Leaflet for FCT 160x**520** mm
die-cut with technical fields - front page
DO NOT move/change the codes!
codes must be in the same color as text
text must fit in the dotted rectangle

Natrapharm

CLINDAMYCIN HCl

Peldacyn®

300 mg Capsule
Antibacterial (Lincosamide)

Rx

FORMULATION
Each capsule contains approximately 338.47 mg of Clindamycin Hydrochloride. 1 H2O equivalent to 300 mg clindamycin.

PHARMACEUTICAL FORM
Capsule, hard
Brown hard gelatin capsule size 0, filled with homogenous white powder

CLINICAL PARTICULARS
Therapeutic indications
Clindamycin is indicated in infections caused by bacteria susceptible to clindamycin (see Pharmacodynamic properties), such as:

- Infections of upper respiratory tract, such as chronic or recurrent tonsillitis, pharyngitis, sinusitis, otitis media and scarlet fever, if there is no response to primary antibiotics or if they cannot be used.
- Infections of lower respiratory tract, such as bacterial bronchitis, pneumonia, empyema, lung abscess
- Difficult to treat skin and soft tissue infections, such as acne, furunculosis, cellulitis, impetigo, abscesses, wound infections, erysipelas, nail wall infections
- Bone and joint infections such as osteomyelitis and septic arthritis
- Gynaecological infections, such as endometritis, tubo-ovarian abscess, salpingitis, infections of the cervical area and inflammatory diseases of the pelvic area in combination with an antibiotic which is effective against gram-negative aerobic bacteria. In case of cervicitis caused by Chlamydia trachomatis clindamycin treatment can be given in monotherapy.
- Intra-abdominal infections, such as peritonitis and abdominal abscess in combination with an antibiotic which is effective against gram-negative aerobic bacteria.
- Dental infections, such as periodontal abscess and periodontitis

In case of severe clinical status intravenous therapy is preferred to oral therapy.

Clindamycin is effective in many anaerobic infections (see Pharmacodynamic properties). In aerobic infections, clindamycin is an alternative when other antimicrobial agents are not active or are contraindicated.

Consideration should be given to official/local guidance with regard to resistance to antibiotics and to the appropriate use of antibacterial agents.

Dosage and method of administration
Adults, adolescents over 14 years of age and older people:
600-1800 mg/day divided into 3-4 equal doses.

For doses that cannot be reached by clindamycin, 450 mg or clindamycin 600 mg tablets other pharmaceutical forms with lower doses are available.

Children and adolescents
Depending on location and severity of infection children and adolescents (4 weeks to 14 years) take 8 to 25 mg clindamycin/kg bodyweight/day.

For this age group other pharmaceutical forms with lower doses are available.

Patients with hepatic impairment
Prolongation of clindamycin half-life has been observed in patients with mild to moderate hepatic impairment. However, pharmacokinetic studies have shown that accumulation occurs only rarely when clindamycin is administered every 8 hours.
In patients with severe liver insufficiency the blood level of clindamycin should be monitored carefully. Accordingly, dose reduction or prolongation of the dose interval can be necessary.

Patients with renal impairment
Prolongation of clindamycin half-life has been observed in patients with renal impairment. However, in patients with mild to moderate renal impairment dose reduction is not necessary.

In patients with severe renal insufficiency or anuria, the blood level of clindamycin should be monitored carefully. Accordingly, dose reduction or prolongation of the dosage interval to 8 or even 12 hours can be necessary.

Dosage in haemodialysis patients
Clindamycin cannot be removed by haemodialysis. No increase in dose is therefore required before or after dialysis.

Method and duration of treatment
To avoid oesophageal irritation the tablets should always be taken with a full glass of water!

Treatment should last for at least 10 days in infections due to β-haemolytic streptococci.

Contraindications
Hypersensitivity to the active substance clindamycin, to lincomycin or to any of the excipients.

Special warnings and precautions for use
Severe hypersensitivity reactions, including severe skin reactions such as drug reaction with eosinophilia and systemic symptoms (DRESS), Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and acute generalised exanthematous 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 Contraindications and Undesirable effects).

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 diarrhoea (CDAD) and is a primary cause of “antibiotic-associated colitis”.

It is important to consider the diagnosis of CDAD in patients who present with diarrhoea 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 diarrhoea 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 gastro-intestinal 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, renal and hepatic function tests should be performed.

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

Treatment with clindamycin is possibly an alternative treatment in case of penicillin allergy (penicillin hypersensitivity). An allergic cross-reaction between clindamycin and penicillin is not known and not expected because of the structural differences of 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 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.

Antagonism in vitro has been observed between clindamycin and erythromycin. Due to possible clinical significance the two medicinal products should not be administered concurrently.

Clindamycin is metabolised predominantly by CYP3A4, and to a lesser extent by CYP3A5, to the major metabolite clindamycin sulfoxide and minor metabolite N-desmethylclindamycin. Therefore, inhibitors of CYP3A4 and CYP3A5 may reduce clindamycin clearance and inducers of these isoenzymes may increase clindamycin clearance. In the presence of strong CYP3A4 inducers such as rifampicin, monitor for loss of effectiveness.

In vitro studies indicate that clindamycin does not inhibit CYP1A2, CYP2C9, CYP2C19, CYP2E1 or CYP2D6 and only moderately inhibits CYP3A4. Therefore, clinically important interactions between clindamycin and co-administered drugs metabolised by these CYP enzymes are unlikely.

Cross-resistance between clindamycin and lincomycin has been observed.

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 monitored in patients treated with vitamin K antagonists.

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

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.

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

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
Common: Pseudomembranous colitis* (see Special warnings and precautions for use)
Not known: Clostridium difficile colitis*, vaginal infection*

Blood and lymphatic system disorders
Common: Eosinophilia
Not known: Agranulocytosis*, neutropenia*, thrombocytopenia*, leukopenia*

Immune system disorders
Not known: Anaphylactic shock*, anaphylactoid reaction*, anaphylactic reaction*, hypersensitivity*

Nervous system disorders
Uncommon: Dysgeusia, neuromuscular blocking activity
Not known: Dizziness, drowsiness, headache

Gastrointestinal disorders
Common: Diarrhoea
Uncommon: Abdominal pain, nausea, vomiting
Not known: Oesophageal ulcer*, oesophagitis*

Hepatobiliary disorders
Not known: Jaundice

Skin and subcutaneous tissue disorders
Common: Rash maculopapular
Uncommon: Urticaria
Rare: Erythema multiforme, pruritus
Not known: Toxic epidermal necrolysis (TEN)*, Stevens-Johnson syndrome*, drug reaction with eosinophilia and systemic symptoms (DRESS)*, acute generalised exanthematous pustulosis (AGEP)*, angioedema*, dermatitis exfoliative*, dermatitis bullous*, rash morbilliform*

Musculoskeletal and connective tissue disorders
Very rare: Polyarthritis

Investigations
Common: Liver function test abnormal

* ADR identified post-marketing.

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

PHARMACOLOGICAL PROPERTIES
Pharmacodynamic properties
Pharmacotherapeutic group: Antibacterials for systemic use; macrolides, lincosamides and streptogramins; lincosamides
ATC code: J01FF01

Clindamycin is a semi-synthetic pyranoside. Pyranosides do not show a relationship with other known antibiotics.

Mechanism of action:
The mechanism of action of clindamycin is based on the inhibition of protein biosynthesis due to binding to the 50s subunit of the bacterial ribosome, resulting in a bacteriostatic effect for the most part.

46258400 188

Leaflet for FCT 160x**520** mm
die-cut with technical fields - rear page
DO NOT move/change the codes!
codes must be in the same color as text
text must fit in the dotted rectangle

Relationship between pharmacokinetics and pharmacodynamics
The efficacy mainly depends on the duration of time during which the agent level is above the minimum inhibitory concentration (MIC) of the pathogen.

Mechanisms of resistance
A resistance to clindamycin may be based on the following mechanisms:
The resistance in staphylococci and streptococci is mostly based on an increased incorporation of methyl groups into 23S rRNA (so-called constitutive MLSB resistance) with the binding affinity of clindamycin to the ribosome considerably reduced thereby.
The majority of methicillin-resistant S. aureus (MRSA) shows the constitutive MLSB phenotype and is therefore clindamycin-resistant. Infections due to macrolide-resistant staphylococci should not be treated with clindamycin even in case of proven in vitro sensitivity, as there is the risk that mutants with constitutive MLSB resistance are selected during therapy.

In strains with constitutive MLSB resistance, there is complete cross resistance of clindamycin with lincomycin, macrolides (e.g. azithromycin, clarithromycin, erythromycin, roxithromycin, spiramycin) as well as streptogramin B.

Breakpoints
Clindamycin was tested while using the usual dilution series. The following minimal inhibitory concentrations were determined for susceptible and resistant germs:

EUCAST (European Committee on Antimicrobial Susceptibility Testing) breakpoints

Microorganism	Susceptible (mg/L)	Resistant (mg/L)
Staphylococcus spp.	≤0.25[1]	>0.5[1]
Streptococcus spp. (Group A, B, C, G)	≤0.5[1]	>0.5[1]
Streptococcus pneumoniae	≤0.5[2]	>0.5[2]
Viridans group streptococci	≤0.5[2]	>0.5[2]
Gram-negative anaerobes	≤4	>4
Gram-positive anaerobes except Clostridium difficile	≤4	>4
Corynebacterium	≤0.5	>0.5

1 Inducible clindamycin resistance can be detected by antagonism of clindamycin activity by a macrolide agent. If not detected, then report as susceptible. If detected, then report as resistant and consider adding this comment to the report: "Clindamycin may still be used for short-term therapy of less serious skin and soft tissue infections as constitutive resistance is unlikely to develop during such therapy".

2 Inducible clindamycin resistance can be detected by antagonism of clindamycin activity by a macrolide agent. If not detected, then report as susceptible. If detected, then report as resistant.

The prevalence of acquired resistance may vary geographically and with time for selected species and local information on resistance is desirable, particularly when treating severe infections. As necessary; expert advice should be sought when the local prevalence of resistance is such that the utility of the agent in at least some types of infections is questionable. Particularly in severe infections or if therapy has failed, microbiological diagnosis is to be attempted with the proof of the pathogen and its sensitivity to clindamycin.

Prevalence of acquired resistance on the basis of data of the past 5 years gained in national resistance monitoring projects and studies in Germany (dated: December 2008):

Commonly susceptible species
Aerobe Gram-positive micro-organisms
Actinomyces israelii°
Staphylococcus aureus (Methicillin susceptible)
Streptococcus agalactiae
Streptococcus pyogenes
Streptococci of the "Viridans"-group ^
Anaerobe micro-organisms
Bacteroides spp. (except B. fragilis)
Clostridium perfringens°
Fusobacterium spp.°
Peptococcus spp °
Peptostreptococcus spp.
Prevotella spp.
Propionibacterium spp. °
Veillonella spp. °
Other micro-organisms
Chlamydia trachomatis
Chlamydophila pneumoniae°
Gardnerella vaginalis°
Mycoplasma hominis
Species for which acquired resistance may be a problem
Aerobe Gram-positive micro-organisms
Staphylococcus aureus
Staphylococcus aureus (Methicillin resistant)+
Staphylococcus epidermidis+
Staphylococcus haemolyticus
Staphylococcus hominis
Streptococcus pneumoniae
Aerobe Gram-negative micro-organisms
Moraxella catarrhalis$
Anaerobe micro-organisms
Bacteroides fragilis
Inherently resistant organisms
Aerobe Gram-positive micro-organisms
Enterococcus spp.
Listeria monocytogenes
Aerobe gram-negative micro-organisms
Escherichi coli
Haemophilus influenza
Klebsiella spp.
Pseudomonas aeruginosa
Anaerobe micro-organisms
Clostridium difficile
Other micro-organisms
Ureaplasma urealyticum
Mycoplasma pneumoniae

° No updated data were available when the tables were published. In primary literature, standard literature and treatment recommendations, susceptibility is assumed.
$ The natural susceptibility of most isolates is in the intermediate range.
+ The rate of resistance is more than 50% in at least one region.
^ Collective name for a heterogeneous group of streptococci species. Rate of resistance can vary depending on the relevant streptococci species.

Pharmacokinetic properties
Absorption
Clindamycin hydrochloride is absorbed quickly when administered orally.

The peak concentration in serum is achieved in 45 to 60 minutes if taken on empty stomach and after two hours if taken at mealtimes, because absorption is delayed slightly by simultaneous intake of food.

The concentration remains above minimum inhibiting concentration (MIC) for most gram-positive organisms for at least six hours when normal recommended doses are used.
The biological half-life of the product is 2.4 hours.
The serum half-life is extended in patients with impaired renal function and moderate to severe hepatic insufficiency.

Distribution
After absorption clindamycin is distributed quickly in body fluids, tissues including bone, but it does not reach the CSF in significant concentrations, even if the meninges are inflamed. It diffuses across the placenta into the foetal circulation and has been reported to appear in breast milk. High concentrations occur in bile. It accumulates in leucocytes and macrophages.
The binding of clindamycin to plasma proteins is concentration-dependent and lies in the therapeutic range between 60% and 94%.
The average volume of distribution is 1.1 L/kg.

Biotransformation
Most of a clindamycin dose undergoes metabolism, and less than 10% of the dose is excreted unchanged in the urine. The known metabolites of clindamycin are N-demethyl clindamycin, clindamycin sulphoxide and N-demethyl clindamycin sulphoxide, which are excreted mainly in the faeces.
Some metabolites have an anti-microbial activity. Agents which act as enzyme inducers in the liver reduce the mean dwell time of clindamycin in the body.

Elimination
Clindamycin is eliminated for 2/3 in the faeces and 1/3 in the urine.

Preclinical safety data
Symptoms of intoxication are decreased activity of the animals and convulsions.

After repeated doses (i.m.) of clindamycin to dogs an increase of the SGOT and SGPT was reported. And also a slight increase of the liver-weight without morphologic changes was documented. Long term administration of clindamycin to dogs induced damages to the gastric mucosa and to the gallbladder.

Mutagenicity and cancerogenicity
In vitro and in vivo studies did not reveal any mutagenic potential of clindamycin. Long-term studies in animals with regard to a tumorigenic potential of clindamycin have not been carried out.

Reproduction toxicity
Studies with clindamycin in rats and mice did neither give a hint on fertility disorders nor embryofoetotoxic properties.

PHARMACEUTICAL PARTICULARS
Incompatibilities
Not Applicable

Storage
Store at temperatures not exceeding 25 °C.

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

ADR REPORTING
For suspected adverse drug reaction, report to the FDA: www.fda.gov.ph
The patient is advised to seek IMMEDIATE medical attention at the first sign of adverse drug reaction.

AVAILABILITY
Alu-white PVC/PVDC blister pack x 10's (box of 30's)

REGISTRATION NUMBER
DRP-3712-02

DATE OF FIRST AUTHORIZATION
November 2019

DATE OF REVISION
December 2019
CDSv05

Manufactured by: **S.C. Sandoz S.R.L.**
Str. Livezeni Nr. 7A, Targu Mures, Jud. Mures, Code 540472, Romania

Under license from: **1A Pharma GmbH**
Keltenring 1+3, 82041 Oberhaching, Germany

Imported by: **Sandoz Philippines Corporation**
5th and 6th Floor Ayala North Exchange Tower 1 (HQ), Ayala Ave. cor. Salcedo and Amorsolo Sts., Brgy. San Lorenzo, Makati City

Distributed by: **Natrapharm, Inc.**
The Patriot Bldg., South Luzon Express Way, Parañaque, Metro Manila

46258400 188

PRINTED PACKAGING MATERIAL SPECIFICATIONS (SPC)			
FILE NAME NATRA_Clinda-NATRA_300mg per 5mL_GOS_PIL		**VERSION** v1.01	**PREPARED & DRAWN BY** Daryll Fadol
DIMENSIONS 160x520 mm	**COLORS USED** Pantone Black C	**MATERIAL NO.** 46258400	**PHARMACODE** 188