

New Zealand Data Sheet

1. PRODUCT NAME

Topicil 150 mg Capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each Topicil Capsule contains clindamycin hydrochloride 162.87 mg (equivalent to clindamycin 150 mg).

Excipient(s) with known effect

Topicil Capsules contain lactose. For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Topicil Capsules are white/white hard gelatin capsules with a marking of 'CLIN 150' on the capsule body.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Clindamycin hydrochloride has been shown to be effective in the treatment of the following infections when caused by susceptible anaerobic bacteria or susceptible strains of gram-positive bacteria such as streptococci, staphylococci and pneumococci:

- Upper respiratory infections including tonsillitis, pharyngitis, sinusitis, otitis media and scarlet fever.
- Lower respiratory infections including bronchitis, pneumonia, emphysema and lung abscess.
- Skin and soft tissue infections including acne, furuncles, cellulitis, impetigo, abscesses, and wound infections. For specific skin and soft tissue infections like erysipelas and paronychia (panaritium), it would seem logical that these conditions would respond very well to clindamycin therapy.
- Bone and joint infections including osteomyelitis and septic arthritis.
- Pelvic infections including endometritis, cellulitis, vaginal cuff infection, tubo-ovarian abscesses, salpingitis and pelvic inflammatory disease when given in conjunction with an antibiotic of appropriate gram-negative aerobic spectrum. In cases of cervicitis due to *Chlamydia trachomatis*, mono therapy with clindamycin has been shown to be effective in eradicating the organism.
- Intra-abdominal infections including peritonitis and abdominal abscess when given in conjunction with an antibiotic of appropriate gram-negative aerobic spectrum.

- Septicaemia and endocarditis - the effectiveness of clindamycin in the treatment of selected cases of endocarditis has been documented when clindamycin is determined to be bactericidal to the infecting organism by *in vitro* testing of appropriate achievable serum concentrations.
- Dental infections such as periodontal abscess and periodontitis.
- As an alternative therapy when used in combination with quinine or amodiaquine for the treatment of multi-drug resistant *Plasmodium falciparum* infection.

4.2. Dose and method of administration

If significant diarrhoea occurs during therapy, this antibiotic should be discontinued (see section 4.4).

Dose

Paediatric population

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

Serious infections: 8 – 16 mg/kg/day divided into three or four equal doses.

More severe infections: 16 – 25 mg/kg/day divided into three or four equal doses.

Adults

Serious infections: 150 mg – 300 mg every six hours.

More severe infections: 300 mg – 450 mg every six hours.

For the treatment of anaerobic infections

Clindamycin phosphate solution for injection should be used initially. This may be followed by oral therapy with clindamycin capsules at the discretion of the physician.

For treatment of Pelvic Inflammatory Disease - inpatient treatment

Clindamycin phosphate 900 mg (i.v.) every 8 hours daily plus an antibiotic with an appropriate gram-negative aerobic spectrum administered i.v.; e.g. gentamicin 2.0 mg/kg followed by 1.5 mg/kg every 8 hours daily in patients with normal renal function. Continue (i.v.) drugs for at least 4 days and at least 48 hours after the patient improves. Then continue oral clindamycin hydrochloride 450 mg every 6 hours daily to complete 10 - 14 days total therapy.

For treatment of cervicitis due to Chlamydia trachomatis

Clindamycin hydrochloride by mouth 450 mg 4 times daily for 10 - 14 days.

For treatment of beta-haemolytic streptococci infections

In cases of beta-haemolytic streptococci infections, treatment should continue for at least ten days to diminish the likelihood of subsequent rheumatic fever or glomerulonephritis.

For the treatment of multi-drug resistant Plasmodium falciparum infection

Limited data from uncontrolled studies using a variety of doses suggest that clindamycin, orally at a dose of 5 - 10 mg/kg twice daily for minimum of 5 days, is a useful alternative therapy when used in combination with quinine or amodiaquine for the treatment of multidrug resistant Plasmodium falciparum infection.

Food

Absorption of clindamycin is not appreciably modified by the presence of food.

Renal and hepatic function

Clindamycin dosage modification is not necessary in patients with renal or liver disease (refer to section 4.4).

Elderly patients

No dosage alteration is necessary for the elderly with normal hepatic function and normal (age-adjusted) renal function (refer to section 5.2).

Monitoring

During prolonged therapy, periodic liver and kidney function tests and blood counts should be performed.

Method of Administration

To avoid the possibility of oesophageal irritation, Topical Capsules should be taken with a full glass of water and in an upright position.

4.3. Contraindications

Clindamycin is contraindicated in patients previously found to be sensitive to clindamycin or lincomycin or any of the excipients listed in section 6.1.

4.4. Special warnings and precautions for use

Colitis and diarrhoea

As has been reported with other antibiotics, clindamycin therapy has been associated with severe colitis, which may be fatal. It should not be used in patients with nonbacterial infections. Studies indicate a toxin(s) produced by Clostridia is one primary cause of antibiotic associated colitis. Cholestyramine and colestipol resins have been shown to bind the toxin *in vitro*. The colitis is usually characterised by mild watery diarrhoea to severe, persistent diarrhoea, leukocytosis, fever, severe abdominal cramps which may be associated with the passage of blood and mucous and if allowed to progress may produce peritonitis, shock and toxic megacolon. Endoscopic examination may reveal pseudomembranous colitis.

Mild cases usually respond to drug discontinuation alone. However, in moderate to severe cases,

appropriate therapy with a suitable oral antibacterial agent effective against *C. difficile* should be considered. Fluids, electrolytes and protein replacement should be provided when indicated.

Drugs which delay peristalsis, e.g. opiates and diphenoxylate hydrochloride with atropine sulfate (Lomotil), may prolong and/or worsen the condition and should not be used. Antibiotic-associated colitis and diarrhoea (due to *C. difficile*) occur more frequently and may be more severe in debilitated and/or elderly patients (>60 years). When clindamycin is indicated in these patients, they should be carefully monitored for change in bowel frequency.

Clostridium difficile associated diarrhoea (CDAD) has been reported with use of nearly all antibacterial agents, including clindamycin, and may range in severity from mild diarrhoea to fatal colitis. Treatment with antibacterial agents alters the normal flora of the colon leading to overgrowth of *C. difficile*.

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 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.

Stool culture for *Clostridium difficile* and stool assay for *C. difficile* toxin may be helpful diagnostically.

When significant diarrhoea occurs, the drug should be discontinued or, if necessary, continued only with close observation of the patient. Large bowel endoscopy has been recommended.

Antiperistaltic agents such as opiates and diphenoxylate with atropine (Lomotil) may prolong and/or worsen the condition. Vancomycin has been found to be effective in the treatment of antibiotic associated pseudomembranous colitis produced by *Clostridium difficile*. The usual adult dose is 500 mg to 2 g of vancomycin orally per day in three to four divided doses administered for seven to ten days. Cholestyramine or colestipol 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.

Diarrhoea, colitis, and pseudomembranous colitis have been observed to begin up to several weeks following cessation of therapy with clindamycin.

Review of experience to date suggests that a sub-group of older patients with associated severe illness may tolerate diarrhoea less well. When clindamycin is indicated in these patients, they should be carefully monitored for change in bowel frequency.

Clindamycin should be prescribed with caution in individuals with a history of gastrointestinal disease, particularly colitis.

Mild cases of colitis may respond to drug discontinuance alone. Moderate to severe cases should be managed with fluid, electrolyte and protein supplementation as indicated.

Systemic corticoids and corticoid retention enemas may help relieve the colitis. Other causes of colitis should also be considered.

A careful inquiry should be made concerning previous sensitivities to medicines and other allergens.

Use in meningitis

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

Monitoring

During prolonged therapy, periodic liver and kidney function tests and blood counts should be performed.

Renal and hepatic function

Clindamycin dosage modification is not necessary in patients with renal disease. In patients with moderate to severe liver disease, prolongation of the half-life of clindamycin has been found, but a pharmacokinetic study has shown that, when given every eight hours, accumulation of clindamycin should rarely occur. Therefore, dosage reduction in liver disease is not considered necessary.

Patients with very severe renal disease and/or very severe hepatic disease accompanied by severe metabolic aberrations should be dosed with caution, and serum clindamycin levels monitored during high-dose therapy.

Other precautions

Certain infections may require incision and drainage or other indicated surgical procedures in addition to antibiotic therapy. The use of clindamycin occasionally results in overgrowth of non susceptible organisms, particularly yeasts. Should superinfection occur, appropriate measures should be taken as indicated by the clinical situation.

Clindamycin should not be used in patients with non-bacterial infections.

Clindamycin should be prescribed with caution in atopic individuals.

Topical Capsules contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take Topical Capsules.

Use in the elderly

Refer to Colitis and diarrhoea.

Use in children

Safety and appropriate dosage in infants less than one month old have not been established. When clindamycin is administered to newborns and infants, appropriate monitoring of organ system functions is desirable.

4.5. Interaction with other medicines and other forms of interaction

Pharmacokinetic interactions

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

Pharmacodynamic interactions

Nil

4.6. Fertility, pregnancy and lactation

Pregnancy

Category A.

Clindamycin crosses the placenta in humans. After multiple doses, amniotic fluid concentrations were approximately 30% of maternal concentrations. Clindamycin should be used in pregnancy only if clearly needed.

There is no evidence of teratogenic effect in animals.

Breast-feeding

Clindamycin has been reported to appear in breast milk in ranges of 0.7 - 3.8 µg/mL. Therefore, it is not recommended for nursing mothers.

Fertility

Fertility studies in rats treated orally with up to 300 mg/kg/day (approximately 1.1 times the highest recommended adult human dose based on mg/m²) revealed no effects on fertility or mating ability.

4.7. Effects on ability to drive and use machines

Not relevant.

4.8. Undesirable effects

The following reactions have been reported with the use of clindamycin.

Gastrointestinal

Abdominal pain, oesophagitis and oesophageal ulcer, nausea, vomiting and diarrhoea (see section 4.4).

Hypersensitivity reactions

Maculo-papular rash and urticaria have been observed during drug therapy. Generalised mild to moderate morbilli form-like skin rashes are the most frequently reported of all adverse reactions. Rare instances of erythema multiforme, some resembling Stevens - Johnson syndrome have been associated with clindamycin. A few cases of anaphylactoid reactions have been reported. If a hypersensitivity reaction occurs, the medicine should be discontinued. The usual agents (adrenaline, corticosteroids, antihistamines, colloid infusion) should be available for emergency treatment of serious reactions.

Liver

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

Renal

Although no direct relationship of clindamycin to renal damage has been established, renal dysfunction as evidenced by azotemia, oliguria, and/or proteinuria has been observed in rare instances.

Haematopoietic

Transient neutropenia (leukopenia) and eosinophilia have been reported. Reports of agranulocytosis and thrombocytopenia have been made. No direct aetiological relationship to concurrent clindamycin therapy could be made in any of the foregoing.

Musculoskeletal

Rare instances of polyarthritis have been reported.

Skin and mucous membranes

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

Nervous system

Dysgeusia.

Post-marketing experience

Rare cases of toxic epidermal necrolysis have been reported during post-marketing surveillance.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected reactions <https://nzphvc.otago.ac.nz/reporting/>

4.9. Overdose

Symptoms

Overdosage with orally administered clindamycin has been rare. Adverse reactions similar to those seen with normal doses can be expected; however, unexpected reactions could occur (see section 4.8).

The minimal toxic or lethal dose is not well established. At therapeutic doses, the primary toxic effects may involve the gastrointestinal tract and may include severe diarrhoea and pseudomembranous colitis that may result in death. Dermatitis, nephrotoxicity, hepatotoxicity, and various haematological abnormalities are toxic effects that occur less frequently. Rapid administration of large doses intravenously has resulted in ventricular dysrhythmias, hypotension and cardiac arrest.

Treatment

No specific antidote is known. Support respiratory and cardiac function. In cases of overdose, drug levels of clindamycin are not clinically useful. However, monitoring serum concentrations in patients with markedly reduced renal and hepatic function may be indicated during high-dose therapy. Monitor full blood count in patients with significant exposure as clindamycin may produce abnormalities of the haematopoietic system. Because clindamycin may cause hepatotoxicity, monitor liver function tests in patients with significant exposure.

The serum biological half-life of clindamycin is 2.4 hours. Neither haemodialysis nor peritoneal dialysis appears to be effective in reducing clindamycin levels significantly.

Serious anaphylactoid reactions require immediate emergency treatment with adrenaline. Oxygen and intravenous corticosteroids should also be administered as indicated.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: Lincosamides; ATC classification: J01FF01

Clindamycin is a lincosamide antibiotic with a primarily bacteriostatic action. Clindamycin binds to the 50S subunit of the bacterial ribosome and inhibits the early stages of protein synthesis.

Microbiology

Clindamycin has been shown to have *in vitro* activity against isolates of the following organisms.

Aerobic gram-positive cocci, including:

- *Staphylococcus aureus*
- *Staphylococcus epidermidis* (penicillinase and non-penicillinase producing strains). When tested by *in vitro* methods, some staphylococcal strains, originally resistant to erythromycin, rapidly develop resistance to clindamycin.
- *Streptococci* (except *S. faecalis*)
- *Pneumococci*

Anaerobic gram-negative bacilli, including:

- *Bacteroides* species
- *Fusobacterium* species

Anaerobic gram-positive non-spore forming bacilli, including:

- *Propionibacterium* species
- *Eubacterium* species
- *Actinomyces* species

Anaerobic and microaerophilic gram-positive cocci, including:

- *Peptococcus* species
- *Peptostreptococcus* species
- Microaerophilic *streptococci*
- *Clostridia*: Clostridia are more resistant than most anaerobes to clindamycin. Most *C. perfringens* are susceptible, but other species, e.g. *C. sporogenes* and *C. tertium* are frequently resistant to clindamycin.

Susceptibility testing should be done.

Cross-resistance has been demonstrated between clindamycin and lincomycin.

Disc susceptibility testing

Dilution or diffusion techniques – either quantitative (MIC) or breakpoint, should be used

following a regularly updated, recognised and standardised method (e.g. NCCLS). Standardised susceptibility testing procedures require the use of laboratory control microorganisms to control the technical aspects of laboratory procedures.

A report of “Susceptible” indicates that the pathogen is likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations usually achievable.

A report of “Intermediate” indicates that the result should be considered equivocal, and if the microorganism is not fully susceptible to alternative, clinically feasible drugs, the test should be repeated. This category implies possible clinical applicability in body sites where the drug is physiologically concentrated or in situations where high dosage of drug can be used. This category also provides a buffer zone, which prevents small, uncontrolled technical factors from causing major discrepancies in interpretation.

A report of “Resistant” indicates that the pathogen is not likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations usually achievable and other therapy should be selected.

The prevalence of resistance may vary geographically for selected species and local information on resistance is desirable, particularly when treating severe infections.

Breakpoints:

The following MICs have been proposed to separate susceptible from intermediately susceptible and resistant organisms:

- Susceptible: $\leq 1.6 \mu\text{g/mL}$
- Intermediate: $> 1.6 - \leq 4.8 \mu\text{g/mL}$
- Resistant: $> 4.8 \mu\text{g/mL}$

The BSAC-recommended breakpoints for staphylococci are

S: $\leq 0.5 \mu\text{g/mL}$; R: $\geq 1.0 \mu\text{g/mL}$

5.2. Pharmacokinetic properties

Serum level studies with a 150 mg oral dose of clindamycin in 24 normal adult volunteers showed that clindamycin was rapidly absorbed after oral administration. An average peak serum level of 2.50 micrograms/mL was reached in 45 minutes; serum levels averaged 1.51 micrograms/mL at three hours and 0.70 micrograms/mL at six hours. Absorption of an oral dose is virtually complete (90%).

Concomitant administration of food does not appreciably modify the serum concentrations; serum levels have been uniform and predictable from person to person and dose to dose. Serum level studies following multiple doses of clindamycin hydrochloride for up to 14 days show no evidence of accumulation or altered metabolism of drug. Multiple-dose studies in newborns and infants up to 6 months of age show that the drug does not accumulate in the serum and is excreted rapidly.

Serum half-life of clindamycin is increased slightly in patients with markedly reduced renal function. Haemodialysis and peritoneal dialysis are not effective in removing clindamycin from the serum.

Concentrations of clindamycin in the serum increased linearly with increased dose. Serum levels exceed the MIC (minimum inhibitory concentration) for most indicated organisms for at least six hours following administration of the usually recommended doses.

Clindamycin is widely distributed in body fluids and tissues including bones. The average biological half-life is 2.4 hours. Approximately 10% of the bioactivity is excreted in the urine and 3.6% in the faeces; the remainder is excreted as bioinactive metabolites. Clindamycin is mainly eliminated by hepatic metabolism and biliary excretion.

Doses of up to 2 g of clindamycin per day for 14 days have been well tolerated by healthy volunteers, except that the incidence of gastrointestinal side effects is greater with the higher doses.

No significant levels of clindamycin are attained in the cerebrospinal fluid, even in the presence of inflamed meninges.

Pharmacokinetic studies in elderly volunteers (61 - 79 years) and younger adults (18 – 39 years) indicate that age alone does not alter clindamycin pharmacokinetics (clearance, elimination half-life, volume of distribution, area under the serum concentrations time curve) after i.v. administration of clindamycin phosphate. After oral administration of clindamycin, elimination half-life is increased to approximately 4.0 hours (range 3.4 - 5.1 h) in the elderly compared to 3.2 hours (range 2.1 - 4.2 h) in younger adults. The extent of absorption however, is not different between age groups and no dosage alteration is necessary for the elderly with normal hepatic function and normal (age-adjusted) renal function.

5.3. Preclinical safety data

Mutagenicity

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

Carcinogenicity

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

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

The other ingredients of Topicil Capsules are the pharmaceutical ingredients lactose monohydrate, maize starch, talc, magnesium stearate, gelatin, titanium dioxide (E171), Shellac, iron oxide black (E172), and propylene glycol (E1520).

6.2. Incompatibilities

Not applicable.

6.3. Shelf life

24 months.

6.4. Special precautions for storage

Store at or below 25°C and protect from light.

6.5. Nature and contents of container

Packs of 16, 24 and 100 capsules, containing PVC/Aluminium blister strips.
Not all pack sizes may be marketed.

6.6. Special precautions for disposal and other handling

No special requirements.

7. MEDICINE SCHEDULE

Prescription Medicine.

8. SPONSOR

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9. DATE OF FIRST APPROVAL

18 July 2013

10. DATE OF REVISION OF THE TEXT

14 December 2018

Summary table of changes

Section Changed	Summary of new information
6.5	Addition of 16 capsule pack.