**DALCINEX Injection (Clindamycin phosphate)**

**Black Box Warning**

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

Because clindamycin phosphate therapy has been associated with severe colitis, which may end fatally, it should be reserved for serious infections where less toxic antimicrobial agents are inappropriate, as described in the INDICATIONS and DOSAGE AND ADMINISTRATION section. It should not be used in patients with non-bacterial infections such as most upper respiratory tract infections. *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 a colectomy. CDAD must be considered in all patients who present with diarrhoea following antibiotic use. Detailed medical history is necessary since CDAD has been reported to occur over 2 months after the administration of antibacterial agents.

If CDAD is suspected or confirmed, ongoing antibiotic use not directed against *C. difficile* may need to be discontinued. Appropriate fluid and electrolyte management, protein supplementation, antibiotic treatment of *C. difficile*, and surgical evaluation should be instituted as clinically indicated.

**Composition**

**DALCINEX Injection (2 mL and 4 mL)**

Each ml contains
- Clindamycin phosphate USP equivalent to clindamycin .......... 150 mg
- Benzyl Alcohol IP (as preservative) .......................... 9.45 mg
- Water for injection IP .......................................................... q.s

**Dosage Form**

Solution for injection (intravenous / intramuscular )
Pharmacology

Pharmacodynamics

Clindamycin inhibits bacterial protein synthesis by binding to the 50S subunit of the ribosome. It has activity against Gram-positive aerobes and anaerobes, as well as some Gram-negative anaerobes. Clindamycin is bacteriostatic. Cross-resistance between clindamycin and lincomycin is complete. Antagonism in vitro has been demonstrated between clindamycin and erythromycin. Clindamycin inducible resistance has been identified in macrolide-resistant staphylococci and beta-hemolytic streptococci.

Macrolide-resistant isolates of these organisms should be screened for clindamycin inducible resistance using the D-zone test.

Microbiology

Clindamycin has been shown to be active against most of the isolates of the following microorganisms, both in vitro and in clinical infections, as described in the INDICATIONS AND USAGE section.

**Gram-positive Aerobes**
- *Staphylococcus aureus* (methicillin-susceptible strains)
- *Streptococcus pneumoniae* (penicillin-susceptible strains)
- *Streptococcus pyogenes*

**Anaerobes**
- *Prevotella melaninogenica*
- *Fusobacterium necrophorum*
- *Fusobacterium nucleatum*
- *Peptostreptococcus anaerobius*
- *Clostridium perfringens*

At least 90% of the microorganisms listed below exhibit in vitro minimum inhibitory concentrations (MICs) less than or equal to the clindamycin susceptible MIC breakpoint. However, the efficacy of clindamycin in treating clinical infections due to these microorganisms has not been established in adequate and well-controlled clinical trials.

**Gram-positive aerobes**
- *Staphylococcus epidermidis* (methicillin-susceptible strains)
- *Streptococcus agalactiae*
- *Streptococcus anginosus*
- *Streptococcus oralis*
- *Streptococcus mitis*

**Anaerobes**
- *Prevotella intermedia*
- *Prevotella bivia*
- *Propionibacterium acnes*
- *Micromonas ("Peptostreptococcus") micros*
- *Finegoldia ("Peptostreptococcus") magna*
- *Actinomyces israelii*
**Pharmacokinetics**

Biologically inactive clindamycin phosphate is rapidly converted to active clindamycin. By the end of short-term I.V. infusion, peak serum levels of active clindamycin are reached. Biologically inactive clindamycin phosphate disappears rapidly from the serum; the average elimination half-life is 6 minutes; however, the serum elimination half-life of active clindamycin is about 3 hours in adults and $2^{1/2}$ hours in paediatric patients. After I.M. injection of clindamycin phosphate, peak levels of active clindamycin are reached within 3 hours in adults and 1 hour in paediatric patients.

No significant levels of clindamycin are attained in the cerebrospinal fluid even in the presence of inflamed meninges. Pharmacokinetic studies in elderly volunteers (61 to 79 years of age) and younger adults (18 to 39 years of age) indicate that age alone does not alter clindamycin pharmacokinetics (clearance, elimination half-life, volume of distribution and area under the serum concentration-time curve) after I.V. administration of clindamycin phosphate.

Serum levels of clindamycin can be maintained above the *in vitro* minimum inhibitory concentrations for most indicated organisms by administration of clindamycin phosphate every 8 to 12 hours in adults and every 6 to 8 hours in paediatric patients, or by continuous I.V. infusion. An equilibrium state is reached by the third dose.

Biologically inactive clindamycin phosphate disappears rapidly from the serum; the average elimination half-life is 6 minutes; however, the serum elimination half-life of active clindamycin is about 3 hours in adults and 2 hours in paediatric patients.

**Special Populations**

**Renal/Hepatic Impairment**

The elimination half-life of clindamycin is increased slightly in patients with markedly reduced renal or hepatic function. Haemodialysis and peritoneal dialysis are not effective in removing clindamycin from the serum. Dosage schedules need not be modified in the presence of mild or moderate renal or hepatic disease.

Renal impairment

Clindamycin dosage modification is not necessary in patients with mild-to-moderate renal impairment.

Hepatic impairment

Clindamycin dosage modification is not necessary in patients with mild-to-moderate hepatic impairment.

**Use in Elderly**

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 I.V. administration.

Serum assays for active clindamycin require an inhibitor to prevent *in vitro* hydrolysis of clindamycin phosphate.
**Indications**

**DALCINEX Injection** has been shown to be effective in the treatment of the following infections when caused by susceptible anaerobic bacteria, susceptible strains of Gram-positive aerobic bacteria such as streptococci, staphylococci and pneumococci; and susceptible strains of *Chlamydia trachomatis*.

**Upper respiratory tract infections**, including tonsillitis, pharyngitis, sinusitis, otitis media and scarlet fever.

**Lower respiratory tract infections**, including bronchitis, pneumonia, empyema, and lung abscess.

**Skin and skin structure 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

**Gynaecological infections**, including endometritis, non-gonococcal tubo-ovarian abscess, pelvic cellulitis, vaginal cuff infection, salpingitis and pelvic inflammatory disease, when given in conjunction with an antibiotic of appropriate gram-negative aerobic spectrum. In cases of cervicitis caused by *Chlamydia trachomatis*, single-drug therapy has shown to be effective in eradicating the organism.

**Intra-abdominal infections**, including peritonitis and intra-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 concentrations.

**Dental infections** such as periodontal abscess and periodontitis.

**Toxoplasmic encephalitis in patients with AIDS**: In patients who are intolerant to conventional treatment, clindamycin in combination with pyrimethane has shown to be efficacious.

**Pneumocystis carinii pneumonia in patients with AIDS**: In patients who are intolerant to, or do not respond adequately to conventional treatment, clindamycin may be used in combination with primaquine

**Malaria**, including multi-resistant *Plasmodium falciparum*, when given alone or in combination with quinine or chloroquine.

**Prophylaxis of infection in neck and head surgery**: Clindamycin phosphate, diluted in normal saline, is used as an intra-operative irrigant in the surgical field

Clindamycin phosphate, when used concurrently with an aminoglycoside antibiotic such as gentamicin or tobramycin, has been shown to be effective in preventing peritonitis or intra-abdominal abscess after bowel perforation and bacterial contamination secondary to trauma.

To reduce the development of drug-resistant bacteria and maintain the effectiveness of **DALCINEX**
Injection and other antibacterial drugs, DALCINEX Injection should be used only to treat or prevent infections that are proven or strongly suspected to be caused by susceptible bacteria. When culture and susceptibility information are available, they should be considered in selecting or modifying antibacterial therapy. In the absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy.

Its use should be reserved for penicillin-allergic patients or other patients for whom, in the judgement of the physician, penicillin is inappropriate. Because of the risk of antibiotic-associated pseudomembranous colitis, as described in the WARNING box, before selecting clindamycin, the physician should consider the nature of the infection and the suitability of less toxic alternatives.

Bacteriologic studies should be performed to determine the causative organisms and their susceptibility to clindamycin.

Dosage And Administration

Dosage
If diarrhoea occurs during therapy, this antibiotic should be discontinued (see WARNING box).

Patients with Normal Renal Function
Adults
For infections in the abdominal area, female pelvis and other complicated and serious infections, the dosage is 2,400-2,700 mg in two, three or four equal doses.

Less complicated infections due to more susceptible microorganisms may respond to lower doses of 1,200-1,800 mg/day in three or four equal doses.

I.V. doses of as much as 4,800 mg daily have been given to adults.

Single I.M. doses of greater than 600 mg are not recommended.

Alternatively, the drug may be administered in the form of a single rapid infusion of the first dose followed by continuous I.V. infusion as follows:

<table>
<thead>
<tr>
<th>To maintain serum clindamycin levels</th>
<th>Rapid infusion rate</th>
<th>Maintenance infusion rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Above 4 mcg/mL</td>
<td>10 mg/min for 30 minutes</td>
<td>0.75 mg/minutes</td>
</tr>
<tr>
<td>Above 5 mcg/mL</td>
<td>15 mg/min for 30 minutes</td>
<td>1.00 mg/minutes</td>
</tr>
<tr>
<td>Above 6 mcg/mL</td>
<td>20 mg/min for 30 minutes</td>
<td>1.25 mg/minutes</td>
</tr>
</tbody>
</table>

In Specific Indications

- Treatment of beta-haemolytic streptococcal infections
  Treatment should be continued for at least 10 days.

- Inpatient treatment of pelvic inflammatory disease
  I.V. administration of 900 mg every 8 hours plus an antibiotic with an appropriate gram-negative aerobic spectrum, 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 450-600 mg every 6 hours daily to
complete 10-14 days of total therapy.

- **Treatment of Chlamydia trachomatis cervicitis**
  Clindamycin hydrochloride capsules orally 450-600mg 4 times daily for 10-14 days.

- **Treatment of toxoplastic encephalitis in patients with AIDS**
  600-1,200 mg I.V. every 6 hours for 2 weeks followed by 300-400 mg oral clindamycin hydrochloride every 6 hours. The usual total duration of therapy is 8-10 weeks. The dose of pyrimethamine is 25-75 mg orally each day for 8-10 weeks. Folinic acid 10-20 mg/day should be given with higher doses of pyrimethamine.

- **Treatment of pneumocystitis carinni pneumonia in patients with AIDS.**
  600-900 mg I.V. every 6 hours or 900 mg I.V. every 8 hours and primaquine 15-30 mg dose orally once daily for 21 days.

- **Treatment of acute streptococcal tonsillitis/pharyngitis**
  Clindamycin hydrochloride capsules 300 mg orally twice daily for 10 days.

- **Treatment of malaria**
  10-20 mg/kg/day every 12 hours for 7 days alone, or in combination with quinine (12 mg/kg every 12 hours) or chloroquine (15-25 mg every 24 hours) for 3-5 days.

- **Prophylaxis**
  Antibiotic prophylaxis must be of short duration and, most frequently, restricted to the pre-operative period, sometimes for 24 hours but never more than 48 hours. Clindamycin phosphate 900 mg diluted in 1,000 mL normal saline for use as an intra-operative irrigant in contaminated head and neck surgery prior to wound closure.

**Paediatric Use (over 1 month of age)**
20-40 mg/kg/day in three or four equal doses.

Treatment of Malaria
10 mg/kg/day in equal doses every 12 hours for 7 days alone, or in combination with quinine (12 mg/kg every 12 hours) or chloroquine (15-25 mg every 24 hours) for 3-5 days.

**Neonates (less than 1 month of age)**
15-20 mg/kg/day in three or four equal doses. The lower dosage may be adequate for small premature infants.

**Patients with Impaired Renal Function and Elderly Patients**
Dosage adjustment not necessary.

**Patients with Impaired Hepatic Function**
Dosage adjustment not necessary.

**Method of preparation and administration**
Clindamycin phosphate must be diluted prior to I.V. administration. The concentration of clindamycin in the diluent for infusion should not exceed 18 mg per mL. Infusion rates should not exceed 30 mg per minute. The usual infusion dilutions and rates are as follows:

<table>
<thead>
<tr>
<th>Dose</th>
<th>Diluent</th>
<th>Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>300 mg</td>
<td>50 mL</td>
<td>10 minutes</td>
</tr>
<tr>
<td>600 mg</td>
<td>50 mL</td>
<td>20 minutes</td>
</tr>
<tr>
<td>900 mg</td>
<td>50-100 mL</td>
<td>30 minutes</td>
</tr>
<tr>
<td>1,200 mg</td>
<td>100 mL</td>
<td>40 minutes</td>
</tr>
</tbody>
</table>
Administration of more than 1,200 mg in a single 1-hour infusion is not recommended. Parenteral drug products should be inspected visually for particulate matter and discolouration prior to administration, whenever solution and container permit.

**Contraindications**

Clindamycin is contraindicated in patients previously found to be sensitive to clindamycin or lincomycin or to any component of the formulation.

**Warnings And Precautions**

**General**

See **WARNING** box.

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

This product contains benzyl alcohol as a preservative. Benzyl alcohol has been associated with a fatal "gasping syndrome" in premature infants.

If therapy is prolonged, liver and kidney function tests should be performed.

Serious anaphylactic reactions require immediate emergency treatment with epinephrine, and oxygen and I.V. corticosteroids should also be administered as indicated. Review of experience to date suggests that a subgroup 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.

**DALCINEX Injection** should be prescribed with caution in individuals with a history of gastrointestinal disease, particularly colitis. It should be prescribed with caution in atopic individuals. Certain infections may require incision and drainage or other indicated surgical procedures in addition to antibiotic therapy.

The use of **DALCINEX Injection** may result in the overgrowth of non-susceptible organisms, particularly yeasts. Should superinfections occur, appropriate measures should be taken as indicated by the clinical situation.

**DALCINEX Injection** should not be I.V. injected undiluted as a bolus, but should be infused over at least 10-60 minutes as directed in the **DOSAGE AND ADMINISTRATION** section.

**Drug interactions**

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

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.
Renal impairment

Clindamycin dosage modification is not necessary in patients with mild-to-moderate renal impairment.

Hepatic impairment

Clindamycin dosage modification is not necessary in patients with mild-to-moderate hepatic impairment.

Pregnancy

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

Lactation

Clindamycin has been reported to appear in breast milk in the range of 0.7 to 3.8 mcg/mL at dosages of 150 mg orally to 600 mg intravenously. Because of the potential for adverse reactions due to clindamycin in neonates (see Paediatric Use), the decision to discontinue the drug should be made, taking into account the importance of the drug to the mother.

Paediatric use

When administered to the paediatric population (birth to 16 years) appropriate monitoring of organ system functions is desirable. Refer to DOSAGE AND ADMINISTRATION.

Usage in Newborns and Infants

This product contains benzyl alcohol as a preservative. Benzyl alcohol has been associated with a fatal "Gasping Syndrome" in premature infants.

The potential for the toxic effect in the paediatric population from chemicals that may leach from the single dose premixed IV preparation in plastic has not been evaluated.

Geriatric Use

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.

Undesirable Effects

The following reactions have been reported with the use of clindamycin.
Gastrointestinal: Antibiotic-associated colitis (see WARNINGS), pseudomembranous colitis, abdominal pain, nausea, and vomiting. The onset of pseudomembranous colitis symptoms may occur during or after antibacterial treatment (see WARNINGS). An unpleasant or metallic taste occasionally has been reported after intravenous administration of the higher doses of clindamycin phosphate.

Hypersensitivity Reactions: Maculopapular rash and urticaria have been observed during drug therapy. Generalized mild to moderate morbilliform-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 drug should be discontinued. The usual agents (epinephrine, corticosteroids, antihistamines) should be available for emergency treatment of serious reactions.

Skin and Mucous Membranes: Pruritus, vaginitis, and rare instances of exfoliative dermatitis have been reported (see Hypersensitivity 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.

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

Local Reactions: Pain, induration and sterile abscess have been reported after intramuscular injection and thrombophlebitis after intravenous infusion. Reactions can be minimized or avoided by giving deep intramuscular injections and avoiding prolonged use of indwelling intravenous catheters.

Musculoskeletal: Rare instances of polyarthritis have been reported.

Cardiovascular: Rare instances of cardiopulmonary arrest and hypotension have been reported following too rapid intravenous administration. (See DOSAGE AND ADMINISTRATION section.)

Overdosage

Significant mortality was observed in mice at an intravenous dose of 855 mg/kg and in rats at an oral or subcutaneous dose of approximately 2618 mg/kg. In the mice, convulsions and depression were observed.

Haemodialysis and peritoneal dialysis are not effective in removing clindamycin from the serum.

Incompatibility

Solutions of clindamycin salts have a low pH and incompatibilities may reasonably be expected with
alkaline preparations or drugs unstable at a low pH.

Incompatibility has been reported with ampicillin sodium, phenytoin sodium, ceftriaxone sodium, barbiturates, aminophylline, calcium gluconate, magnesium sulphate, idarubicin hydrochloride and ranitidine hydrochloride.

It may be incompatible with tobramycin sulphate under certain circumstances. Admixtures in syringe and solutions in glucose injection have been reported to be unstable.

### Storage And Handling Instructions

Store at 2-8°C (refrigerate, but do not freeze).

### Packaging Information

**DALCINEX Injection**: Ampoules of 2 ml and 4 ml

*Last reviewed: September 2013*

*Last updated: January 2012*