Approved Professional Information for Clindamycin 600 mg/4 ml Fresenius

SCHEDULING STATUS S4

1. NAME OF THE MEDICINE

CLINDAMYCIN 600 mg/4 ml FRESENIUS solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 4 ml CLINDAMYCIN 600 mg/4 ml FRESENIUS contains 600 mg clindamycin (as clindamycin phosphate).

Excipients with known effect

Benzyl alcohol 0,036 ml per 4 ml (see sections 4.3 and 4.4).

Sodium 0,27 mg per 4 ml (prior to dilution).

For the full list of excipients, see section 6.1.

Sugar free.

3. PHARMACEUTICAL FORM

Solution for injection.

A clear colourless to faint yellow solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Bacteriological studies to determine the causative organism should be performed and its susceptibility to CLINDAMYCIN 600 mg/4 ml FRESENIUS tested. It is indicated in the treatment of infections caused by susceptible strains of:

Staphylococcus aureus: abscesses, bacteraemia, endocarditis, pneumonia and osteomyelitis, but not in meningitis or in methicillin-resistant organisms.

Streptococcus (anaerobic species): bacteraemia, endocarditis, abscesses and upper respiratory infections (sinusitis).

Streptococcus pneumoniae: pneumonia, arthritis and upper respiratory infections.

Clostridium perfringens: gas gangrene.

Campylobacter jejuni: enteritis.

Bacteroides species: oral disease, upper respiratory tract infections and lung abscess.

Fusobacterium nucleatum: ulcerative pharyngitis, lung abscess, empyema, genital infections, gingivitis.

4.2 Posology and method of administration

Posology

Intramuscular injection:

Adults:

Moderate to severe infections: 600 – 1 200 mg/day in 2, 3 or 4 equally divided doses.

Severe infections: 1 200 – 2 700 mg/day in 2, 3 or 4 equal doses.

Paediatric population

Children:

Over the age of 1 month: 15 – 40 mg/kg body mass daily in divided doses.

Severe infections: Not less than 300 mg daily (irrespective of body mass).

Neonates:

Safety and appropriate dosages in infants less than one month old have not been established (see section 4.3).

Intravenous infusion:

CLINDAMYCIN 600 mg/4 ml FRESENIUS may be administered in the form of a single rapid infusion of the initial dose followed by continuous IV infusion. This will maintain the serum levels of clindamycin at the following levels:

Serum clindamycin level	**Rapid infusion rate**	**Maintenance infusion rate**
above 4 µg/ml	10 mg/min for 30 min	0,75 mg/min
above 5 µg/ml	15 mg/min for 30 min	1,00 mg/min
above 6 µg/ml	20 mg/min for 30 min	1,25 mg/min

In the treatment of beta-haemolytic streptococcal infections, a therapeutic dose must be administered for at least 10 days to diminish the likelihood of subsequent severe complications such as rheumatic fever or glomerulonephritis.

Method of administration

IM or IV infusion.

Infusion rates are as follows:

Dose	Diluent	Time
300 mg	50 ml	10 min
600 mg	100 ml	20 min
900 mg	150 ml	30 min
1 200 mg	200 ml	45 min

Administration of more than 1 200 mg in a single 1-hour infusion is not recommended.

CLINDAMYCIN 600 mg/4 ml FRESENIUS should not be injected intravenously as an undiluted bolus, but should rather be infused over at least 20 to 60 minutes.

Since intramuscular injections of greater than 600 mg are not recommended, CLINDAMYCIN 600 mg/4 ml FRESENIUS must be diluted prior to intravenous administration to a dilution of 300 mg in 50 ml of diluent (6 mg/ml) or more.

Suitable diluents may contain: sodium chloride, dextrose.

4.3 Contraindications

- Hypersensitivity to clindamycin, lincomycin, doxorubicin or to any of the excipients of CLINDAMYCIN 600 mg/4 ml FRESENIUS, listed in section 6.1.

- Patients with diarrhoeal states or gastrointestinal disease, particularly those with a history of colitis.
- Treatment of meningitis. No significant levels of CLINDAMYCIN 600 mg/4 ml FRESENIUS are attained in the cerebrospinal fluid, even in the presence of inflamed meninges.
- CLINDAMYCIN 600 mg/4 ml FRESENIUS must not be given to premature babies or neonates because of the benzyl alcohol content (see sections 4.4 and 4.6).

4.4 Special warnings and precautions for use

Benzyl alcohol may cause fatal "gasping syndrome" in neonates.

CLINDAMYCIN 600 mg/4 ml FRESENIUS contains benzyl alcohol (0,036 ml/4 ml). Intravenous administration of the preservative benzyl alcohol has been associated with serious adverse events and death in paediatric patients, including neonates, characterised by central nervous system depression, metabolic acidosis, gasping respirations, cardiovascular failure and haematological anomalies ("gasping syndrome"). Although normal therapeutic doses of CLINDAMYCIN 600 mg/4 ml FRESENIUS ordinarily deliver amounts of benzyl alcohol that are substantially lower than those reported in association with the "gasping syndrome", the minimum amount of benzyl alcohol at which toxicity may occur is not known. Use only if there are no alternatives available. If given in high volumes, CLINDAMYCIN 600 mg/4 ml FRESENIUS should be used with caution and preferably for short-term treatment in patients with liver or kidney impairment, because of the risk of accumulation and toxicity (metabolic acidosis) due to benzoic acid (a metabolite of benzyl alcohol).

Premature and low birth mass infants may be more likely to develop toxicity.

Benzyl alcohol-containing products should not be used in preterm or full term neonates.

Benzyl alcohol can cross the placenta (see section 4.6).

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 600 mg/4 ml FRESENIUS should be discontinued and appropriate therapy should be initiated (see sections 4.3 and 4.8).

Antibiotic-associated diarrhoea (AAD) and *Clostridium difficile*-associated diarrhoea (CDAD):

CLINDAMYCIN 600 mg/4 ml FRESENIUS should be used with caution in patients with gastrointestinal disease, particularly those with a history of colitis.

CLINDAMYCIN 600 mg/4 ml FRESENIUS therapy has been associated with severe colitis which may end fatally. Toxin(s) produced by Clostridia (especially *Clostridium difficile*) is the principal direct cause of antibiotic-associated colitis.

CLINDAMYCIN 600 mg/4 ml FRESENIUS should be reserved for serious infections where less toxic antimicrobial medicines are inappropriate. In considering the use of the CLINDAMYCIN 600 mg/4 ml FRESENIUS, the health care provider 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 600 mg/4 ml FRESENIUS.

Treatment with antibacterial medicines alters the normal flora of the colon leading to overgrowth of *Clostridium difficile*. This has been reported with use of nearly all antibacterial medicines, 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, and severe abdominal cramps, which may be associated with the passage of blood and mucus. When significant diarrhoea occurs, the medicine should be discontinued. If allowed to progress, it may produce peritonitis, shock and toxic megacolon. The presence of the disease may be further confirmed by culture of the stool for *Clostridium 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 medicines. 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 medicines, including CLINDAMYCIN 600 mg/4 ml FRESENIUS, 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. Medicines 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 diarrhoea, CDAD and pseudomembranous colitis have been observed commencing up to several weeks following cessation of therapy with CLINDAMYCIN 600 mg/4 ml FRESENIUS.

Fluid, electrolyte and protein supplementation and use of an antibacterial medicine against *Clostridium* spp. should be considered for severe antibiotic-associated colitis.

Since clindamycin does not diffuse adequately into cerebrospinal fluid, CLINDAMYCIN 600 mg/4 ml FRESENIUS should not be used in the treatment of meningitis.

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

Superinfection

Prolonged administration of CLINDAMYCIN 600 mg/4 ml FRESENIUS may result in superinfection due to organisms resistant to clindamycin. The use of CLINDAMYCIN 600

mg/4 ml FRESENIUS may result in the overgrowth of non-susceptible organisms, particularly yeasts.

Reduced efficacy of oral contraceptives

Antibiotics, including CLINDAMYCIN 600 mg/4 ml FRESENIUS, 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.

Special populations

Infants

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

When used in infants of less than 1 month in age, appropriate monitoring of organ system functions is desirable.

Atopic patients

Care should be observed in the use CLINDAMYCIN 600 mg/4 ml FRESENIUS in atopic individuals, particularly those with asthma.

Patients with renal and hepatic disorders

Patients with renal and/or hepatic disease should be treated with caution. Periodic liver and kidney function and haematology tests should be carried out during prolonged therapy.

Patients with porphyria

CLINDAMYCIN 600 mg/4 ml FRESENIUS is possibly porphyrinogenic.

Sodium content

CLINDAMYCIN 600 mg/4 ml FRESENIUS contains less than 1 mmol sodium (23 mg) per 4 ml, that is to say essentially sodium free.

4.5 Interaction with other medicines and other forms of interaction

CLINDAMYCIN 600 mg/4 ml FRESENIUS has neuromuscular blocking activity in high doses and may enhance the effect of other medicines with this action, with a potential danger of respiratory depression. Therefore, CLINDAMYCIN 600 mg/4 ml FRESENIUS should be used with caution in patients receiving such medicines.

CLINDAMYCIN 600 mg/4 ml FRESENIUS may antagonise the activity of parasympathomimetics.

Antagonism has been demonstrated between clindamycin and erythromycin *in vitro*. Because of possible clinical significance, CLINDAMYCIN 600 mg/4 ml FRESENIUS and erythromycin should not be administered concurrently.

Increased coagulation tests, Prothrombin Time and International Normalized Ratio (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 metabolised predominantly by CYP3A4, and to a lesser extent by CYP3A5, to the major metabolite clindamycin sulphoxide and minor metabolite *N*-desmethylclindamycin. Therefore, inhibitors of CYP3A4 and CYP3A5 may reduce CLINDAMYCIN 600 mg/4 ml FRESENIUS clearance and inducers of these isoenzymes may increase CLINDAMYCIN 600 mg/4 ml FRESENIUS 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 600 mg/4 ml FRESENIUS and co-administered medicines metabolised by these CYP enzymes are unlikely.

4.6 Fertility, pregnancy and lactation

Pregnancy

The safety for use of CLINDAMYCIN 600 mg/4 ml FRESENIUS in pregnancy has not been established.

CLINDAMYCIN 600 mg/4 ml FRESENIUS crosses the placenta in humans. After multiple doses, amniotic fluid concentrations were approximately 30 % of maternal blood concentrations.

Benzyl alcohol can cross the placenta (see section 4.4).

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.

Breastfeeding

CLINDAMYCIN 600 mg/4 ml FRESENIUS is distributed into breast milk and it should be used with caution during breastfeeding.

CLINDAMYCIN 600 mg/4 ml FRESENIUS appears in human breast milk in ranges from < 0,5 to 3,8 µg/ml.

CLINDAMYCIN 600 mg/4 ml FRESENIUS 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 CLINDAMYCIN 600 mg/4 ml FRESENIUS is required by a nursing mother, it is not a reason to discontinue breastfeeding, but an alternate medicine may be preferred. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for CLINDAMYCIN 600 mg/4 ml FRESENIUS and any potential adverse effects on the breastfed child from CLINDAMYCIN 600 mg/4 ml FRESENIUS or from the underlying maternal condition.

4.7 Effects on ability to drive and use machines

No or negligible influence.

4.8 Undesirable effects

Infections and infestations:

Frequent: Pseudomembranous colitis, *clostridium difficile* colitis (see section 4.4).

Frequency unknown: Vaginal infection.

Blood and lymphatic system disorders:

*Frequency unknow*n*:* Leucopenia, eosinophilia and polyarthritis, agranulocytosis, neutropenia, thrombocytopenia.

Immune system disorders:

Frequent: Hypersensitivity reactions including skin rashes.

Frequency unknown: Anaphylactic shock, anaphylactoid reaction, anaphylactic reaction, hypersensitivity reactions: urticaria, unpleasant or metallic taste after high intravenous doses.

Nervous system disorders:

Less frequent: Dysgeusia.

Cardiac disorders:

Less frequent: Cardiopulmonary arrest following too rapid intravenous administration.

Vascular disorders:

Frequent: Thrombophlebitis with IV injection.

Less frequent: Hypotension following too rapid intravenous administration.

Respiratory, thoracic and mediastinal disorders:

Frequency unknown: Benzyl alcohol may cause fatal “gasping syndrome” in neonates.

Gastrointestinal disorders:

Less frequent: Diarrhoea, nausea which can be severe and persistent.

Frequency unknown: Vomiting, abdominal cramps, oesophageal ulcers, oesophagitis.

Hepato-biliary disorders:

Frequent: Abnormalities of liver function tests.

Frequency unknown: Jaundice, hepatic damage.

Skin and subcutaneous tissue disorders:

Frequent:	Generalised mild to moderate morbilliform-like skin rashes, maculopapular rash.
Less frequent:	Urticaria, erythema multiforme, pruritus, exfoliative and vesiculobullous dermatitis.
Frequency unknown:	Serious cutaneous adverse reaction (SCAR), toxic epidermal necrolysis (TEN), Stevens-Johnson syndrome (SJS), drug reaction with eosinophilia and systemic symptom (DRESS), acute generalised exanthematous pustulosis (AGEP), exfoliative dermatitis, bullous dermatitis.

Renal and urinary disorders:

Less frequent:	Uraemia, oliguria and/or proteinuria.
Frequency unknown:	Acute kidney injury (see section 4.4).

General disorders and administration site conditions:

Less frequent:	Pain; injection site abscess with IM injection.
Frequency unknown:	Injection site irritation.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of CLINDAMYCIN 600 mg/4 ml FRESENIUS is important. It allows continued monitoring of the benefit/risk balance of CLINDAMYCIN 600 mg/4 ml FRESENIUS. Health care providers are asked to report any

suspected adverse reactions via the **"6.04 Adverse Drug Reaction Reporting Form"**, found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8.

Health care providers are asked to report any suspected Adverse Drug Reactions to the Holder of the Certificate of Registration at the following email address: safety.fksa@fresenius-kabi.com, and to the relevant medicine's regulatory authority in the country where the product is marketed.

4.9 Overdose

Treatment should be symptomatic and supportive.

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

Category and class: A 20.1.1. Broad and medium spectrum antibiotics.

Pharmacotherapeutic group: Lincosamide antibiotics, ATC code: J01FF01.

5.1 Pharmacodynamic properties

Clindamycin exhibits its action by binding to the 50S subunit of the bacterial ribosome and thereby suppressing protein synthesis.

Clindamycin has shown activity against isolates of Gram-positive and Gram-negative organisms (*in vitro* sensitivity does not necessarily imply *in vivo* efficacy).

Clindamycin is not active against most strains of *Streptococcus faecalis*, *Escherichia coli*, *Shigella spp.*, *Salmonella spp.*, *Proteus spp.* and *Pseudomonas spp*.

Resistance

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

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.

Clindamycin is resistant to the following organisms:

- 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

Absorption

Following parenteral administration, the phosphate ester is rapidly hydrolysed to clindamycin. Following intramuscular injection, peak plasma concentrations are only attained after 3 hours in adults and 1 hour in children. The peak plasma concentrations obtained following intramuscular administration are: 6 µg/ml with a 300 mg dose and 9 µg/ml with a 600 mg dose in adults. When the same doses are infused intravenously, peak concentrations of 7 and 10 µg/ml, respectively, are achieved by the end of infusion.

Distribution

Clindamycin is 90 % plasma protein bound. It is widely distributed in many fluids and tissues including bone, but not in sufficient concentrations in the cerebrospinal fluid. It does, however, cross the placental barrier into the foetal circulation and appears in breast milk.

High concentrations occur in bile. It accumulates in polymorphonuclear leucocytes and alveolar macrophages.

In vitro studies in human liver and intestinal microsomes indicated that clindamycin is predominantly oxidised by CYP3A4, with minor contribution from CYP3A5, to form clindamycin sulphoxide and a minor metabolite, *N*-desmethylclindamycin.

The half-life is 2 to 3 hours, although this may be prolonged in preterm neonates and patients with severe renal impairment. The dosage in these patients should be adjusted according to plasma concentrations. Accumulation may also occur in patients with hepatic failure.

Elimination

About 10 % of clindamycin is excreted in the urine as active medicine 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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Disodium edetate

Hydrochloric acid (for pH-adjustment)

Sodium hydroxide (for pH-adjustment)

0,9 % *v/v* Benzyl alcohol (as a preservative)

Water for injection.

6.2 Incompatibilities

Solutions containing vitamin B complex are incompatible. CLINDAMYCIN 600 mg/4 ml FRESENIUS is also incompatible with aminophylline, ampicillin sodium, barbiturates, calcium gluconate, magnesium sulphate and phenytoin sodium.

6.3 Shelf life

24 months.

6.4 Special precautions for storage

Store at or below 25 °C.

6.5 Nature and contents of container

5 ml clear type I glass ampoule.

Pack size: Ten ampoules per carton.

6.6 Special precautions for disposal and other handling

CLINDAMYCIN 600 mg/4 ml FRESENIUS ampoules are not for multiple dosing and any unused portion must be discarded in accordance with local requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Fresenius Kabi Manufacturing SA (Pty) Ltd

6 Gibaud Road

Korsten 6020

Gqeberha

South Africa

8. REGISTRATION NUMBER

Y/20.1.1/254

9. DATE OF FIRST AUTHORISATION

05 November 1991

10. DATE OF REVISION OF THE TEXT

16 May 2022