated diarrhea or antibiotic-associated colitis is suspected or confirmed, ongoing treatment with antibacterial agents, including clindamycin, should be discontinued and adequate therapeutic measures should be initiated immediately. Medicinal products inhibiting peristalsis are contraindicated in this situation.

Caution should be used when prescribing clindamycin to individuals with a history of gastrointestinal disease, especially colitis.

Since clindamycin does not diffuse adequately into cerebrospinal fluid, the medicinal product should not be used in the treatment of meningitis.

If therapy is prolonged, liver and kidney function tests should be performed.

The use of clindamycin may result in overgrowth of non-susceptible organisms, particularly yeasts.

Clindamycin should not be injected intravenously undiluted as a bolus but should be infused over at least 10-60 minutes.

Treatment with clindamycin is possibly an alternative treatment in case of penicillin allergy (penicillin hypersensitivity). An allergic cross-reaction between clindamycin and penicillins is not known and not expected because of the structural differences of the both substances. However, (in isolated cases) anaphylaxis has been observed after clindamycin treatment of patients with existing penicillin allergy. This should be taken into consideration before treating penicillin allergic patients with clindamycin.

Interaction with other medicinal products and other forms of interaction
Clindamycin administered by injection 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.

If possible, clindamycin should not be combined with erythromycin, as an antagonistic effect has been observed regarding the antibacterial *effect in vitro*.

Vitamin K antagonists
Increased coagulation tests (PT/INR) and/or bleeding, have been reported in patients treated with clindamycin in combination with a vitamin K antagonist (e.g. warfarin, acenocoumarol and fluindione). Coagulation tests, therefore, should be frequently performed in patients treated with vitamin K antagonists.

Pregnancy and lactation
Pregnancy
Oral and subcutaneous reproductive toxicity studies in rats and rabbits revealed no evidence of impaired fertility or harm to the fetus due to clindamycin, except at doses that caused maternal toxicity. Animal reproduction studies are not always predictive of human response.

Clindamycin crosses the placenta in humans. After multiple doses, amniotic fluid concentrations were approximately 30% of maternal blood concentrations.

Benzyl alcohol can cross the placenta (see Contraindications and Special warnings and precautions for use).

In clinical trials with pregnant women, the systemic administration of clindamycin during the second and third trimesters has not been associated with an increased frequency of congenital abnormalities. There are no adequate and well-controlled studies in pregnant women during the first trimester of pregnancy.

Clindamycin should be used in pregnancy only if clearly needed.

Lactation
Orally and parenterally administered clindamycin has been reported to appear in human breast milk in ranges from 0.7 to 3.8 µg/mL. Because of the potential for serious adverse reactions in nursing infants, clindamycin should not be taken by nursing mothers.

Fertility
Fertility studies in rats treated orally with clindamycin revealed no effects on fertility or mating ability.

Effects on ability to drive and use machines
Clindamycin has no or negligible influence on the ability to drive and use machines.

Undesirable effects
The list below shows the adverse reactions identified through clinical trial experience and post-marketing surveillance by system organ class and frequency. The frequency grouping is defined using the following convention: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1.000 to <1/100); rare (≥1/10,000 to <1/1.000); very rare (<1/10,000), and not known (cannot be estimated from the available data). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Infections and infestations
Not known: Vaginal infection

Blood and lymphatic system disorders
Not known: Agranulocytosis, leukopenia, neutropenia, thrombocytopenia, eosinophilia

Immune system disorders
Not known: Anaphylactoid reaction, drug reaction with eosinophilia and systemic symptoms (DRESS)

Nervous system disorders
Uncommon: Dysgeusia, neuromuscular blocking activity

Cardiac disorders
Uncommon: Cardiorespiratory arrest, hypotension

Vascular disorders
Common: Thrombophlebitis

Gastrointestinal disorders
Common: Pseudomembranous colitis (see Special warnings and precautions for use)
Uncommon: Diarrhoea, nausea
Not known: Abdominal pain, vomiting

Hepatobiliary disorders
Common: Liver function test abnormal
Not known: Jaundice

Skin and subcutaneous tissue disorders
Common: Rash maculopapular
Uncommon: Erythema multiforme, pruritus, urticaria
Not known: Toxic epidermal necrolysis, Stevens-Johnson syndrome, acute generalised exanthematous pustulosis (AGEP), dermatitis exfoliative, dermatitis bullous, rash morbilliform

General disorders and administration site conditions
Uncommon: Pain, abscess
Not known: Injection site irritation

Overdose
Haemodialysis and peritoneal dialysis are not effective in removing clindamycin from the serum.

PHARMACOLOGICAL PROPERTIES
Pharmacodynamic properties
Pharmacotherapeutic group: Antibiotic

Clindamycin is a semi-synthetic derivative of lincomycin. It belongs to the group of lincosamides which –as pyranosides– are not related with antibiotics known to date. Clindamycin has predominantly bacteriostatic action and –depending on the concentration at the infection site and on the sensitivity of pathogens– bactericidal action. Clindamycin is usually well-effective against staphylococci (*Staphylococcus aureus, Staphylococcus epidermidis*), pneumococci (in penicillin-resitant pneumococci, partially considerably pronounced resistance also against clindamycin was found), streptococci of group A (*St. pyogenes*), *Viridans* streptococci, diphtheria bacilli, *Bacillus anthracis, Bacteroides spp., Fusobacteria, Actinomycetes, peptococci, peptostreptococci, Veillonella, Propionibacteria, Chlamydiae, Mycoplasma hominis, Toxoplasma gondii, Plasmodium falciparum,* and *Babesia microti*.
The sensitivity of *Clostridia* spp. varies, some species are resistant against clindamycin. Secondary development of resistance is rare.
The following is to be regarded as resistant: Enterococci (*E. faecalis, E. faecium*), gonococci and meningococci, *Haemophilus spp., Enterobacteria* such as *E.coli, Klebsiellae, Enterobacter, Serratia, Proteus* spp., *Pseudomonas, Salmonellae* and Shigellae as well as *Nocardia*.
There is complete cross-resistance of pathogens in clindamycin and lincomycin and partial cross-resistance of pathogens in clindamycin and erythromycin.

Pharmacokinetic properties
It must be differentiated between the clindamycin derivatives used only up to the time of absorption and splitting of esters. Afterwards, clindamycin is present as free base (active form) in organism. The esters are to be viewed as prodrugs.

Clindamycin-2-dihydrogenphosphate is a water-soluble ester for parenteral administration. With an intramuscular injection of 300 mg, maximum serum levels are approx. 6 µg/mL after 3 hours, after intravenous administration of 300 mg, mean serum concentrations of approx. 4-6 µg/mL are found after one hour.

The binding of clindamycin to plasma proteins depends on the concentration and is between 60 and 94% in the therapeutic range.

Clindamycin has good tissual patency, crosses the placental barrier and passes into mother's milk. Diffusion into spinal subarachnoid area is insufficient even in inflamed meninges. High concentrations are reached in bone tissue.

Clindamycin is mainly metabolised in the liver. Some metabolites are microbiologically effective. Medicinal products acting as enzyme inducers in the liver shorten the mean residence time of clindamycin in the body.

Clindamycin is eliminated at approx. two third with the faeces and one third with urine.

The serum half-life of clindamycin is approx. 3 hours in adults and approx. 2 hours in children. The half-life is prolonged in impaired renal function and moderate to severe hepatic insufficiency.

Clindamycin is not dialysable.

Preclinical safety data
Acute toxicity
Studies of acute toxicity of clindamycin and its salts in various animal species revealed LD_{50} values between 1,800 and 2,620 mg/kg after oral administration and between 245 and 820 mg/kg after intravenous administration. The intoxication picture showed considerably reduced activity of animals as well as convulsions.

Chronic toxicity
Repeated administration of clindamycin over 6 days in rats (subcutaneous administration) and in dogs (intravenous and intramuscular administration) did not cause any systemic toxic effects. After administration of clindamycin phosphate over 1 month in rats (s.c.) and dogs (i.m. and i.v.), no substance-induced influences on the development of body weight, on clinical-chemical parameters and on haematological parameters as well as on organic histopathology were detected either. In dogs, increases in SGOT and SGPT as well as a mild dose-dependent increase in the relative liver weight were identified after intramuscular administration of 30-90 mg/kg daily without any evidence of morphological alterations.
Local reactions around the site of injection (inflammations, hemorrhages and tissual damage) were observed in intramuscular and subcutaneous administration with the concentration of the applied solution for exceeding the maximum concentration therapeutically admissible.

Mutagenic and tumorigenic potential
In vitro and *in vivo* studies of the mutagenicity of clindamycin did not provide any evidence of a mutagenic potential.
No long-term studies of a tumorigenic potential of clindamycin have been performed.

Reproductive toxicity
Studies with clindamycin in rats and mice did not reveal any evidence of disordered fertility or embryofetotoxic properties. A major study in pregnant animals in which approx. 650 neonates exposed in the first trimester of pregnancy were also studied did not show elevated malformation rates.
Clindamycin was measured in cord blood with approx. 50% of the maternal serum concentration. It is to be assumed that the therapeutic concentrations can be achieved in the fetus. Transfer into the mother's milk is proven. The concentrations were up to 4 µg/mL after maternal doses of 600 mg and up to 2 µg/mL after doses of 300 mg. Except one single case report, no signs of adverse reactions on breastfed infants have become known so far.

PHARMACEUTICAL PARTICULARS
Incompatibilities
Clindamycin must not be administered in a mixed syringe together with ampicillin, phenytoin sodium, barbiturates, aminophylline, calcium gluconate and magnesium sulphate. These substances must be administered separately.

Storage
Store at temperatures not exceeding 25°C
Clindamycin solutions are to be protected from light and warmth.

Stability after opening
After opening, the residuals are to be discarded.

After dilution to the solution for infusion, Clindamycin phosphate is stable for 24 hours at a maximum.

Instructions for use and handling
For intravenous infusion, Clindamycin phosphate can be diluted with 5% glucose solution or 0.9% sodium chloride solution respectively.

CAUTION
Foods, Drugs, Devices, and Cosmetics Act prohibits dispensing without prescription.

AVAILABILITY
Type I clear and colorless glass ampoule (box of 5's)

Manufactured by: Salutas Pharma GmbH
Otto-von-Guericke-Allee-1
D-39179 Barleben, Germany
Imported by: Sandoz Philippines Corporation
7th Floor, Asian Reinsurance Bldg.
cor. Gamboa and Salcedo Sts.
Legazpi Village, Makati City, Philippines
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Reg. IPOPHIL

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