

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Clindamycin Kalceks 150 mg/ml

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml of solution contains clindamycin phosphate equivalent to 150 mg clindamycin.

Excipient with known effect:

Each ml of solution contains 6.5 mg sodium.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for Injection/Infusion.

Clear, colourless to almost colourless solution, practically free from visible particles.

Sterile solution for intramuscular or intravenous use.

pH of solution 5.5-7.0.

Osmolality 700 to 830 mOsmol/kg.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Clindamycin Kalceks 150 mg/ml (clindamycin phosphate) is indicated for the treatment of infections caused by susceptible anaerobic bacteria.

Clindamycin does not penetrate the blood/brain barrier in therapeutically effective quantities.

4.2 Posology and method of administration

Posology

Parenteral (IM or IV administration). Clindamycin Kalceks (clindamycin phosphate) **must** be diluted prior to IV administration and should be infused over at least 10-60 minutes.

Adults: Serious infections: 600 mg - 1.2 g/day in two, three or four equal doses.

More severe infections: 1.2-2.7 g/day in two, three or four equal doses.

Single IM injections of greater than 600 mg are not recommended nor is administration of more than 1.2 g in a single one-hour infusion.

For more serious infections, these doses may have to be increased. In life-threatening situations, doses as high as 4.8 g daily have been given intravenously to adults.

Alternatively, the drug may be administered in the form of a single rapid infusion of the first dose followed by continuous IV infusion.

Paediatric population

Children (over 1 month of age): Serious infections: 15-25 mg/kg/day in three or four equal

doses.

Clindamycin should be dosed based on total body weight regardless of obesity.

More severe infections: 25-40 mg/kg/day in three or four equal doses. In severe infections it is recommended that children be given no less than 300 mg/day regardless of body weight.

Elderly patients: The half-life, volume of distribution and clearance, and extent of absorption after administration of clindamycin phosphate are not altered by increased age. Analysis of data from clinical studies has not revealed any age-related increase in toxicity. Dosage requirements in elderly patients should not be influenced, therefore, by age alone. See *Precautions* for other factors which should be taken into consideration.

Dosage in renal/hepatic impairment:

Clindamycin dosage modification is not necessary in patients with renal or hepatic insufficiency.

The concentration of clindamycin in diluent for infusion should not exceed 18 mg per ml and INFUSION RATES SHOULD NOT EXCEED 30 MG PER MINUTE. The usual infusion rates are as follows:

<u>Dose</u>	<u>Diluent</u>	<u>Time</u>
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

4.3 Contraindications

Clindamycin Kalceks 150 mg/ml is contra-indicated in patients previously found to be sensitive to clindamycin, lincomycin, any component of the formulation, or to any of the excipients listed in section 6.1.

4.4 Special warnings and special precautions for use

Warnings

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 generalized 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 sections 4.3 and 4.8).

Clindamycin Kalceks 150 mg/ml should only be used in the treatment of serious infections. In considering the use of the product, the practitioner should bear in mind the type of infection and the potential hazard of the diarrhoea which may develop, since cases of colitis have been reported during, or even two or three weeks following, the administration of clindamycin.

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'. The disease is likely to follow a more severe course in older patients or patients who are debilitated. Diagnosis is usually made by the recognition of the clinical symptoms, but can be substantiated by endoscopic demonstration of pseudomembranous colitis. Colitis is a disease, which has a clinical spectrum from mild, watery diarrhoea to severe, persistent diarrhoea, leucocytosis, fever, severe abdominal cramps,

which may be associated with the passage of blood and mucus. If allowed to progress, it may produce peritonitis, shock and toxic megacolon. This may be fatal. The presence of the disease may be further confirmed by culture of the stool for *C. difficile* on selective media and assay of the stool specimen for the toxin(s) of *C. difficile*.

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 section 4.8), 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. When 125 mg to 500 mg of vancomycin are administered orally four times a day for 7 - 10 days, there is a rapid observed disappearance of the toxin from faecal samples and a coincident clinical recovery from the diarrhoea. Drugs inhibiting peristalsis are contraindicated in this situation.

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 diarrhoea following antibiotic use. Careful medical history is necessary since CDAD has been reported to occur over two months after the administration of antibacterial agents.

Excipient information

Clindamycin Kalceks 150 mg/ml contains 6.5 mg sodium per ml of solution, equivalent to 0.33% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

Precautions

Caution should be used when prescribing Clindamycin Kalceks 150 mg/ml to individuals with a history of gastro-intestinal disease, especially colitis.

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

If therapy is prolonged, liver and kidney function tests should be performed. Such monitoring is also recommended in neonates and infants. Safety and appropriate dosage in infants less than one month old have not been established.

Acute kidney injury, including acute renal failure, has been reported infrequently. In patients suffering from pre-existing renal dysfunction or taking concomitant nephrotoxic drugs, monitoring of renal function should be considered (see section 4.8).

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

Prolonged administration of Clindamycin Kalceks 150 mg/ml, as with any anti-infective, may result in super-infection due to organisms resistant to clindamycin.

Care should be observed in the use of Clindamycin Kalceks 150 mg/ml in atopic individuals.

Clindamycin Kalceks 150 mg/ml should not be injected intravenously undiluted as a bolus, but should be infused over at least 10-60 minutes as directed in section 4.2.

4.5 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.

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.

Co-administration of clindamycin with inhibitors of CYP3A4 and CYP3A5

Clindamycin is metabolized 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 metabolized by these CYP enzymes are unlikely.

4.6 Fertility, 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.

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.

Breast-feeding

Orally and parenterally administered clindamycin has been reported to appear in human breast milk in ranges from <0.5 to 3.8 µg/ml. Clindamycin has the potential to cause adverse effects on the breastfed infant's gastrointestinal flora such as diarrhoea or blood in the stool, or rash. If oral or intravenous clindamycin is required by a nursing mother, it is not a reason to discontinue breastfeeding, but an alternate drug may be preferred. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for clindamycin and any potential adverse effects on the breastfed child from clindamycin or from the underlying maternal condition.

Fertility

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

4.7 Effects on ability to drive and use machines

Clindamycin Kalceks 150 mg/ml has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

The table below lists 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 ($\geq 1/10$); Common ($\geq 1/100$ to $< 1/10$); Uncommon ($\geq 1/1,000$ to $< 1/100$); Rare ($\geq 1/10,000$ 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.

System Organ Class	Common $\geq 1/100$ to $< 1/10$	Uncommon $\geq 1/1,000$ to $< 1/100$	Rare $\geq 1/10,000$ to $< 1/1,000$	Very Rare $< 1/10,000$	Not Known (cannot be estimated from available data)
Infections and Infestations	pseudomembranous colitis* [#]				vaginal infection*
Blood and Lymphatic System Disorders					agranulocytosis*, neutropenia*, thrombocytopenia*, leukopenia*, eosinophilia
Immune System Disorders					anaphylactic shock*, anaphylactoid reaction*, anaphylactic reaction*, hypersensitivity*
Nervous System Disorders		dysgeusia			
Cardiac Disorders		cardio-respiratory arrest ^{†§}			
Vascular Disorders	thrombophlebitis [†]	hypotension ^{†§}			
Gastrointestinal Disorders		diarrhoea, nausea			abdominal pain, vomiting, oesophageal ulcers, oesophagitis
Hepatobiliary Disorders					jaundice*
Skin and Subcutaneous Tissue Disorders	rash maculopapular	urticaria erythema multiforme, pruritus			toxic epidermal necrolysis (TEN)*, Stevens-Johnson syndrome (SJS)*, drug reaction with eosinophilia and systemic symptom (DRESS)*, acute generalised exanthematous pustulosis (AGEP)*, dermatitis exfoliative*, dermatitis bullous*, cutaneous vasculitis*, rash morbilliform*, symmetrical drug-related intertriginous

					and flexural exanthema*
Renal and urinary disorders					Acute kidney injury [#]
General Disorders and Administrative Conditions		pain [†] , injection site abscess [†]			injection site irritation ^{†*}
Investigations	liver function test abnormal				

* ADR identified post-marketing.

† ADRs apply only to injectable formulations.

See section 4.4.

§ Rare instances have been reported following too rapid intravenous administration (see section 4.2).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form: <https://sideeffects.health.gov.il/>

4.9 Overdose

In cases of overdosage no specific treatment is indicated.

The serum biological half-life of lincomycin is 2.4 hours. Haemodialysis and peritoneal dialysis are not effective in removing clindamycin from the serum.

If an allergic adverse reaction occurs, therapy should be with the usual emergency treatments, including corticosteroids, adrenaline and antihistamines.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Lincosamide antibiotics, ATC Code J01FF01.

Mode of action

Clindamycin is a lincosamide antibiotic with a primarily bacteriostatic action against gram-positive aerobes and a wide range of anaerobic bacteria. Lincosamides such as clindamycin bind to the 50S subunit of the bacterial ribosome similarly to macrolides such as erythromycin and inhibit protein synthesis. The action of clindamycin is predominantly bacteriostatic although high concentrations may be slowly bactericidal against sensitive strains. Although clindamycin phosphate is inactive *in vitro*, rapid *in vivo* hydrolysis converts this compound to the antibacterially active clindamycin.

Resistance

Resistance to clindamycin usually occurs via macrolide-lincosamide-streptogramin B (MLS_B) type of resistance, which may be constitutive or inducible.

Breakpoints

The minimum inhibitory concentrations (MIC) breakpoints are as follows:
EUCAST

Staphylococci: sensitive ≤ 0.25 resistant > 0.5
Streptococci ABCG and *pneumoniae*: sensitive ≤ 0.5 resistant > 0.5
gram positive anaerobes: sensitive ≤ 4 resistant > 4
gram negative anaerobes: ≤ 4 resistant > 4

PK/PD relationship

Efficacy is related to the ratio of the area of the concentration-time curve of unbound antibiotic to the MIC for the pathogen (fAUC/MIC).

Susceptibility

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 local prevalence of resistance is such that the utility of the agent in at least some types of infections is questionable.

Species

Susceptible

Gram-positive aerobes

*Staphylococcus aureus**
Staphylococcus epidermidis
Streptococcus pneumoniae
Streptococcus pyogenes
Viridans streptococci

Anaerobes

Bacteroides fragilis group
Prevotella formerly known as *Bacteroides melaninogenicus*
Bifidobacterium spp.
Clostridium perfringens
Eubacterium spp.
Fusobacterium spp.
Peptococcus spp.
Peptostreptococcus spp.
Propionibacterium spp.
Veillonella spp.

Resistant

Clostridia spp.
Enterococci
Enterobacteriaceae

*Up to 50% of methicillin-susceptible *S. aureus* have been reported to be resistant to clindamycin in some areas. More than 90% of methicillin-resistant *S. aureus* (MRSA) are resistant to clindamycin and it should not be used while awaiting susceptibility test results if there is any suspicion of MRSA.

Most gram-negative aerobic bacteria, including the Enterobacteriaceae, are resistant to clindamycin. Clindamycin demonstrates cross-resistance with lincomycin. When tested by *in vitro* methods, some staphylococcal strains originally resistant to erythromycin rapidly developed resistance to clindamycin. The mechanisms for resistance are the same as for erythromycin, namely methylation of the ribosomal binding site, chromosomal mutation of the ribosomal protein and in a few staphylococcal isolates enzymic inactivation by a plasmid-mediated adenyltransferase.

5.2 Pharmacokinetic properties

General characteristics of active substance

Following parenteral administration, the biologically inactive clindamycin phosphate is hydrolysed to clindamycin. When the equivalent of 300 mg of clindamycin is injected intramuscularly, a mean peak plasma concentration of 6 microgram/ml is achieved within three hours; 600 mg gives a peak concentration of 9 microgram/ml. In children, peak concentration may be reached within one hour. When the same doses are infused intravenously, peak concentrations of 7 and 10 micrograms per ml respectively are achieved by the end of infusion.

Clindamycin is widely distributed in body fluids and tissues including bone, but it does not reach the cerebrospinal fluid in significant concentrations. It diffuses across the placenta into the foetal circulation and appears in breast milk. High concentrations occur in bile. It accumulates in leucocytes and macrophages. Over 90% of clindamycin in the circulation is bound to plasma proteins. In vitro studies in human liver and intestinal microsomes indicated that clindamycin is predominantly oxidized by CYP3A4, with minor contribution from CYP3A5, to form clindamycin sulfoxide and a minor metabolite, N-desmethylclindamycin. The half-life is 2 to 3 hours, although this may be prolonged in pre-term neonates and patients with severe renal impairment.

Clindamycin undergoes metabolism, to the active *N*-demethyl and sulfoxide metabolites and also some inactive metabolites. About 10% of the drug is excreted in the urine as active drug or metabolites and about 4% in the faeces; the remainder is excreted as inactive metabolites. Excretion is slow and takes place over several days. It is not effectively removed from the blood by dialysis.

Characteristics in patients

No special characteristics. See section 4.4 for further information.

Obese paediatric patients aged 2 to less than 18 years and obese adults aged 18 to 20 years

An analysis of pharmacokinetic data in obese paediatric patients aged 2 to less than 18 years and obese adults aged 18 to 20 years demonstrated that clindamycin clearance and volume of distribution normalized by total body weight are comparable regardless of obesity.

5.3 Preclinical safety data

Impairment of fertility

Fertility studies in rats treated orally with up to 300 mg/kg/day (2-fold the human exposure based on mg/m²) revealed no effects on fertility or mating ability.

Pregnancy

In oral embryo-foetal development studies in rats and subcutaneous embryo-foetal development studies in rats and rabbits, embryo-foetal toxicity was observed at doses that produced maternal toxicity. In rats, maternal death occurred with an exposure ratio of approximately 1 relative to patient exposure. In rabbits, maternal toxicity, including abortions, occurred at exposure ratio of approximately 0.1. Embryo-foetal toxicity, including post-implantation loss and decreased viability, occurred in rabbits at an exposure ratio of 0.2.

Carcinogenesis

Long term studies in animals have not been performed with clindamycin to evaluate carcinogenic potential.

Mutagenesis

Genotoxicity tests performed included a rat micronucleus test and an Ames test. Both tests were negative.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium hydroxide
Disodium edetate
Water for injections

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

Solutions of clindamycin salts have a low pH and incompatibilities may reasonably be expected with alkaline preparations or drugs unstable at low pH. Incompatibility has been reported with: ampicillin sodium, aminophylline, barbiturates, calcium gluconate, ceftriaxone sodium, ciprofloxacin, diphenylhydantoin, idarubicin hydrochloride, magnesium sulfate, phenytoin sodium and ranitidine hydrochloride.

6.3 Shelf-life

The expiry date of the product is indicated on the packaging materials.

Shelf life after opening the ampoule: the product should be used immediately.

Shelf life after dilution

Chemical and physical in use stability has been demonstrated for 48 hours at 25 °C and 2-8 °C.

From a microbiological point of view, the product should be used immediately. If not used immediately, in use storage times and conditions prior to use are the responsibility of the user and would not normally be longer than 24 hours at 2-8 °C, unless dilution has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

Do not store above 25 °C. Do not refrigerate or freeze. Keep the ampoules in the outer carton in order to protect from light.

For storage conditions after first opening and dilution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

2 ml or 4 ml of solution filled in colourless glass ampoules with one point cut.
Each pack contains 10 ampoules.
Not all package sizes may be marketed.

6.6 Special precautions for disposal and other handling

For single use only. Discard any unused portion.

The medicinal product should be visually inspected prior to use. Do not use if there are any visible signs of deterioration (e.g. particles). Only clear solutions free from visible particles should be used.

May be diluted with:

- 9 mg/ml (0.9%) sodium chloride solution for infusion;
- 50 mg/ml (5%) glucose solution for infusion.

The concentration of clindamycin in the diluent should not exceed 18 mg/ml. See section 4.2

for further recommendations on dilution of the product before administration.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. LICENSE HOLDER AND MANUFACTURER

License holder:

A.L. Medi-Market Ltd., 3 Hakatif street, Emek Hefer Industrial Park, 3877701, Israel

Manufacturer:

AS Kalceks, Krustpils iela 71E, Riga, LV-1057, Latvia

8. REGISTRATION NUMBER

179-48-37689-99

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