SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

CLINDAMYCIN VIANEX

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ampoule 4 ml contains Clindamycin (clindamycin phosphate) 600 mg.

3. PHARMACEUTICAL FORM

Solution for injection 600 mg/4 ml AMP.

4. CLINICAL PARTICULARS

4.1. Therapeutic Indications

Serious infections due to Gram positive cocci (including staphylococci), various anaerobic bacteria, particularly *Bacteroides fragilis* (intra-peritoneal, gynecological infections, e.t.c.), osteomyelitis.
Toxoplasmic, encephalitis in patients with AIDS. In patients who are intolerant to conventional treatment, clindamycin in combination with pyrimethamine has been shown to be efficacious.
Pneumocystis carinii pneumonia in patients with AIDS. In patients who are intolerant to or do not respond to convential treatment, clindamycin can be used in combination with primaquin.
Clindamycin use should be restricted to absolute indications or when other safer antibiotics cannot be used because of severe undesirable effects, particularly pseudomembranous colitis.

4.2. Posology and Method of Administration

Adults:
By intramuscular injection or by slow intravenous infusion: 600 mg to 2400 mg/day given in 2 - 4 equal doses.
Must be diluted with isotonic sodium chloride or dextrose solutions.
Intramuscular administration of more than 600 mg in a single dose is not recommended.

Children: 15 to 40 mg/kg/day given in 3 or 4 equal doses.

TOXOPLASMIC ENCEPHALITIS IN PATIENTS WITH AIDS:
Clindamycin phosphate I.V. 600-1200 mg every 6 hours for two weeks. The usual total duration of therapy is 8 to 10 weeks.
The dose of pyrimethamine is 25-75 mg daily given orally for 8 to 10 weeks.
Folinic acid 10-20 mg daily should be given with higher doses of pyrimethamine.

***Pneumocystis carinii* pneumonia in patients with AIDS:**
Clindamycin phosphate I.V. 600-900 mf every 6 hours or 900 mg I.V. every 8 hours for 21 days and primaquin in a single oral dose 10-30 mg daily for 21 days.

IMPORTANT INFORMATION
No ampoule file s needed to open the ampoules. The neck of the ampoule is pre-scored at the point of constriction.

DILUTION AND INFUSION RATE
The concentration of clindamycin in diluent for infusion should not exceed 18 mg per ml and THE INFUSION RATE SHOULD NOT EXCEED 30 mg PER 1st MINUTE.

The usual infusion rate is as following:

Dose	Diluent	Time
300 mg	50 ml	the first 10 minutes
600 mg	50 ml	the first 20 minutes
900 mg	50-100 ml	the first 30 minutes
1200 mg	100 ml	the first 40 minutes

Administration of more than 1200 mg in a single 1-hour infusion is not recommended.

4.3 Contraindications

Hypersensitivity to clindamycin or lincomycin, diarrheal syndrome, history of colitis or enteritis or antibiotic-associated colitis.

4.4 Special warnings and precautions for use

Caution in administration
Rapid intravenous injection (risk of cardiac arrest) and administration of a single dose more than 600 mg, should be avoided. The intramuscular injection should be performed deeply in the muscles.
It should be used with caution in patients with allergy to medicines and other allergens.

Special warnings
CLINDAMYCIN VIANEX Solution for injection contains benzyl alcohol. Benzyl alcohol has been reported to be associated with a fatal "Gasping Syndrome" in premature infants.
Administration of the sterile solution for injection in neonates is forbidden. Also, it should not be administered during the first two years of life, as it contains benzyl alcohol as preservative.

Treatment with clindamycin has been associated with severe antibiotic-associated colitis which may be fatal.
Colitis has a clinical spectrum from mild to severe, persistent diarrhea, leukocytosis, fever, severe abdominal cramps which may be associated with the passage of blood and mucus, and which, if allowed to progress, may produce peritonitis, shock and toxic megacolon.

The diagnosis of antibiotic-associated colitis is usually made by recognition of the clinical symptoms. Endoscopic examination may reveal pseudomembranous colitis and be confirmed further by stool culture for detection of *Clostridium difficile* in selective substrates and assay of the stool sample for the toxin(s) of *Clostridium ~~difficil.~~*
Antibiotic-associated colitis may occur during the administration or even two or three weeks after the administration of the antibiotic. Antibiotic-associated colitis may be more sever in elderly and/or in debilitated patients. In case of mild antibiotic-associated colitis, discontinuation of the clindamycin is recommended. Treatment with resins, cholestyramin and colestipole is recommended, because these medicines have been proved to bind the toxin in vitro.

The recommended dose for colestipole is 5 g three times daily and for cholestyramin is 4 g three times daily.
Severe cases of antibiotic-associated colitis should be managed with fluids, electrolytes and proteins.
Studies indicate a toxin(s) produced by *Closrtidium difficile* is the primary cause of antibiotic-associated colitis and that toxigenic Clostridium usually sensitive in vitro to vancomycin. When 125 mg to 500 mg of vancomycin is administered orally 4 times a day, there is a rapid observed disappearance of the toxin from fecal samples and a coincidental recovery from the diarrhea.
In rare cases, colitis may relapse after cessation of treatment with vancomycin. Cholestyramin and colestipole resins bind vancomycin in vitro. If both a resin and vancomycin are to be administered concurrently, it may be advisable to separate the time of administration of each drug. As an alternative treatment, oral bacitracin 25.000 units could be given every day for 7 to 10 days.
Medicines which cause intestinal stasis should be avoided.
Clindamycin should be prescribed with caution in patients with a history of gastrointestinal disease, particularly colitis.

Clindamycin should not be used in the treatment of meningitis since the drug does not diffuse adequately into cerebrospinal fluid.
The use of clindamycin phosphate may result in overgrowth of non susceptible organisms, particularly yeasts.
Clindamycin phosphate should not be injected intravenously undiluted as a bolus, but should be infused over at least 10-60 minutes.
In patients with moderate to severe hepatic disease, prolongation of half-life of clindamycin has been found, but a pharmacokinetic study has shown that, when given every 8 hours, accumulation of clindamycin rarely occurs. Therefore, dosage reduction in liver disease is not generally considered necessary.
During prolonged treatment, periodic liver and kidney function tests should be performed.

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

When administered with general anesthetics or neuromuscular blocking agents, respiratory depression or paralysis may occur (managed by administering calcium salts and anticholinesterasics).
Chloramphenicol and erythromycin antagonize clindamycin activity. Adsorbents (kaolin, e.t.c) decrease clindamycin absorption.

4.6 Pregnancy and lactation

Reproduction studies have been performed in rats and mice using subcutaneous doses of clindamycin up to 250 mg/kg/day and oral doses of clindamycin up to 600 mg/kg/day and revealed no evidence of impaired fertility ~~of~~ harm to the fetus due to clindamycin. In one mouse strain, cleft palates were observed in treated fetuses; this response was not produced in other mouse strains or in other species and therefore may be a strain specific effect.
Safety for use in pregnancy has not been established, so, its use in pregnancy should be avoided.
Clindamycin has been reported to appear in breast milk in range of 0,7 to 3,8 μg/ml.
Therefore, special caution should be paid and, as a rule, it is recommended discontinuation of nursing.

4.7. Effects on ability to drive and use machines

None effect.

4.8 Undesirable effects

Vomiting, diarrhea, which impose the immediate discontinuation of treatment, pseudomembranous colitis often life threatening.

- **Gastrointestinal system**

Abdominal pain, nausea, vomiting and diarrhea (see Special warnings)

- Hypersensitivity reactions

Maculopapular rash and urticaria have been observed during drug therapy. Generalized mild to moderate morbilliform-like skin rashes are the most frequently reported reactions. Rare instances of erythema multiform, some resembling Stevens-Johnson syndrome, have been associated with clindamycin. A few cases of anaphylactoid reactions have been reported.

- **Liver**

Jaundice and abnormalities in liver function tests have been observed during clindamycin therapy.

- Renal

Renal dysfunction has rarely been reported (causative relationship of clindamycin to this effect has not been established).

- **Skin and mucous membranes**

Pruritus, vaginitis and rare instances of exfoliative and vesiculobullous dermatitis have been reported.

- **Haemopoietic system**

Transient neutropenia (leucopenia) and eosinophilia have been reported. Rare cases of agranulocytosis and thrombocytopenia have been reported.

- **Cardiovascular**

Rare instances of cardiopulmonary arrest and hypotension have been reported following too rapid intravenous administration.

- **Local reactions**

Local irritation, pain, abscess formation have been observed with intramuscular injection and thrombophlevitis have been reported with intravenous injection. These reactions can be minimized by deep intramuscular injection and avoidance of indwelling intravenous catheter.

- Nervous system

Dysgeusia

4.9 Overdose

In case of overdosage and allergic reaction can be occurred. Treatment is symptomatic. Corticosteroids, adrenaline and antihistaminics should be administered.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Clindamycin, the active ingredient of CLINDAMYCIN VIANEX, is a semi-synthetic antibiotic produced by a 7-(S)-chloro-substitution of the 7-(R)-hydroxyl group of the parent compound lincomycin.
Clindamycin may be either bactreriostatic or bactericidal, depending on the susceptibility of the microorganism and the concentrations of the antiobiotic.
Clindamycin has been shown to have in vitro activity against isolates of the following microorganisms:

1. Aerobic Gram-positive cocci, including:
Staphylococcus aureus
Staphylococcus epidermidis
(penicillinase and non-penicillinase producing strains). When tested in vitro methods some staphylococcal strains, originally resistant to erythromycin, rapidly develop resistance to clindamycin.
Streprococci (except S. faecalis)
~~Pneumonococci~~

2. Anaerobic Gram-negative bacilli, including:
Bacteroides species (including B. fragilis group and B. melaninogenicus ~~gropup)~~
Fusobacterium spp

3. Anaerobic Gram-positive non-spore forming bacilli, including:
Propionibacterium
Eubacterium
Actinomyces spp

4. Anaerobic and microaerophilic Gram-positive cocci, including:
Peptococcus spp

Peptostreptococcus spp
Microaerophilic streptococci
Clostridia: Clostridia are more resistant than most anaerobes to clindamycin. Most of Clostridia perfringens are susceptible, but other species, e.g. C. sporogenes and C. tertium are frequently resistant to clindamycin.
Susceptibility testing should be done.

5. Various microorganisms including:
Chlamidia trachomatis, Toxoplasma gondii, Plasmodium falciparum and Pneumocuystis carinii (in combination with primaquin).

The following microorganisms are generally resistant to clindamycin:
Aerobic Gram-negative bacilli
Streptococcus faecalis
Nocardia spp
Neisseria meningitidis

Staphylococcus aureus strains resistant to methicillin and Haemophilus influenzae (depending on the regions where it is known that resistant prevails).

Cross-resistance has been demonstrated between clindamycin and lincomycin. Antagonism has been demonstrated between clindamycin and erythromycin. Although clindamycin hydrochloride is active so in vivo as in vitro, clindamycin phosphate is inactive in vitro. Nevertheless, rapid in vivo hydrolysis converts this compound to the antibacterially active clindamycin –base.

5.2 Pharmacokinetic properties

- Absorption
After intramuscular injection of 600 mg clindamycin phosphate, peak serum levels of active clindamycin 9 μg/ml are reached within 1-3 hours after administration.

After intravenous infusion of 300 mg over 10 minutes or respectively 600 mg over 20 minutes, peak serum levels of active clindamycin 7 μg/ml and 10 μg/ml respectively are reached by the end of infusion. Table 1 shows the average peak serum levels after dosing with clindamycin phosphate. Serum levels of clindamycin can be maintained above the in vitro minimum inhibitory concentrations for the most susceptible microorganism by administration of clindamycin phosphate every 8-12 hours in adults and every 6-8 hours in children or by continuous intravenous infusion. Steady-state is reached by the third dose.

Table 1

Dose **Adults (in steady-state)**	**Clindamycin** **μg/ml**
300 mg I.V. over 10 minutes every 8 hours	7
600 mg I.V. over 20 minutes every 8 hours	10
900 mg I.V. over 30 minutes every 12 hours	11
1200 mg I.V. over 45 minutes every 12 hours	14

300 mg I.M. every 8 hours	6
600 mg I.M. every 12 hours	9

Dose **Children (first dose)** (1)	**Clindamycin** **µg/ml**
5-7 mg/kg I.V. in 1 hour	10
3-5 mg/kg I.M.	4
5-7 mg/kg I.M.	8
(1) Data in this group from patients being treated for infection.	

- Distribution

From 80% to 90% of the administered dose is bound to plasma proteins, clindamycin penetrates easily into the most body fluids and tissues, crosses via the placenta to fetus and to breast milk. Into osteal tissue it is concentrated about 40% (20-75%) of that of the serum level, in breast milk 50-100%, in articular fluid 50%, in sputum 30-75%, in peritoneal fluid 50%, in fetus blood 40%, in pus 30%, in pleural fluid 50-90%. On the contrary, clindamycin does not penetrate into cerebrospinal fluid, even in case of ~~mengitidis.~~

- Biotransformation

The half –life of clindamycin is about 1,5-3,5 hours. Half-life is increased slightly in patients with markedly reduced renal or hepatic function. Dosage schedule need not to be modified in the presence of mild to moderate renal or hepatic disease. Clindamycin is metabolized relatively hardly.

- Excretion

Approximately 10-20% of the microbiologically active form is excreted in the urine and about 4% in the feces. The remainder is excreted as biologically inactive metabolites. It is excreted mainly in the bile and the feces. Hemodialysis and peritoneal dialysis are not effective in removing clindamycin.

5.3 Preclinical safety data

No long-term carcinogenicity studies in animals have been conducted. Genetoxicity and fertility studies have been conducted and the results were negative (see also 4.6).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Benzyl alcohol, Dosidium edentate, Sodium hydroxide, Water for injections.

6.2 Incompatibilities

The following drugs are physically incompatible with clindamycin phosphate: ampicillin, phenytoin sodium, barbiturates, aminophylline, calcium glyconate and magnesium sulfate.

Clindamycin phosphate has been known to be physically and chemically compatible for at least 24 hours in aqua solution of glucose 5% and sodium chloride 0,9% containing the following antibiotics in usually administered concentrations:amikacin sulfate, aztreonam, cephamandole nafate, cefazolin sodium, cefotaxime sodium, cefoxitin sodium, ceftazidime sodium, ceftizoxime, gentamycin sulfate, metilmicin sulfate, piperacillin and tobramycin.
The compatibility and duration of stability of drug mixtures will vary depending on concentration and other conditions.

6.3 Shelf life

24 months.

6.4 Special precautions for storage

Room temperature

6.5 Nature and contents of container

Carton containing 1 ampoule of 4 ml.

6.6 Special precautions for use and handling

See dosage and method of administration.

7. MARKETING AUTHORIZATION HOLDER
VIANEX S.A. – Tatoiou Str., 146 71 Nea Erythrea, Greece

8. MARKETING AUTHORIZATION NUMBER

9. DATE OF FIRST AUTHORISATION / RENEWAL OF THE AUTHORISATION

10. DATE OF REVISION OF THE TEXT