

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Clindamycin 150 mg/ml Solution for Injection or Infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

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

Each 2ml ampoule contains 300mg clindamycin

Each 4ml ampoule contains 600mg clindamycin

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for Injection or Infusion

Clindamycin 150 mg/ml Solution for injection or Infusion is a clear colourless solution in a clear ampoule.

pH=5.5 – 7.0

osmolality= 760 – 900 mosm/Kg

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Clindamycin is indicated for the treatment of following (see section 4.4 and 5.1)

Severe infections caused by anaerobic bacteria including:

- Intra-abdominal infections
- Skin and soft tissue infections
- Infections of the lower respiratory tract such as aspiration pneumonitis
- Pelvic inflammatory disease

As needed clindamycin should be administered in conjunction with another antibacterial agent that is active against gram negative aerobic bacteria

Consideration should be given to official guidance on the appropriate use of antibacterial agents.

4.2 Posology and method of administration

Parenteral (IM or IV administration). Clindamycin 150 mg/ml solution for injection or infusion must be diluted prior to IV administration and should be infused over at least 10- 60 minutes.

Adults

- Serious infections: 600mg to 1.2g/ day in two, three, or four divided doses
More severe infections: 1200 to 2700 mg clindamycin in 2-4 equal doses.

In life-threatening infections doses up to 4800 mg/day have been given.

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

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

Children

Children (over 1 month of age up to 12 years):

Serious infections: 15 – 25 mg/kg/day in 3 or 4 equal doses.

More severe infections: 25 – 40 mg/kg/day in 3 or 4 equal doses. In severe infections it is recommended that children be given no less than 300 mg/day regardless of body weight.

Elderly patients

Pharmacokinetic studies with Clindamycin have shown no clinically important differences between young and elderly subjects with normal hepatic function and normal (age-adjusted) renal function after oral or intravenous administration. Therefore, dosage adjustments are not necessary in the elderly with normal hepatic function and normal (age-adjusted) renal function (see Section 5.2 Pharmacokinetic Properties).

Dosage in presence of liver diseases

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

Dosage in presence of kidney diseases

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

Treatment for infections caused by beta-haemolytic streptococci should be continued for at least 10 days to guard against subsequent rheumatic fever or glomerulonephritis.

Clindamycin **must** be diluted prior to IV administration (not exceeding 18 mg clindamycin per ml) and should be infused over at least 10 – 40 minutes (nor exceeding 30 mg/min). It can never be injected as an IV bolus. The usual infusion rates are the follows:

<u>Dose</u>	<u>Diluent</u>	<u>Minimum infusion-time</u>
300 mg	50 ml	10 minutes
600 mg	50 ml	20 minutes
900 mg	100 ml	30 minutes
1200 mg	100 ml	40 minutes

Clindamycin may be diluted with 0.9% sodium chloride solution, 5% glucose solution or Ringer’s lactate. Intramuscular administration is indicated when intravenous infusion is not possible for any reasons.

4.3 Contraindications

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

4.4 Special warnings and precautions for use

Clindamycin should only be used in the treatment of serious infections. In considering the use of clindamycin, 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.

Studies indicate a toxin(s) produced by clostridia (especially *Clostridium difficile*) is the principal direct cause of antibiotic-associated 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 product peritonitis, shock and toxic megacolon. This may be fatal. The appearance of marked diarrhoea should be regarded as an indication that the product should be discontinued immediately. The disease is likely to follow a more severe course in older patients or patients who are debilitated. Diagnosis is usually made by recognition of the clinical symptoms, but can be substantiated by endoscopic demonstration of pseudomembranous colitis. The presence of the disease may be further confirmed by culture of the stool for *Clostridia difficile* on selective media and assay of the stool specimen for the toxin(s) of *C. Difficile*.

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*. [134-147]

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. [134-147]

Safety and appropriate dosage in infants less than one month old have not been established.

Prolonged administration of, as with any anti-infective, may result in super-infection due to organisms resistant to Clindamycin 150mg/ml solution for injection. The use of Clindamycin 150mg/ml solution for injection may also result in the overgrowth of non-susceptible organisms particularly yeasts.

The drug should be used with caution in patients with the atopic syndrome, particularly with asthma.

Since Clindamycin 150mg/ml solution for injection does not diffuse adequately into cerebrospinal fluid, the drug should not be used in the treatment of meningitis.

Precautions

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

Regular monitoring of liver function, renal function and haematology should be carried out during prolonged use of the drug, and in infants under the age of one year. Safety and appropriate dosage in infants less than one month old have not been established.

Prolonged administration of Clindamycin 150mg/ml Solution for Injection and Infusion, 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 150mg/ml Solution for Injection and Infusion in atopic individuals. Antibiotics can reduce the efficacy of the combined oral contraceptive pill. Additional contraceptive precautions should be taken during treatment and for up to seven days after stopping treatment.

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

4.5 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. It should be used with caution, therefore, in patients receiving such agents.

Antagonism has been demonstrated between clindamycin and erythromycin *in vitro*. Because of possible clinical significance, the two drugs should not be administered concurrently.

Cross-resistance can be demonstrate with lincomycin and particularly in the case of staphylococci, with erythromycin

The reliability of the contraceptive effect of oral contraceptives applied concomitantly with clindamycin is subject to

question. Hence, during clindamycin therapy, other, non hormonal contraceptive measures should be taken in addition.

4.6 Fertility, pregnancy and lactation

Pregnancy:

Safety for use in pregnancy has not been established.

Caution should be exercised when prescribing to pregnant women.

Lactation:

Clindamycin is distributed into human breast milk. Therefore the possibility of sensitisation, diarrhoea and yeast colonisation of the mucous membranes cannot be excluded. When applied during lactation the benefits and risks must be carefully weighed against each other.

Fertility:

Animal studies do not indicate reproductive toxicity (see section 5.3).

4.7 Effects on ability to drive and use machines

Side effects like dizziness, sleepiness and headaches can constrict the ability to drive and use machines.

In isolated cases side effects (e.g. anaphylactic shock) have been observed (see section 4.8) which render patients incapable of participating actively in road traffic or operating machines and working without suitable precautions owing to unsteadiness.

4.8 Undesirable effects

Side effects are described according to the estimate of frequency they may occur. For this purpose, the following categories of frequency and designation were used:

Very common: affecting more than 1 user in 10

Common: affecting 1 to 10 users in 100

Uncommon: affecting 1 to 10 users in 1.000

Rare: affecting 1 to 10 users in 10.000

Very rare: affecting less than 1 user in 10.000

Not known: the frequency cannot be estimated from the available data

Very common

Gastrointestinal disorders: gastrointestinal disturbances occur in the form of nausea, vomiting, stomach pains or diarrhoea, which are usually slight and often subside during or otherwise after discontinuing therapy. These adverse reactions are dependent on the mode of application and the dosage. Also possible are oesophagitis and inflammation of the oral mucosa.

Common

Hepatobiliary disorders: mild, transient increase of the serum transaminases.

General disorders and administration site conditions: intramuscular injection may be followed by local irritations, pain, indurations and sterile abscess at the injection site.

Uncommon

Blood and lymphatic system disorders: reversible effects on the haemogram, which may be of an allergic and toxic nature and be expressed in the form of trombocytopenia, leucopenia, eosinophilia, neutropenia and granulocytopenia.

Nervous system disorders: neuromuscular-blocking effect.

Gastrointestinal disorders: pseudomembranous enterocolitis may develop during or after treatment with clindamycin (see section 4.4).

Skin and subcutaneous tissue disorders: allergies in the form of morbilliform exanthema as well as pruritus and urticaria.

General disorders and administration site conditions: pain and thrombophlebitis following intravenous application. Following rapid intravenous injections hypersensitive reactions may occur in the form of flushing or feeling of nausea.

Rare

Cardiovascular disorders: instances of cardiopulmonary arrest and hypotension have been reported following too rapid intravenous administration. (Clindamycin must therefore not be administered by intravenous injections but only by infusion of the diluted solution.)

Skin and subcutaneous tissue disorders: itching, colpitis as well as desquamatus and bullous cutaneous inflammation.

General disorders and administration site conditions: swellings (Quincke's oedema and articular swelling), drug fever as well as erythema exudativum multiforme (e.g., Stevens-Johnson syndrome) and toxic epidermal necrolysis (Lyell's syndrome).

Very rare

Hepatobiliary disorders: transient hepatitis with cholestatic jaundice.

Musculoskeletal and connective tissue disorders: polyarthritis may be observed very rarely.

General disorders and administration site conditions: severe acute allergic reactions such as anaphylactic shock. In some cases, these reactions occur even after the first application. In this event, treatment, with clindamycin must be discontinued immediately and the standard appropriate emergency measures should be implemented (see section 4.4)

Unknown (there are no data available relating to the frequency of these side effects):

Taste and smell perversion, headaches, sleepiness, dizziness.

4.9 Overdose

In cases of overdosage no specific treatment is indicated.

The serum biological half-life of Clindamycin is 2.4 hours. Clindamycin cannot readily be removed from the blood by dialysis or peritoneal dialysis.

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: Lincosamides

ATC code: J01FF01

Mode of action

Clindamycin binds to the 50S subunit of the bacterial ribosome and inhibits protein synthesis. Clindamycin has a predominately bacteriostatic action.

Pharmacokinetic/pharmacodynamic relationship

The efficacy is basically dependent on the time period, in which the agent level is above the minimum inhibitory concentration (MIC) of the pathogen.

Mechanism(s) of resistance

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

Breakpoints

Following minimum inhibitory concentrations for susceptible and resistant germs were defined:

EUCAST

Breakpoints

Pathogen	Susceptible	Resistant
<i>Staphylococcus</i>	≤ 0.25mg/l	> 0.5 mg/l
<i>Streptococcus A,B,C,G</i>	≤ 0.5mg/l	> 0.5 mg/l
<i>S.pneumoniae</i>	≤ 0.5mg/l	> 0.5 mg/l
Gram-negative anaerobes	≤ 4 mg/l	> 4 mg/l
Gram-positive anaerobes	≤ 4mg/l	> 4 mg/l

Prevalence of acquired resistance

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

Common susceptible species
<i>Aerobic gram-positive micro-organisms</i>
<i>Actinomyces israelii</i> °
<i>Staphylococcus aureus</i> (Methicillin-sensitive)
<i>Streptococcus agalactiae</i>
<i>Streptococci of viridians</i> - group^
<i>Anaerobic micro-organisms</i>
<i>Bacteroides</i> spp, ° (excl. <i>B. Fragilis</i>)
<i>Fusobacterium</i> spp.°
<i>Peptococcus</i> spp.°
<i>Prevotella</i> ssp.
<i>Veillonella</i> spp.°
<i>Other micro-organisms</i>
<i>Chlamydia trachomatis</i> °
<i>Chlamydphila pneumoniae</i> °
<i>Gardnerella vaginalis</i> °
<i>Mycoplasma hominis</i> °

Species for which acquired resistance may be a problem
<i>Aerobic gram-positive micro-organism</i>
<i>Staphylococcus aureus</i>
<i>Staphylococcus aureus</i> (Methicillin-resistant)
<i>Staphylococcus epidermidis</i> +
<i>Staphylococcus haemolyticus</i>
<i>Staphylococcus hominis</i>
<i>Streptoccus pneumonia</i>
<i>Aerobic gram-negative micro-organisms</i>
<i>Moraxella catarrhalis</i> \$

Anaerobic micro-organisms
<i>Bacteroides fragilis</i>
<i>Clostridium perfringens</i>
<i>Peptostreptococcus</i> spp.
<i>Propionibacterium</i> spp.

Inherently resistant organisms
Aerobic gram-positive micro-organisms
<i>Enterococcus</i> spp.
<i>Listeria monocytogenes</i>
Aerobic gram-negative micro-organisms
<i>Esterococcus</i> spp.
<i>Listeria monocytogenes</i>
Aerobic gram-negative micro-organisms
<i>Escherichia coli</i>
<i>Haemophilus influenza</i>
<i>Klebsiella</i> spp.
<i>Neisseria gonorrhoeae</i>
<i>Neisseria meningitides</i>
<i>Pseudomonas aeruginosa</i>
Anaerobic micro-organisms
<i>Clostridium difficile</i>
Other micro-organisms
<i>Mycoplasma pneumonia</i>
<i>Ureaplasma urealyticum</i>

° No updated data were available at release of tables. Primary literature, scientific standard literature and therapeutic recommendations assume susceptibility.
\$ Inherent susceptibility of most of the isolates shows intermediate resistance.
+ At least on region shows resistance rates higher than 50%.
^Collective name for a heterogeneous group of streptococci species. Resistance rate may vary according to the streptococci species present.

5.2 Pharmacokinetic properties

Absorption

Clindamycin phosphate is a water soluble ester for parenteral application. After intramuscular injection of 300 mg, peak serum levels after 3 hours are approximately 6 µg/ml, following intravenous application of 300 mg of the mean serum concentrations after one hour are approximately 4 to 6 µg/ml.

Distribution

The degree of binding of clindamycin to plasma proteins is concentration-dependent and lies within the therapeutic range of between 40 and 94 %.

Clindamycin readily distributes into the tissues, passes through the placental barrier and distributes into breast milk. Even if the meninges are inflamed, diffusion into the subarachnoid space is inadequate. High concentrations are achieved in bone tissue, synovial fluid, pleural fluid, expectorations and pus. The following concurrent serum concentrations of the drug are reported: in bone tissue 40% (20-75%), in synovial fluid 50%, in peritoneal fluid 50%, in pleural fluid 50-90%, in expectorations 30-75% and in pus 30%.

Metabolism

Clindamycin is metabolised primarily in the liver. The serum half-life of clindamycin is approximately 3 hours in adults and approximately 2 hours in children. In the presence of renal insufficiency and moderate to severe hepatic insufficiency, the half-life is prolonged.

Some metabolites are microbiologically active (N-demethyl and sulfoxide). Medicinal products that act as enzyme inducers in the liver shorten the mean retention time of clindamycin in the body.

Elimination

Clindamycin is eliminated via the faeces at 2/3 and via the urine at 1/3 of the dose. Less than 10% of the dose is excreted unchanged in the urine.

Clindamycin cannot be dialysed.

5.3 Preclinical safety data

Preclinical data reveal no special hazard for humans based on studies of repeat dose toxicity, reproductive toxicity or genotoxicity. Carcinogenicity studies have not been conducted.

In dogs, repeated high oral doses produced ulceration of the mucosa of the stomach and gall bladder

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Edetate disodium

Sodium hydroxide (for pH adjustment)

Water for injection

6.2 Incompatibilities

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

The following drugs are physically incompatible with clindamycin: ampicillin, phenytoin sodium, barbiturates, aminophylline, calcium gluconate, ciprofloxacin, magnesium sulphate, ceftriaxone sodium, diphenylhydantoin, idarubicin hydrochloride. Solutions of clindamycin salts have a low pH and incompatibility may reasonably be expected with alkaline preparations or with drugs unstable at low pH.

6.3 Shelf life

1 year.

After dilution:

Chemical and physical in-use stability has been demonstrated for 48 hours at 25°C with 0.9% sodium chloride solution, 5% glucose solution or Ringer's lactate solutions.

From a microbiologic point of view, once diluted, the product should be used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not 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

Store below 25°C

Store in the original package in order to protect from light

Do not refrigerate or freeze

For storage conditions of the reconstituted and diluted medicinal product, see section 6.3.

6.5 Nature and contents of container

Type I, clear glass ampoules

Pack sizes

2ml: carton box with 5 ampoules

4ml: carton box with 5 ampoules

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Clindamycin has shown to be compatible with 0.9% sodium chloride solution, 5% glucose solution or Ringer's lactate solutions

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

7 MARKETING AUTHORISATION HOLDER

Fannin (UK) Limited
DCC Vital, Westminster Industrial Estate
Repton Road
Measham
DE12 7DT
United Kingdom

8 MARKETING AUTHORISATION NUMBER

PA1585/001/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of First Authorisation: 5th December 2011

10 DATE OF REVISION OF THE TEXT

May 2017