PROFESSIONAL INFORMATION

SCHEDULING STATUS **S4**

1. NAME OF THE MEDICINE

CLINDAHEXAL150 (capsules)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each CLINDAHEXAL 150 capsule contains: clindamycin hydrochloride equivalent to 150 mg clindamycin base.

Each CLINDAHEXAL 150 mg capsule contains sugar (78,80 mg lactose monohydrate).

3. PHARMACEUTICAL FORM

Opaque brown/red-brown hard gelatine capsules, size 1, filled with homogenous powder.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Clindamycin is indicated in serious infections caused by organisms susceptible to its action. *In vitro* susceptibility studies should be performed. Infections due to susceptible organisms, which respond to an effective dose, include:

- infections of the upper and lower respiratory tract (pharyngitis, tonsillitis, sinusitis, otitis media, bronchitis, pneumonia), (ß haemolytic streptococci, *Diplococcus pneumoniae*)
- infections of the skin and soft tissue (abscesses, cellulitis, infected wounds, ß *haemolytic streptococci, Corynebacterium acnes*), and
- dental infections (periapical abscesses and gingivitis), (*Actinomyces israelii*)

4.2 Posology and method of administration

Adults:

Mild to moderately severe infection: 150 mg every six hours.

Severe infections: 300 mg to 450 mg every six hours.

Clindamycin should be taken with meals. Should clindamycin be taken between meals, it should be taken with a full glass of water, to avoid oesophageal irritation.

Note: For beta haemolytic streptococcal infections, treatment with clindamycin should continue for at least 10 days to diminish the likelihood of subsequent rheumatic fever or glomerulonephritis.

The serum half-life of clindamycin in patients with markedly reduced renal function is approximately twice that of the half-life of the compound in normal patients. The dose of clindamycin should be appropriately adjusted.

Method of administration:

Oral

4.3 Contraindications

- CLINDAHEXAL is contraindicated in patients previously found to be hypersensitive to clindamycin. Patients with a hypersensitivity to, lincomycin or to any excipients of CLINDAHEXAL listed in section 6.1.
- Safety for use in pregnancy and lactation has not been established.
- Clindamycin is not indicated for use in infants below 30 days of age.

4.4 Special warnings and precautions for use

Cross-resistance has been demonstrated between lincomycin hydrochloride and clindamycin.

Antagonism has been demonstrated with erythromycin.

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, CLINDAHEXAL should be discontinued and appropriate therapy should be initiated (see sections 4.3 and 4.8).

The choice of clindamycin should be based on factors such as severity of the infection, the prevalence of resistance to other suitable medicines and the risk of selecting clindamycin-resistant bacteria.
CLINDAHEXAL should only be used in the treatment of serious infections. When considering the use of CLINDAHEXAL, the practitioner 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 CLINDAHEXAL.

Treatment with antibacterial agents can significantly alter the normal flora of the colon leading to overgrowth of *Clostridium difficile*. This has been reported with use of nearly all antibacterial agents, 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”.
It is important to consider the diagnosis of CDAD in patients who present with diarrhoea subsequent to the administration of antibacterial agents. This may progress to colitis, including pseudomembranous colitis (see section 4.8). Colitis is a disease which has a clinical spectrum

from mild, watery diarrhoea to severe persistent diarrhoea, leucocytosis, fever, severe abdominal cramps, which may be associated with the passage of blood and mucous. If allowed to progress, it may produce peritonitis, shock and toxic megacolon. This may be fatal.

The appearance of marked diarrhoea should be regarded as an indication that CLINDAHEXAL should be discontinued immediately.
Diagnosis is usually made by the recognition of the clinical symptoms but can be substantiated by endoscopic demonstration of pseudomembranous colitis. 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 *Clostridium difficile.*

Clostridium Difficile Associated Diarrhoea (CDAD) has been reported with the 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 *Clostridium difficile*.
Clostridium difficile produces toxins A and B which contribute to the development of (CDAD).

Hypertoxin producing strains of *Clostridium 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.

If antibiotic-associated diarrhoea or antibiotic-associated colitis is suspected or confirmed, ongoing treatment with antibacterial agents, including clindamycin, should be discontinued and adequate therapeutic measures should be initiated immediately. Medicines inhibiting peristalsis are contraindicated in this situation.

Caution is advised when using CLINDAHEXAL in patients with a history of gastro-intestinal disease, especially colitis.

Clindamycin does not penetrate the blood/brain barrier in therapeutically effective quantities. Since CLINDAHEXAL does not diffuse adequately into cerebrospinal fluid, it should not be used in the treatment of meningitis.

Periodic liver and kidney function tests should be carried out during prolonged therapy.

Acute kidney injury, including acute renal failure, has been reported infrequently. In patients suffering from pre-existing renal dysfunction or taking concomitant nephrotoxic drugs, monitoring of renal function should be considered (see section 4.8).
Prolonged administration of CLINDAHEXAL may result in super-infection due to organisms resistant to clindamycin.

Care should be observed in the use of CLINDAHEXAL in atopic individuals.
Treatment with clindamycin is possibly an alternative treatment in case of penicillin allergy (penicillin hypersensitivity). An allergic cross-reaction between clindamycin and penicillin is not known and not expected because of the structural differences of both substances. However, (in isolated cases) anaphylaxis has been observed after clindamycin treatment for patients with existing penicillin allergy. This should be taken into consideration before treating penicillin allergic patients with CLINDAHEXAL

Porphyria: There is no evidence that CLINDAHEXAL cannot be used in porphyria.

CLINDAHEXAL contains lactose. Patients with rare hereditary problems of galactose intolerance, e.g. galactosaemia the Lapp lactase deficiency or glucose-galactose malabsorption or fructose intolerance should not take CLINDAHEXAL.

CLINDAHEXAL contains lactose which may have an effect on the gylcaemic control of patients with diabetes mellitus.

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 medicines.

Antagonism *in vitro* has been observed between clindamycin and erythromycin. Due to possible clinical significance between the two, CLINDAHEXAL should not be administered concurrently.

Vitamin K antagonists:

Increased coagulation tests (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 metabolized 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 medicines metabolized by these CYP enzymes are unlikely.

4.6 Fertility, pregnancy and lactation

Pregnancy:

Oral and subcutaneous reproductive toxicity studies in rats and rabbits revealed no evidence of impaired fertility or harm to the foetus due to clindamycin, except at doses that caused maternal toxicity. Animal reproduction studies are not always predictive of human response.

Clindamycin crosses the placenta in humans. After multiple doses, amniotic fluid concentrations were approximately 30 % of maternal blood concentrations.

In clinical trials with pregnant women, 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.

CLINDAHEXAL should be used in pregnancy only if a safer alternative is not available.

Lactation:

Orally and parentally administered clindamycin has been reported to appear in human breast milk in ranges from 0,7 to 3,8 µg/ml. Because of the potential for serious adverse reactions in

breastfed infants, CLINDAHEXAL should not be taken by mothers who are breastfeeding their infants. Mothers taking CLINDAHEXAL should not breastfeed.

Fertility:

Fertility studies in rats treated orally with clindamycin revealed no effects on fertility or mating ability. The effect on human fertility is unknown.

4.7 Effects on ability to drive and use machines

CLINDAHEXAL has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

The evaluation of side effects is based on the following information on frequencies:

Frequent, less frequent and not known (cannot be estimated from available data):

Infections and infestations:

Frequent: Pseudomembranous colitis (see section 4.4).

Not known: *Clostridium difficile*, colitis, vaginal infection.

Blood and lymphatic system disorders:

Not known: Agranulocytosis, leukopenia, neutropenia, thrombocytopenia, eosinophilia.

Immune system disorders:

Not known: Anaphylactic shock, anaphylactoid reaction, anaphylactic reaction, hypersensitivity.

Nervous system disorders:

Not known: Dysgeusia.

Gastrointestinal disorders:

Frequent: Abdominal pain, diarrhoea.

Less frequent: Nausea, vomiting.

Not known: Oesophageal ulcer, oesophagitis.

Hepatobiliary disorders:

Not known: Jaundice.

Renal and Urinary Disorders:

Not known: Acute kidney Injury.

Skin and subcutaneous tissue disorders:

Less frequent: Rash maculopapular, urticaria.

Not known: Toxic Epidermal Necrolysis (TEN), Stevens-Johnson Syndrome (SJS), drug reaction with eosinophilia and systemic symptoms (DRESS), Acute Generalised Exanthematous Pustulosis (AGEP), angioedema, erythema multiforme, dermatitis exfoliative, dermatitis bullous, rash morbilliform, pruritus.

Investigations:

Frequent: Liver function test abnormal.

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. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the “6.04 Adverse Drug

Reactions Reporting Form", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8

Suspected side effects can also be reported directly to the HCR via Patientsafety.sacg@novartis.com.

4.9 Overdose

The incidence of gastrointestinal side effects increase with increased dose. Treatment is supportive and symptomatic.

The serum biological half-life of clindamycin 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

Pharmacological classification: A 20.1.1 Broad and medium spectrum antibiotics.

Pharmacotherapeutic group: Anti-infectives for systemic use, ATC code: J01FF01

5.1 Pharmacodynamic properties

Mode of action:

Clindamycin binds exclusively to the 50S subunit of the bacterial ribosomes and suppresses protein synthesis.

Depending on the sensitivity of the organism and the concentration of the antibiotic, it may be either bactericidal or bacteriostatic.

Clindamycin has antibacterial activity against Gram-positive organisms and to a lesser degree against Gram-negative organisms.

Resistance:

Resistance to clindamycin is most often due to mutations on the site of antibiotic binding to rRNA or to the methylation of specific nucleotides of the 23S RNA of the 50S ribosomal subunit. These alterations may determine in vitro cross-resistance to macrolides and streptogramins B (MLSB phenotype).

Resistance mechanisms may be due to active efflux.

Resistance to clindamycin can be induced by macrolides in macrolide-resistant bacterial strains.

There is complete cross-resistance between clindamycin and lincomycin.

The incidence of clindamycin resistance is higher among methicillin-resistant strains of staphylococci and pneumococcal strains with decreased sensitivity to penicillin.

Susceptibility:

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.

CLASSES:

Usually, susceptible species:

Gram-positive aerobes:

Bacillus cereus

Corynebacterium diphtheriae

Methicillin-susceptible staphylococcus

Streptococcus agalactiae

Gram-negative aerobic bacteria:

Campylobacter

Anaerobic bacteria:

Actinomyces

Capnocytophaga

Clostridium perfringens

Eubacterium

Fusobacterium

Gardnerella vaginalis

Porphyromonas

Prevotella

Propionibacterium acnes

Veillonella

Other:

Chlamydia trachomatis

Leptospires

Mycoplasma hominis

Mycoplasma pneumoniae

Not consistently susceptible species:

(Acquired resistance > 10 %)

Gram-positive aerobic bacteria:

Enterococcus faecium

Erysipelothrix

Methicillin-resistant staphylococcus

Streptococcus pneumoniae

Streptococcus pyogenes

Oral streptococci

Anaerobic bacteria

Bacteroides

Clostridium (other than C. difficile and C. perfringens)

Mobiluncus

Peptococcus

Peptostreptococcus

Naturally resistant species:

Gram-positive aerobic bacteria:

Corynebacterium jeikeium

*Enterococcus spp. (*other than *Enterococcus faecium)*

Listeria

Nocardia asteroides

Rhodococcus equi

Gram-negative aerobic bacteria:

Nonfermenting gram-negative bacilli:

(Acinetobacter, Pseudomonas)

Enterobacter

Haemophilus

Legionella

Branhamella catarrhalis

Neisseria

Pasteurella

Anaerobic bacteria

Clostridium difficile

Other:

Mycobacteria

Ureaplasma urealyticum

5.2 Pharmacokinetic properties

General characteristics of active substance:

About 90 % of a dose of clindamycin hydrochloride is absorbed from the gastro-intestinal tract; concentrations of 2 to 3 micrograms per ml occur within one hour after a 150 mg dose of clindamycin, with average concentrations of about 0,7 micrograms per ml after 6 hours. After doses of 300 and 600 mg peak plasma concentrations of 4 and 8 micrograms per ml, respectively, have been reported. Absorption is not significantly diminished by food in the stomach, but the rate of absorption may be reduced.

Clindamycin is widely distributed in body fluids and most tissues, including bone, but it does not reach the cerebrospinal fluid in significant concentrations, even in the presence of inflamed meninges. It diffuses across the placenta into the foetal circulation and has been reported to appear in breast milk. High concentrations occur in bile. It accumulates in leucocytes and macrophages. Over 90 % of clindamycin in the circulation is bound to plasma proteins. The half-life is 2 to 3 hours, although this may be prolonged in pre-term neonates and patients with severe renal impairment.

Clindamycin undergoes metabolism, presumably in the liver, to the active N-demethyl and sulphoxide metabolites, and also some inactive metabolites. About 10 % of a dose is excreted in the urine as active substance 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.

Characteristics in patients:

No special characteristics. See section 4.4 for further information.

5.3 Preclinical safety data

None stated.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate, magnesium stearate, pregelatinised maize starch, talc.

The hard gelatine capsules are composed of: Black iron oxide (E172), gelatine, red iron oxide (E172), titanium dioxide (E171), yellow iron oxide (E172).

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months.

6.4 Special precautions for storage

Store at or below 25 °C.

6.5 Nature and contents of container

White opaque PVC/Aluminium blisters containing 10 capsules each. 2 (10) blister strips to be packed into a carton i.e. 20 capsules per carton or 10 (10) blister strips to be packed into a carton i.e. 100 capsules per carton, or

White Polypropylene securitainers containing 20 or 100 capsules.

Not all packs may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Sandoz SA (Pty) Ltd[1]

Magwa Crescent West

Waterfall City

Jukskei View

Midrand

2090

8. REGISTRATION NUMBER

32/20.1.1/0038

9. DATE OF FIRST AUTHORISATION

29 March 1999

10. DATE OF REVISION OF THE TEXT

11 April 2023

Additional countries registration details:

Additional country registration details:

Country	*Product name*	*Scheduling status (or Category of distribution)*	*Registration number*
Botswana	Clindahexal 150	S2	BOT1202235/A
Namibia	Clindahexal 150	NS2	04/20.1.1/1320
Zambia	Clindahexal 150	POM	039/033

Pharmacological classification: A 20.1.1 Broad and medium spectrum antibiotics

Name and address of manufacturer:

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D-39179
Barleben, Germany

or

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Str. Livezeni nr.7A
Târgu Mureş
Jud. Mureş, Romania

[1]Company Reg. No.: 1990/001979/07