NEW ZEALAND DATA SHEET

PRODUCT NAME

DALACIN® C 150 mg capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each DALACIN C 150mg capsule contains 177.515 mg clindamycin hydrochloride equivalent to 150 mg clindamycin.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Capsules.

The capsules consist of a white cap and white body imprinted with ‘Clin 150’ and ‘Pfizer’ in edible black ink.

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:

1. Upper respiratory infections including tonsillitis, pharyngitis, sinusitis, otitis media and scarlet fever.
2. Lower respiratory infections including bronchitis, pneumonia, emphyema and lung abscess.
3. 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.
4. Bone and joint infections including osteomyelitis and septic arthritis.
5. 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.
6. Intra-abdominal infections including peritonitis and abdominal abscess when given in conjunction with an antibiotic of appropriate gram negative aerobic spectrum.
7. Septicemia 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.

8. Dental infections such as periodontal abscess and periodontitis.

9. As an alternative therapy when used in combination with quinine for the treatment of multi-drug resistant Plasmodium falciparum infection.

4.2 Dose and method of administration

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

To avoid the possibility of oesophageal irritation, DALACIN C capsules should be taken with a full glass of water.

Adults
- Serious Infections: 150 mg – 300 mg every six hours.
- More severe infections: 300 mg – 450 mg every six hours.

Children
- 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.

DALACIN C capsules should only be used for children who are able to swallow capsules.

The use of capsules may not be suitable to provide the exact mg/kg doses required for the treatment of children.

For the treatment of anaerobic infections
DALACIN C Phosphate Solution for Injection should be used initially. This may be followed by oral therapy with DALACIN C capsules at the discretion of the physician.

For the treatment of Pelvic Inflammatory Disease - Inpatient treatment
Clindamycin phosphate 900 mg (IV) q8h daily plus an antibiotic with an appropriate gram negative aerobic spectrum administered IV; e.g. gentamicin 2.0 mg/kg followed by 1.5 mg/kg q8h daily in patients with normal renal function. Continue (IV) drugs for at least 4 days and at least 48 hours after the patient improves. Then continue oral clindamycin hydrochloride 450 mg q6h daily to complete 10-14 days total therapy.

For the treatment of Cervicitis due to Chlamydia trachomatis
Clindamycin hydrochloride by mouth 450 mg 4 times daily for 10-14 days.
For the treatment of β-hemolytic streptococci infections

In cases of β-hemolytic streptococci infections, treatment should continue for at least ten days.

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 useful alternative therapy when used in combination with quinine, for the treatment of multi-drug resistant *Plasmodium falciparum* infection.

4.3 Contraindications

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

4.4 Special warnings and precautions for use

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 should be discontinued and appropriate therapy should be initiated (see section 4.3 and section 4.8). The usual agents (adrenaline, corticosteroids, antihistamines, colloid infusion) should be available for emergency treatment of serious reactions.

As has been reported with other antibiotics, clindamycin therapy has been associated with severe colitis, which may end fatally. It should not be used in patients with non-bacterial 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 characterized by mild watery diarrhoea to severe, persistent diarrhoea leukocytosis, fever, severe abdominal cramps which may be associated with the passage of blood and mucus 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 con-currently, 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.

DALACIN C 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.

**Paediatric Use**

When DALACIN C is administered to newborns and infants, appropriate monitoring of organ system functions is desirable. For formulation reasons, DALACIN C capsules are not recommended in newborns, infants and children.
Use in Meningitis
Since clindamycin does not diffuse adequately into the cerebrospinal fluid the medicine should not be used in the treatment of meningitis.

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

DALACIN C should be prescribed with caution in atopic individuals.

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

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

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.

4.5 Interaction with other medicines and other forms of interaction

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.

Clindamycin is metabolised 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 metabolised by these CYP enzymes are unlikely.

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.

**Breast-feeding**

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

**4.7 Effects on ability to drive and use machines**

The effect of clindamycin on the ability to drive or operate machinery has not been systematically evaluated.

**4.8 Undesirable effects**

The adverse effects listed in the table below are presented by system organ class. Within each frequency category, the adverse effects are presented in the order of frequency and then by decreasing medical seriousness.

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>Common (≥1/100 to &lt;1/10)</th>
<th>Uncommon (≥1/1000 to &lt;1/100)</th>
<th>Rare (≥1/10000 to &lt;1/1000)</th>
<th>Frequency not known (cannot be estimated from available data)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infections and infestations</td>
<td>Pseudomembranous colitis</td>
<td>Eosinophilia</td>
<td>Agranulocytosis, neutropenia, thrombocytopenia, leucopenia</td>
<td>Vaginal infection</td>
</tr>
<tr>
<td>Blood and lymphatic system disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Immune system disorders</td>
<td></td>
<td></td>
<td></td>
<td>Anaphylactoid reaction</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>Diarrhoea, abdominal pain</td>
<td>Vomiting, nausea</td>
<td></td>
<td>Oesophagitis\‡, oesophageal ulcer\‡</td>
</tr>
<tr>
<td>Hepatobiliary disorders</td>
<td></td>
<td></td>
<td></td>
<td>Jaundice</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>Rash maculo-papular</td>
<td>Urticaria</td>
<td>Erythema multiforme, pruritus</td>
<td>Toxic epidermal necrolysis (TEN), Steven Johnson syndrome (SJS), drug reaction with eosinophilia and systemic symptoms (DRESS), acute generalised exanthematous pustulosis (AGEP), dermatitis exfoliative, dermatitis bullous, rash morbilliform</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td></td>
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<td></td>
<td>Poliarthritis</td>
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<tr>
<td>Renal and urinary disorders</td>
<td></td>
<td></td>
<td></td>
<td>Renal dysfunction (as evidenced by azotemia, oliguria, and/or proteinuria)</td>
</tr>
<tr>
<td>Investigations</td>
<td>Liver function test abnormal</td>
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</tbody>
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\(\text{\‡}\) Dose-related event.
CIOMS III categories: Very Common ≥1/10 (≥10%); Common ≥1/100 to <1/10 (≥1% and <10%); Uncommon ≥1/1000 to <1/100 (≥0.1% and <1%); Rare ≥1/10,000 to <1/1000 (≥0.01% and <0.1%); Very Rare <1/10,000 (<0.01%)

‡ Adverse reactions apply only to oral formulation.

**Post-Marketing Experience**

The following additional adverse reactions have been reported during post-marketing experience.

**Infections and infestations**

Not known: *Clostridium difficile* colitis.

**Immune system disorders**

Not known: Anaphylactic shock, anaphylactic reaction, hypersensitivity.

**Skin and subcutaneous tissue disorders**

Not known: Angioedema.

**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 adverse reactions https://nzphvc.otago.ac.nz/reporting/.

**4.9 Overdose**

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. Rapid administration of large doses intravenously has resulted in ventricular dysrhythmias, hypotension and cardiac arrest. Dermatitis, nephrotoxicity, hepatotoxicity, and various haematological abnormalities are toxic effects that occur less frequently.

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.

Neither haemodialysis nor peritoneal dialysis appear 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 Pharmacodynamics effects

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.

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 DALACIN HCl 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. *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 sulfoxide and a minor metabolite, N-desmethylclindamycin. 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.

5.3 Preclinical safety data

None stated.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate
Magnesium stearate
Starch maize
Purified talc

Capsule shell
Titanium dioxide
Gelatin with traces of edible black ink.

6.2 Incompatibilities

None stated.

6.3 Shelf life

60 months.

6.4 Special precautions for storage

Store below 25ºC.

6.5 Nature and contents of container

Blister packs of 16, 24 or 100 capsules*.

* Not all pack sizes available.

6.6 Special precautions for disposal

None stated.

7. MEDICINE SCHEDULE

Prescription medicine.
8. SPONSOR

Pfizer New Zealand Ltd
PO Box 3998
Auckland, New Zealand

Toll Free number: 0800 736 363

9. DATE OF FIRST APPROVAL

24 August 1972

10. DATE OF REVISION OF THE TEXT

20 April 2017

Summary of updates (20 April 2017)

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<th>Update</th>
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<tr>
<td>Section 4.2</td>
<td>Clarification regarding administration of capsules in children.</td>
</tr>
<tr>
<td>Section 4.5</td>
<td>Addition of text related to metabolism of clindamycin, and interaction with CYP enzymes, including loss of effectiveness in presence of strong CYP3A4 inhibitors.</td>
</tr>
<tr>
<td>Section 5.2</td>
<td>Addition of text related to the oxidation of clindamycin by CYP3A4.</td>
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