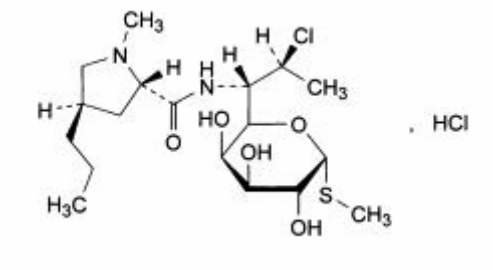
APO-CLINDAMYCIN CAPSULES

NAME OF THE MEDICINE

Clindamycin hydrochloride capsules

Chemical Name: methyl 7-chloro-6,7,8-trideoxy-6-[(2*S*,4*R*)-1-methyl-4-propylpyrrolidine-2-carboxamido]-1-thio-α-L-*threo*-D-*galacto*-octapyranoside

Structural Formula:



Molecular Formula: $C_{18}H_{33}ClN_2O_5S,HCl$

Molecular Weight: 461.5

CAS Registry Number: 21462-39-5

DESCRIPTION

Clindamycin hydrochloride is white or almost white, crystalline powder, very soluble in water, slightly soluble in ethanol (96 per cent). It is a semi- synthetic antibiotic produced by a 7(S)-chloro-substitution of the 7(R)-hydroxyl group of the parent compound lincomycin. The pKa value is 7.6.
Each capsule contains 150 mg of clindamycin hydrochloride as active ingredient.

In addition, each capsule contains the following inactive ingredients: lactose, magnesium stearate, maize starch, purified talc, titanium dioxide and gelatin with black printing ink (shellac, iron oxide black).

PHARMACOLOGY

Pharmacological Actions

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.

Human Pharmacology

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 2.5 micrograms/mL was reached in 45 minutes; serum levels averaged 1.51 micrograms/mL at 3 hours and 0.70 micrograms/mL at 6 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 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 bio-inactive metabolites.

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.

INDICATIONS

Clindamycin hydrochloride capsules are indicated in the treatment of serious infections caused by susceptible anaerobic bacteria.

Clindamycin capsules are also indicated in the treatment of serious infections due to susceptible strains of streptococci, pneumococci and staphylococci.

Its use should be reserved for penicillin-allergic patients or other patients for whom, in the judgement of the physician, a penicillin is inappropriate.

Anaerobes

Serious respiratory tract infections such as empyema, anaerobic pneumonitis and lung abscess; serious skin and skin structure infections; septicaemia; intra-abdominal infections such as peritonitis and intra-abdominal abscess (typically resulting from anaerobic organisms resident in the normal gastrointestinal tract); infections of the female pelvis and genital tract such as endometritis, non-gonococcal tubo-ovarian abscess, pelvic cellulitis and post-surgical vaginal cuff infection.

Streptococci

Serious respiratory tract infections; serious skin and skin structure infections, septicaemia.

Staphylococci

Serious respiratory tract infections; serious skin and skin structure infections; septicaemia; acute haematogenous osteomyelitis.

Pneumococci

Serious respiratory tract infections.

Adjunctive Therapy

In the surgical treatment of chronic bone and joint infections due to susceptible organisms. Indicated surgical procedures should be performed in conjunction with antibiotic therapy.

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

CONTRAINDICATIONS

Clindamycin capsules are contraindicated in individuals with a history of hypersensitivity to preparations containing clindamycin, lincomycin or any of the ingredients as listed under **DESCRIPTION**.

PRECAUTIONS

A few cases of anaphylactoid reactions have been reported. If a hypersensitivity reaction occurs, the drug should be discontinued. The usual agents (adrenaline, corticosteroids, antihistamines, colloid infusion) should be available for emergency treatment of serious reactions.

The use of clindamycin capsules can lead to the development of severe colitis. Fatalities have been reported. Most of these patients have been found to be colonised with C difficile. Therefore, the drug should be reserved for serious infections where less toxic antimicrobial agents are inappropriate, as described in the **INDICATIONS** section. It should not be used in patients with non-bacterial infections such as most upper respiratory tract infections.

It is important to consider the diagnosis of antibiotic associated colitis in patients who develop diarrhoea or colitis associated with antibiotic use. Antibiotic-associated colitis appears to result from a toxin produced by Clostridium difficile in the alimentary tract. The severity of the colitis may range from mild watery diarrhoea to severe, persistent, life- threatening bloody diarrhoea. The diagnosis is usually made by recognition of the clinical symptoms. The symptoms may occur during therapy or up to several weeks after cessation of therapy. Additional confirmatory signs of antibiotic-associated colitis include pseudomembrane formation seen with colonoscopy, C difficile culture from the stool, or assay of the stool for C difficile toxin.

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.

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

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

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

Clindamycin 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 clindamycin occasionally results in overgrowth of non-susceptible organisms - particularly yeasts. Should superinfections occur, appropriate measures should be taken as indicated by the clinical situation.

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.

Effects on Fertility

Fertility was not impaired in rats given 300 mg/kg/day in the diet.

Use in 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.

Use in Lactation

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

Paediatric Use

When clindamycin is administered to newborns and infants, appropriate monitoring of organ system functions is desirable. For formulation reasons, clindamycin capsules are not recommended in newborns, infants and children.

INTERACTIONS WITH OTHER MEDICINES

Clindamycin has been shown to have neuromuscular blocking properties that may enhance the action of other neuromuscular blocking agents. Therefore, clindamycin 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.

ADVERSE 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 of clinical importance.

System Organ Class	Common (≥ 1/100 to < 1/10)	Uncommon (≥1/1000 to < 1/100)	Rare (≥1/10000 to < 1/1000)	Very Rare (<1/10000)	Frequency not known (cannot be estimated from available data)
Infections and infestations	Pseudomembranous colitis				
Blood and lymphatic system disorders		Eosinophilia			Agranulocytosis, leucopenia, neutropenia, thrombocytopenia
Immune system disorders					Anaphylactoid reactions, drug reaction with eosinophilia and systemic symptoms (DRESS) +
Nervous system disorders		Dysgeusia			
Gastrointestinal disorders	Diarrhoea, abdominal pain	Nausea, vomiting			Oesophagitis, oesphageal ulcer
Hepatobiliary disorders	Liver function test abnormal				Jaundice
Skin and subcutaneous tissue disorders	Rash maculo-papular	Urticaria	Erythema multiforme, pruritus		Toxic epidermal necrolysis, Steven Johnson syndrome, dermatitis exfoliative, dermatitis bullous, rash morbilliform, vaginal infection, acute generalised exanthematous pustulosis (AGEP)
Musculoskeletal and connective tissue disorders					Polyarthritis
Renal and urinary disorders					Renal dysfunction (as evidenced by azotemiz, oliguria and /or proteinuria)

System Organ Class	Common (≥ 1/100 to < 1/10)	Uncommon (≥1/1000 to < 1/100)	Rare (≥1/10000 to < 1/1000)	Very Rare (<1/10000)	Frequency not known (cannot be estimated from available data)
*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%)					

DOSAGE AND ADMINISTRATION

Adults

150 mg every six hours
300 mg every six hours - more serious infections
450 mg every six hours - severe infections

Children

For formulation reasons, clindamycin capsules are not recommended in newborns, infants and children.

Absorption of clindamycin is not appreciably modified by ingestion of food, and clindamycin may be taken with meals with no significant reduction of the serum level. To avoid the possibility of oesophageal irritation, clindamycin capsules should be taken with a full glass of water.

In the treatment of anaerobic infections (see **INDICATIONS**), clindamycin phosphate injection should be used initially. This may be followed by oral therapy with clindamycin hydrochloride capsules at the discretion of the physician.

In cases of beta-haemolytic streptococcal infections, treatment should continue for at least 10 days.

OVERDOSAGE

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 **ADVERSE EFFECTS**).

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.

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 information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

PRESENTATION AND STORAGE CONDITIONS

APO-Clindamycin capsules are intended for oral administration. Each capsule contains clindamycin hydrochloride equivalent to 150 mg clindamycin base.

150 mg capsule:

The capsules consist of a white cap and white body imprinted with 'Clin 150'.
Blister Pack Clear (PVC/Aluminium silver foil) of 24 and 100 capsules (AUST R 214377).

Not all strengths, pack types and/or pack sizes may be available.

Storage

Store below 25°C. Protect from light.

NAME AND ADDRESS OF THE SPONSOR

Apotex Pty Ltd
16 Giffnock Avenue
Macquarie Park NSW 2113

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POISON SCHEDULE OF THE MEDICINE

S4 Prescription Only Medicine.

DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (THE ARTG)

22 August 2014

DATE OF MOST RECENT AMENDMENT

26 February 2016