UNILAB

Clindamycin Hydrochloride

Klindex®

ANTIBACTERIAL
150 mg Capsule
300 mg Capsule

FORMULATIONS
Each capsule contains:
Clindamycin (as hydrochloride)..... 150 mg or 300 mg

PRODUCT DESCRIPTIONS
Clindamycin 150 mg capsule: white, size "1" hard gelatin capsule
Clindamycin 300 mg capsule: purple, size "0" hard gelatin capsule

CLINICAL PHARMACOLOGY

PHARMACODYNAMICS
Clindamycin is a lincosamide antibiotic with bacteriostatic or bactericidal action, depending on the concentration of the drug attained at the site of infection and the susceptibility of the infecting organism. Clindamycin hydrochloride is inactive until hydrolyzed to free clindamycin.

Clindamycin appears to inhibit protein synthesis in susceptible organisms by binding to the 50S subunits of the bacterial ribosome which leads to the inhibition of peptide bond formation. This prevents chain prolongation by blocking transpeptidation, halting bacterial multiplication. Clindamycin's site of action appears to be the same as that of erythromycin and chloramphenicol.

ANTIMICROBIAL SPECTRUM OF ACTIVITY
Clindamycin has demonstrated activity *in vitro* and in clinical infections against most strains of the following microorganisms:

Aerobic Gram-positive	Anaerobes
Staphylococcus aureus (methicillin-susceptible strains) *Streptococcus pneumoniae* (penicillin-susceptible strains) *Streptococcus pyogenes*	*Clostridium perfringens* *Peptostreptococcus anaerobius* *Bacteroides* spp (non-fragilis) *Prevotella melaninogenica* *Fusobacterium necrophorum* *Fusobacterium nucleatum*

Clindamycin has demonstrated *in vitro* activity against isolates of the following microorganisms; however, clinical significance is unknown:

Aerobic Gram-positive	Anaerobes
Staphylococcus epidermidis (methicillin-susceptible strains) *Streptococcus agalactiae* *Streptococcus anginosus* *Streptococcus oralis* *Streptococcus mitis* *Arcanobacterium haemolyticum* (formerly *Corynebacterium haemolyticum*)	*Clostridium tetani* *Clostridium clostridioforme* *Corynebacterium diphtheriae* *Propionibacterium acnes* *Eubacterium lentum* *Actinomyces* spp *Peptococcus* spp *Micromonas ("Peptostreptococcus") micros* *Finegoldia ("Peptostreptococcus") magna* Microaerophilic streptococci *Mobiluncus* *Lactobacillus* spp *Bacteroides fragilis* *Veilonellae* spp *Prevotella intermedia* *Prevotella bivia* *Porphyromonas*
Protozoa	**Other Microorganisms**
Plasmodium falciparum *Plasmodium berghei* *Plasmodium cynomolgi* *Pneumocystis jiroveci* *Babesia microti* *Toxoplasma gondii*	*Leptospira* *Chlamydia trachomatis* *Gardnerella vaginalis* *Mycoplasma hominis* *Mycoplasma pneumoniae*

When tested by *in vitro* methods, some staphylococcal strains originally resistant to erythromycin rapidly develop clindamycin resistance.

Cross-resistance has been demonstrated between clindamycin and lincomycin.

It is suggested to carry out susceptibility tests.

PHARMACOKINETICS
About 90% of an oral clindamycin dose is rapidly absorbed from the gastrointestinal (GI) tract. Prior to absorption, clindamycin hydrochloride is hydrolyzed to free clindamycin in the GI tract. The drug is not inactivated by gastric acidity. Clindamycin's serum concentrations appear to be predictable, increasing linearly with increasing doses. The extent of absorption and peak serum concentrations of clindamycin are not appreciably affected when administered with food, although peak serum concentrations may be delayed.

After oral administration of a single 150 mg dose of clindamycin hydrochloride to healthy, fasting adults, peak serum concentrations of clindamycin average 1.9 to 3.9 mcg/mL and are attained within 45-60 minutes; serum clindamycin concentrations average 1.5 mcg/mL at 3 hours and 0.7 mcg/mL at 6 hours.

Clindamycin is distributed into many body tissues and fluids including saliva, ascites fluid, pleural fluid, synovial fluid, bone, and bile. However, even in the presence of inflamed meninges, only small amounts of the drug diffuse into the cerebrospinal fluid (CSF). The concentration of clindamycin in synovial fluid and bone is reported to be 60-80% of concurrent serum concentrations; the degree of penetration does not appear to be affected by joint inflammation. Clindamycin readily crosses the placenta; cord blood concentrations of the drug have been reported to be 46% of concurrent maternal blood concentrations. Clindamycin is distributed into breast milk.

At a concentration of 1 mcg/mL, about 93% of the drug is bound to serum proteins.

Clindamycin's serum half-life ($t_{1/2}$) is 2-3 hours in adults and children with normal renal function. The serum $t_{1/2}$ is increased slightly in patients with markedly reduced renal or hepatic function. Clindamycin's serum concentrations are not appreciably affected by hemodialysis, peritoneal dialysis or prolonged administration in patients with normal renal functions.
Clindamycin is partially metabolized to bioactive and inactive metabolites. The major bioactive metabolites are clindamycin sulfoxide and *N*-demethyl-clindamycin which are excreted in urine, bile and feces. About 10% of the drug undergoes urinary excretion and about 3.6% via fecal excretion as active drug and metabolites within 24 hours; the remainder is excreted as inactive metabolites. Probenecid has no effect on clindamycin excretion.

INDICATIONS
* For the treatment of serious infections caused by susceptible microorganisms:
- Lower respiratory tract infections including bronchitis, pneumonia, empyema, and lung abscess
- Upper respiratory tract infections including tonsillitis, pharyngitis, sinusitis, otitis media, and scarlet fever
- Skin and skin structure infections including inflammatory acne vulgaris, furuncles, cellulitis, impetigo, abscesses, and contaminated wounds. For specific skin and skin structure infections such as erysipelas and paronychia (panaritium), it would seem logical that these conditions would respond very well to clindamycin therapy.
- Gynecological infections including endometritis, pelvic cellulitis, post-surgical vaginal cuff infection, nongonococcal tubo-ovarian abscess, salpingitis and pelvic inflammatory disease when given in conjunction with an antibiotic of appropriate Gram-negative aerobic spectrum.

In cases of cervicitis due to *Chlamydia trachomatis*, monotherapy with clindamycin has been shown to be effective in eradicating the organism.

- Intra-abdominal infections including peritonitis and abdominal abscess when given in conjunction with an antibiotic of appropriate Gram-negative aerobic spectrum
- Bone and joint infections including acute hematogenous osteomyelitis and septic arthritis
- Septicemia and endocarditis: The effectiveness of clindamycin in the treatment of selected cases of endocariditis has been documented when clindamycin is determined to be bactericidal to the infecting organisms by *in vitro* testing of appropriate achievable serum concentrations.
- Dental infections such as periodontal abscess and periodontitis
- *Pneumocystis jiroveci (carinii) pneumonia* in patients with acquired immunodeficiency syndrome (AIDS). In patients who are intolerant to or do not respond to conventional treatment, clindamycin in combination with primaquine has been shown to be efficacious.

* As an alternative treatment of multi-drug resistant *Plasmodium falciparum* infection when used in combination with quinine or amodiaquine.

DOSAGE AND ADMINISTRATION
* Clindamycin capsule should be taken with a full glass of water to avoid the possibility of esophageal irritation.
* Administration of clindamycin with food does not adversely affect clindamycin absorption and the capsule may be taken with meals.

Usual Recommended Oral Adult Dose:
Serious Infections: 150 mg to 300 mg every 6 hours
More Severe Infections: 300 mg to 450 mg every 6 hours

** The duration of treatment is based on the type and severity of infection.*
** Patients with β-hemolytic streptococcal infections should be treated for at least 10 days to diminish the likelihood of subsequent rheumatic fever or glomerulonephritis.*
** Serious anaerobic infections usually necessitate treatment with clindamycin sterile solution for intravenous or intramuscular administration.*

Recommended Oral Adult Dose for Specific Infections:

Indication	Recommended Oral Clindamycin Dose	Duration of Treatment
Acne	150 mg every 12 hours	-
Bacterial vaginosis	300 mg every 12 hours	7 days
Cervicitis due to *Chlamydia trachomatis*	450 mg every 6 hours	10 to 14 days
Pelvic Inflammatory Disease (inpatient treatment)	· Initially with intravenous (IV) Therapy (Clindamycin IV 900 mg every 8 hours plus an IV antibiotic with an appropriate Gram-negative aerobic spectrum) for at least 4 days and at least 48 hours after the patient improves. · Then continue with **oral clindamycin hydrochloride** 450 mg every 6 hours to complete duration of treatment.	10 to 14 days
Prevention of bacterial endocarditis in penicillin-allergic patients	600 mg, 30 to 60 minutes before the procedure	Single dose
Pneumocystis jiroveci (carinii) pneumonia in patients with AIDS*	300 mg to 450 mg every 6 to 8 hours + Primaquine	21 days *Note: If the patient should develop serious hematologic adverse effects, the dosage regimen of primaquine and/or clindamycin should be reduced.*
Alternative treatment of multi-drug resistant *Plasmodium falciparum* infection**	5 to 10 mg/kg twice a day + Quinine or Amodiaquine	At least 5 days
	Or, as prescribed by a physician	

* Clindamycin is used in conjunction with primaquine (See respective product label for prescribing information)
**Clindamycin is used in conjunction with quinine or amodiaquine (See respective product label for prescribing information)

CONTRAINDICATIONS
Known hypersensitivity to clindamycin, lincomycin or any component of the product.

WARNINGS AND PRECAUTIONS

***Clostridium difficile*-associated diarrhea (CDAD) has been reported with use of nearly all antibacterial agents, including clindamycin 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*.**

Since clindamycin therapy has been associated with severe colitis which may be fatal, it should be reserved for serious infections where less toxic antimicrobial agents are inappropriate. It should not be used in patients with nonbacterial infections. *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.

If CDAD is suspected or confirmed, ongoing antibiotic use not directed against *C. difficile* may need to be discontinued. Appropriate fluid and electrolyte management, protein supplementation, antibiotic treatment of *C. difficile*, and surgical evaluation should be instituted as clinically indicated.

- **Serious Allergic Reactions/Severe Skin Reactions**
  Serious allergic reactions, including severe skin reactions such as drug reaction with eosinophilia and systemic symptoms (DRESS), Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) (some with fatal outcome) and acute generalized exenthematous pustulosis (AGEP) have been reported in patients receiving clindamycin therapy. If a hypersensitivity or severe skin reaction occurs, clindamycin should be discontinued and appropriate therapy should be initiated [see **Undesirable Effects**]. The usual agents (adrenaline, corticosteroids, antihistamines and colloid infusion) should be available for emergency treatment of serious reactions.
- A thorough inquiry about the patient's history of hypersensitivity reactions should be made prior to initiating clindamycin therapy.
- Use with caution in atopic individuals, as well as in patients with a history of gastrointestinal disease, particularly colitis.
- Clindamycin has neuromuscular blocking properties which may enhance the effect of other neuromuscular blocking agents [see **Interactions with Other Medicaments**].
- Clindamycin should not be used for the treatment of meningitis since it does not diffuse adequately into the CSF.
- The combination of clindamycin with primaquine may cause hemolytic reactions in patients with G-6-PD deficiency; reference should also be made to the primaquine product monograph for other possible risk groups for other hematologic reactions. Blood examinations should be done routinely during clindamycin therapy with primaquine to monitor potential hematologic toxicities.
- Use with caution in patients with severe renal and/or hepatic impairment accompanied by severe metabolic aberrations; serum clindamycin levels should be monitored during high-dose therapy in these patients.
- Periodic liver and kidney function tests and blood counts should be performed during prolonged therapy.
- Surgical drainage and removal of necrotic tissue should be performed in combination with antibiotic therapy, when indicated.
- Prescribing clindamycin in the absence of a proven or strongly suspected bacterial infection or a prophylactic indication is unlikely to provide benefit to the patient and increases the risk of antibiotic resistance.
- As with other antibacterial drugs, long term or repeated use may result in overgrowth of non-susceptible organisms, including fungi.

INTERACTIONS WITH OTHER MEDICAMENTS
- **Neuromuscular Blocking Agents:** Clindamycin has been shown to have neuromuscular blocking properties that may enhance the neuromuscular blocking actions of other agents such as ether, tubocurarine and pancuronium, with a potential danger of respiratory depression. Clindamycin should be used with caution in patients receiving such agents, and such patients should be observed for prolongation of neuromuscular blockade.
- **Aminoglycosides**: Clindamycin has been reported to antagonize the bactericidal activity of aminoglycosides *in vitro*. However, *in vivo* antagonism has not been demonstrated, and clindamycin has been administered successfully in conjunction with an aminoglycoside with no apparent decrease in activity.
- **Ampicillin**: Clindamycin has been reported to diminish the activity of ampicillin *in vitro* against *Staphylococcus aureus*.
- **Erythromycin**: Antagonism of bactericidal activity *in vitro* has been demonstrated between clindamycin and erythromycin due to competition between the two drugs for the ribosomal binding site.
- **Neostigmine and Physostigmine:** Clindamycin has been reported to antagonize the effect of anticholinesterases neostigmine and physostigmine
- **Estrogens:** Clindamycin may possibly reduce the contraceptive effect of estrogen. Though the risk is small, additional contraceptive precautions are recommended during concomitant use and for seven days after discontinuation of clindamycin.
- **Vaccines:** Oral typhoid vaccine is inactivated by concomitant administration of antibacterials. Thus, clindamycin should be avoided for three days before and after oral typhoid vaccination.
- **Vitamin K antagonists:** Increased coagulation test results (prothrombin time/international normalized ratio) 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 monitored regularly in patients treated with vitamin K antagonists.

Interference with Laboratory Tests
Abnormalities in liver function tests have been observed.

STATEMENT ON USAGE FOR HIGH RISK GROUPS

Pregnancy: (Pregnancy Category B) - Clindamycin crosses the placenta in humans. After multiple doses, amniotic fluid concentrations were about 30% of maternal concentrations. Clindamycin was widely distributed in fetal tissues with the highest concentration found in liver. Since there are no adequate and well controlled studies in pregnant women, clindamycin should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

The US Centers for Disease Control and Prevention recommends that screening and/or treatment for bacterial vaginosis (BV) in pregnant women as clinically indicated should be conducted at the first prenatal visit. For the treatment of BV and reduction in the incidence of adverse pregnancy outcomes associated with BV (e.g., preterm birth), particularly in pregnant women at high risk for complications of pregnancy, oral clindamycin is recommended [see **Dosage and Administration**].

Lactation: Clindamycin is distributed into human milk, achieving breast milk concentrations of 0.7 to 3.8 mcg/mL at dosages of 150 mg orally to 600 mg intravenously. Since clindamycin may cause serious adverse effects to the infant, a decision should be made whether to discontinue breastfeeding or to discontinue the drug, taking into account the importance of the drug to the mother.
Children: Administration of clindamycin in pediatric patients 16 years old and younger warrants organ system function monitoring.

Elderly: Pharmacokinetic studies have shown no clinically important differences between elderly and younger patients with normal hepatic function and normal (age-adjusted) renal function after oral or intravenous administration of clindamycin. Therefore, dosage modifications are not recommended in elderly patients with normal hepatic and normal (age-adjusted) renal function.

Clinical experience has demonstrated that antibiotic-associated diarrhea and colitis may occur more frequently and be more severe in geriatric patients (>60 years old). Therefore, geriatric patients receiving clindamycin should be carefully monitored for the development of diarrhea.

Patients with Hepatic Impairment: Prolongation of the clindamycin $t_{1/2}$ has been observed in patients with moderate to severe liver disease. However, it is postulated from studies that when clindamycin is administered every eight hours, accumulation of the drug should rarely occur. Therefore, dosage reduction of clindamycin in patients with liver disease is not generally considered necessary. Liver enzyme levels should be determined periodically when treating patients with severe liver disease.

Patients with Renal Impairment: Dose modification of clindamycin may not be necessary in patients with renal disease. The serum $t_{1/2}$ of clindamycin is increased slightly in patients with markedly reduced renal function.

UNDESIRABLE EFFECTS

Gastrointestinal: CDAD and colitis/pseudomembranous colitis [frequently accompanied by fever and leukocytosis; rarely, reactive polyarthritis and protein-losing enteropathy (in elderly patients)], nausea, vomiting, diarrhea, abdominal pain/cramps, tenesmus, flatulence, bloating, anorexia, weight loss, esophagitis, esophageal ulcers

Dermatologic and Hypersensitivity Reactions: Generalized mild to moderate morbilliform-like (maculopapular) skin rashes, rash, urticaria, pruritus, fever, hypotension, anaphylaxis/anaphylactoid reactions; erythema multiforme, Stevens-Johnson syndrome; exfoliative and vesiculobullous dermatitis, vesiculobullous rashes, serious cutaneous adverse reaction (SCAR), toxic epidermal necrolysis (TEN), acute generalized exanthematous pustulosis (AGEP), drug reaction eosinophilia and systemic symptoms (DRESS)

Hepatobiliary and Renal: Jaundice, hepatic damage, transient increases in serum bilirubin, alkaline phosphatase, aspartate aminotransferase (AST); although no direct relationship of clindamycin to renal damage has been established, rare cases of renal dysfunction as evidenced by azotemia, oliguria, and/or proteinuria have been observed, abnormalities in liver function tests

Genitourinary: Vaginal infection/vaginitis

Hematologic: Transient neutropenia (leukopenia), eosinophilia, thrombocytopenia, and agranulocytosis have been reported although no direct etiologic relationship to concurrent clindamycin therapy could be made in any of these instances. However, in clindamycin/primaquine combination studies, serious hematologic toxicities (grade III, grade IV neutropenia or anemia, platelet counts <50 x 109/L, or methemoglobin levels of ≥ 15%) have been observed. Leukocytoclastic angiitis has also been reported.

Musculoskeletal: Polyarthritis

Nervous: Dysgeusia

***Other Adverse Effects*:** lymphadenitis

OVERDOSE AND TREATMENT
The minimal toxic or lethal dose of clindamycin is not well established. At therapeutic doses, the primary toxic effects may involve the GI tract and may include severe diarrhea and pseudomembranous colitis that may result in death. Dermatitis, nephrotoxicity, hepatotoxicity, and various hematological abnormalities may occur less frequently.

No specific antidote is known. Supportive management should be initiated during overdose since hemodialysis and peritoneal dialysis are not effective in removing clindamycin from the serum. Monitor full blood count and liver function tests in patients with significant exposure as clindamycin may produce abnormalities of the hematopoietic system, and may cause hepatotoxicity. Monitoring serum concentration in patients with markedly reduced renal and hepatic function may be useful during high-dose therapy.

In cases of serious allergic anaphylactoid reactions, immediate emergency treatment including epinephrine, oxygen and IV corticosteroids should be administered as indicated.

ADVERSE DRUG REACTION REPORTING STATEMENT
For suspected adverse drug reaction, seek medical attention immediately and report to the FDA at www.fda.gov.ph AND Unilab at +632-8-**UNILAB**-1 (+632-8-**864522**-1) for Metro Manila or toll-free +1-800-10-UNILAB-1 for provinces, or email productsafety@unilab.com.ph.

By reporting undesirable effects, you can help provide more information on the safety of this medicine.

STORAGE CONDITIONS
Store at temperatures not exceeding 30°C.
Protect from light and moisture. Keep the products out of sight and reach of children.

AVAILABILITY
Clindamycin HCl (Klindex) 150 mg capsule, flex foil strip x 10's, box of 100's
Clindamycin HCl (Klindex) 300 mg capsule, flex foil strip x 10's, box of 100's

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

Manufactured by: ATRA PHARMACEUTICALS PVT. LTD.
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