Clemizole Penicillin *(BAN, rINN)*

Clemizol penicilina; Clemizole Benzylpenicillin; Clémizole Pénicilline; Clemizolum Penicillinum; Klemitsolipenisilliini; Klemizolpenicillin; Penicillin G Clemizole. 1-[1-(4-Chlorobenzyl)benzimidazol-2-ylmethyl]pyrrolidinium (6*R*)-6-(2-phenylacetamido)penicillanate.

Клемизол Пенициллин

$C_{16}H_{18}N_2O_4S,C_{19}H_{20}ClN_3$ = 660.2.

CAS — 6011-39-8.

Profile

Clemizole penicillin is a long-acting preparation of benzylpenicillin (p.213) with similar properties and uses.

Preparations

Proprietary Preparations (details are given in Part 3)
Chile: Prevepen; ***Mex.:*** Megapenil; ***Switz.:*** Megacilline†.

Multi-ingredient: ***Chile:*** Prevepen Forte; ***Mex.:*** Anapenil; Megapenil Forte; ***Port.:*** Prevecilina; ***Spain:*** Neopenyl.

Clindamycin *(BAN, USAN, rINN)*

Clindamicina; Clindamycine; Clindamycinum; Klindamisin; Klindamycin; Klindamysiini; U-21251. Methyl 6-amino-7-chloro-6,7,8-trideoxy-*N*-[(2*S*,4*R*)-1-methyl-4-propylprolyl]-1-thio-L-*threo*-D-*galacto*-octopyranoside.

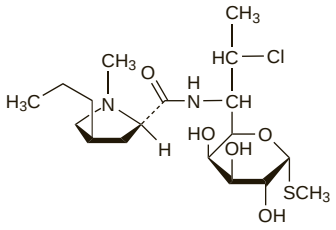
Клиндамицин

$C_{18}H_{33}ClN_2O_5S$ = 425.0.

CAS — 18323-44-9.

ATC — D10AF01; G01AA10; J01FF01.

ATC Vet — QD10AF01; QG01AA10; QJ01FF01.



NOTE. The name Clinimycin, which was formerly used for clindamycin, has also been used for a preparation of oxytetracycline.

Clindamycin Hydrochloride *(BANM, rINNM)*

Chlorodeoxylincomycin Hydrochloride; (7*S*)-Chloro-7-deoxylincomycin Hydrochloride; Clindamycine, chlorhydrate de; Clindamycini hydrochloridum; Hidrocloruro de clindamicina; Klindamicin-hidroklorid; Klindamicino hidrochloridas; Klindamisin Hidroklorür; Klindamycin-hydrochlorid; Klindamycinhydroklorid; Klindamycyny chlorowodorek; Klindamysiinihydrokloridi.

Клиндамицина Гидрохлорид

$C_{18}H_{33}ClN_2O_5S,HCl$ = 461.4.

CAS — 21462-39-5 (anhydrous clindamycin hydrochloride); 58207-19-5 (clindamycin hydrochloride monohydrate).

ATC — D10AF01; G01AA10; J01FF01.

ATC Vet — QD10AF01; QG01AA10; QJ01FF01.

Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), *Jpn*, and *US*.

Ph. Eur. 6.2 (Clindamycin Hydrochloride). A white or almost white, crystalline powder. It contains a variable quantity of water. Very soluble in water; slightly soluble in alcohol. A 10% solution in water has a pH of 3.0 to 5.0. Store in airtight containers.

USP 31 (Clindamycin Hydrochloride). A white or practically white crystalline powder, odourless or has a faint mercaptan-like odour. Freely soluble in water, in dimethylformamide, and in methyl alcohol; soluble in alcohol; practically insoluble in acetone. pH of a 10% solution in water is between 3.0 and 5.5. Store in airtight containers.

Clindamycin Palmitate Hydrochloride

(BANM, USAN, rINNM)

Clindamycine, Chlorhydrate de Palmitate de; Clindamycini Palmitatis Hydrochloridum; Hidrocloruro del palmitato de clindamicina; U-25179E. Clindamycin 2-palmitate hydrochloride.

Клиндамицина Палмитата Гидрохлорид

$C_{34}H_{63}ClN_2O_6S,HCl$ = 699.9.

CAS — 36688-78-5 (clindamycin palmitate); 25507-04-4 (clindamycin palmitate hydrochloride).

ATC — D10AF01; G01AA10; J01FF01.

ATC Vet — QD10AF01; QG01AA10; QJ01FF01.

Pharmacopoeias. In *US*.

USP 31 (Clindamycin Palmitate Hydrochloride). A white to off-white amorphous powder having a characteristic odour. Freely soluble in water, in chloroform, in ether, and in benzene; soluble 1 in 3 of alcohol and 1 in 9 of ethyl acetate; very soluble in dimethylformamide. pH of a 1% solution in water is between 2.8 and 3.8. Store in airtight containers.

Clindamycin Phosphate *(BANM, USAN, rINNM)*

Clindamycine, phosphate de; Clindamycini Dihydrogenophosphas; Clindamycini phosphas; Fosfato de clindamicina; Klindamicin-foszfát; Klindamicino fosfatas; Klindamisin Fosfat; Klindamycin dihydrogen fosfát; Klindamycinfosfat; Klindamysiinifosfaatti; U-28508. Clindamycin 2-(dihydrogen phosphate).

Клиндамицина Фосфат

$C_{18}H_{34}ClN_2O_8PS$ = 505.0.

CAS — 24729-96-2.

ATC — D10AF01; G01AA10; J01FF01.

ATC Vet — QD10AF01; QG01AA10; QJ01FF01.

Pharmacopoeias. In *Eur.* (see p.vii), *Int.*, *Jpn*, and *US*.

Ph. Eur. 6.2 (Clindamycin Phosphate). A white or almost white, slightly hygroscopic powder. It exhibits polymorphism. Freely soluble in water; very slightly soluble in alcohol; practically insoluble in dichloromethane. A 1% solution in water has a pH of 3.5 to 4.5. Store at a temperature not exceeding 30° in airtight containers.

USP 31 (Clindamycin Phosphate). A white to off-white, odourless or practically odourless, hygroscopic, crystalline powder. Soluble 1 in 2.5 of water; slightly soluble in dehydrated alcohol; very slightly soluble in acetone; practically insoluble in chloroform, in ether, and in benzene. pH of a 1% solution in water is between 3.5 and 4.5. Store in airtight containers.

Incompatibility. Solutions of clindamycin salts have an acid pH and incompatibility may reasonably be expected with alkaline preparations, or with drugs unstable at low pH. Licensed product information for the injectable solution of clindamycin states that incompatibility has been reported between clindamycin and the following drugs: ampicillin, aminophylline, barbiturates, calcium gluconate, ceftriaxone, ciprofloxacin, idarubicin, magnesium sulfate, phenytoin, and ranitidine.

Clindamycin phosphate is incompatible with natural rubber closures.

Adverse Effects and Treatment

Clindamycin is reported to produce diarrhoea in up to 20% of patients after systemic use. In some patients severe antibiotic-associated or pseudomembranous colitis (p.171) may develop during therapy or up to several weeks after it, and has proved fatal. It has been reported to be more frequent in middle-aged and elderly women, particularly after surgery; it may also occur rarely after topical use. Clindamycin should be stopped immediately if significant diarrhoea or colitis occurs. Protein supplementation and use of an antibacterial active against *Clostridium* spp. should be considered for severe antibiotic-associated colitis.

Other gastrointestinal effects include nausea, vomiting, abdominal pain or cramps, and oesophagitis; an unpleasant or metallic taste has occasionally been reported after high intravenous doses.

Skin rashes and urticaria, the most common hypersensitivity reactions, occur in up to 10% of patients usually after 1 to 2 weeks of therapy. Erythema multiforme, Stevens-Johnson syndrome, and exfoliative and vesiculobullous dermatitis have been reported rarely, and a few cases of anaphylaxis have occurred.

Other adverse effects include transient leucopenia or occasionally agranulocytosis, eosinophilia, thrombocytopenia, polyarthritis, and abnormalities of liver function tests; in some cases overt jaundice and hepatic damage have been reported. Renal dysfunction, shown by azotaemia, oliguria, and/or proteinuria has been reported rarely.

Although local irritation is rare, intramuscular injection has led to induration and sterile abscess, and thrombophlebitis may occur after intravenous use. Too rapid intravenous infusion can result in rare instances of cardiopulmonary arrest and hypotension. Some parenteral formulations contain benzyl alcohol which may cause fatal 'gasping syndrome' in neonates (see p.1632).

Topical application may be associated with local irritation and contact dermatitis; sufficient clindamycin may be absorbed to produce systemic effects. Cervicitis, vaginitis, or vulvovaginal irritation has been reported with intravaginal use; a small amount of systemic absorption also occurs.

Effects on the cardiovascular system. Cardiac arrest occurred in a 50-year-old woman after rapid injection of 600 mg of undiluted clindamycin phosphate into a central intravenous line. Further injections were given over 30 minutes without cardiovascular complications.[1] There has also been a case of severely prolonged QT interval attributed to the addition of clindamycin to therapy in an elderly woman;[2] the patient developed AV block and subsequent torsade de pointes, and required resuscitation. When clindamycin was stopped, signs of heart block resolved, and the QT interval returned to normal over several days.

1. Aucoin P, *et al.* Clindamycin-induced cardiac arrest. *South Med J* 1982; **75:** 768.
2. Gabel A, *et al.* Ventricular fibrillation due to long QT syndrome probably caused by clindamycin. *Am J Cardiol* 1999; **83:** 813–15.

Effects on the ears. A 14-year-old boy who was treated with topical clindamycin for acne vulgaris developed unilateral tinnitus during therapy and unilateral sensorineural hearing loss 2 months later;[1] symptoms subsequently recurred upon 2 rechallenges.

1. Scissors B, Shwayder T. Topical clindamycin reproducibly causing tinnitus in a 14-year-old boy. *J Am Acad Dermatol* 2006; **54** (suppl): S243–S244.

Effects on the lymphatic system. A report of lymphadenitis associated with clindamycin.[1]

1. Southern PM. Lymphadenitis associated with the administration of clindamycin. *Am J Med* 1997; **103:** 164–5.

Effects on the skin. There have been reports of toxic epidermal necrolysis[1] and acute generalised exanthematous pustulosis[2,3] associated with clindamycin.

1. Paquet P, *et al.* Toxic epidermal necrolysis following clindamycin treatment. *Br J Dermatol* 1995; **132:** 665–6.
2. Valois M, *et al.* Clindamycin-associated acute generalized exanthematous pustulosis. *Contact Dermatitis* 2003; **48:** 169.
3. Kapoor R, *et al.* Acute generalized exanthematous pustulosis induced by clindamycin. *Arch Dermatol* 2006; **142:** 1080–81.

Precautions

Clindamycin should not be given to patients hypersensitive to it or to the closely related drug lincomycin. It should be used with caution in patients with a history of gastrointestinal disease, particularly colitis, and stopped immediately if significant diarrhoea or colitis occurs. Middle-aged and elderly female patients may be at greater risk of severe diarrhoea or pseudomembranous colitis. Caution has also been advised in atopic patients. Periodic tests of liver and kidney function and blood counts have been recommended in patients receiving prolonged therapy, and in infants. Caution is required during parenteral use in neonates, since some parenteral formulations contain benzyl alcohol which may cause fatal 'gasping syndrome' (see p.1632).

AIDS. Clindamycin was poorly tolerated by patients with AIDS in a study of its use for *prophylaxis* of toxoplasmic encephalitis.[1] Despite the use of relatively low doses of clindamycin (300 mg twice daily), 23 of 52 patients reported adverse effects that necessitated temporary or permanent withdrawal of the drug, the most frequent adverse reactions being diarrhoea and skin rash. The clindamycin arm of the study had to be terminated prematurely. Nevertheless, clindamycin has been used successfully in patients with AIDS for the *treatment* of both toxoplasmic encephalitis (see Toxoplasmosis, below) and pneumocystis pneumonia (below).

1. Jacobson MA, *et al.* Toxicity of clindamycin as prophylaxis for AIDS-associated toxoplasmic encephalitis. *Lancet* 1992; **339:** 333–4.

Breast feeding. US licensed product information states that concentrations of clindamycin in breast milk were 0.7 to 3.8 micrograms/mL after doses of 150 mg orally to 600 mg intravenously. No adverse effects have been seen in breast-fed infants whose mothers were receiving clindamycin, and the American Academy of Pediatrics[1] considers that it is therefore usually compatible with breast feeding. Nevertheless, UK product information states that although it is unlikely that a breast-fed infant could absorb significant amounts, caution should be exercised when clindamycin is given during breast feeding.

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 25/05/04)

Interactions

Clindamycin has neuromuscular blocking activity in high doses and may enhance the effect of other drugs with this action (see Atracurium, p.1903), leading to a potential danger of respiratory depression. Clindamycin may antagonise the effects of parasympathomimetics. For mention of synergistic and antagonistic antimicrobial activity with other antibacterials, see Antimicrobial Action, below.

Adsorbents. In 16 healthy subjects given clindamycin alone and with a *kaolin-pectin* suspension it was found that the suspension had no effect on the extent of clindamycin absorption but did markedly reduce the absorption rate.[1]

1. Albert KS, *et al.* Pharmacokinetic evaluation of a drug interaction between kaolin-pectin and clindamycin. *J Pharm Sci* 1978; **67:** 1579–82.

Antimicrobial Action

Clindamycin is a lincosamide antibacterial with a primarily bacteriostatic action against Gram-positive aerobes and a wide range of anaerobic bacteria.

Mechanism of action. Lincosamides such as clindamycin bind to the 50S subunit of the bacterial ribosome, similarly to macrolides such as erythromycin (p.271), and inhibit the early stages of protein synthesis. The action of clindamycin is mainly bacteriostatic, although high concentrations may be slowly bactericidal against sensitive strains.

Spectrum of activity. Clindamycin is active against:

- most aerobic Gram-positive bacteria including streptococci, staphylococci, *Bacillus anthracis*, and *Corynebacterium diphtheriae*
- enterococci are generally resistant
- susceptible Gram-positive anaerobes include *Eubacterium*, *Propionibacterium*, *Peptococcus*, and *Peptostreptococcus* spp., and many strains of *Clostridium perfringens* and *Cl. tetani*
- Gram-negative anaerobes susceptible to clindamycin include *Fusobacterium* spp. (although *F. varium* is usually resistant), *Prevotella* spp., and *Bacteroides* spp., including the *B. fragilis* group
- several *Actinomyces* spp. and *Nocardia asteroides* are reported to be susceptible
- *Mycoplasma* spp. are generally resistant
- most Gram-negative aerobic bacteria, including the Enterobacteriaceae, are resistant to clindamycin; unlike erythromycin, *Neisseria gonorrhoeae*, *N. meningitidis*, and *Haemophilus influenzae* are generally resistant
- fungi, yeasts, and viruses are also resistant; however, clindamycin has been reported to have some antiprotozoal activity against *Toxoplasma gondii* and *Plasmodium* spp.

Activity with other antimicrobials. Synergistic activity has been reported between clindamycin and ceftazidime or metronidazole, and also with ciprofloxacin against some anaerobes. However, there is some evidence that clindamycin inhibits the bactericidal activity of the aminoglycosides, although conflicting reports have suggested variable degrees of synergy against anaerobic organisms. Because of the adjacency of their binding sites on the ribosome, clindamycin may competitively inhibit the effects of macrolides or chloramphenicol. Clindamycin has been reported to diminish the activity of ampicillin *in vitro* against *Staph. aureus*. It is reported to enhance the activity of primaquine against *Pneumocystis jirovecii*. Antagonism between clindamycin and erythromycin has been shown *in vitro*.

Resistance. Most Gram-negative aerobes, such as the Enterobacteriaceae, *Pseudomonas* spp., and *Acinetobacter* spp., are intrinsically resistant to clindamycin, but acquired resistance also occurs in normally sensitive strains. The **mechanisms** of resistance are the same as those for erythromycin, namely methylation of the ribosomal binding site, chromosomal mutation of the ribosomal protein, and, in a few staphylococcal isolates, enzymic inactivation by a plasmid-mediated adenyltransferase. Methylation of the ribosome leads to cross-resistance between the lincosamides and macrolides and streptogramins (the MLS_B phenotype); this type of resistance is usually plasmid-mediated and inducible. Complete cross-resistance exists between clindamycin and lincomycin.

The **incidence** of resistance varies with the organism and the geographical location; it is more frequent in organisms that are also erythromycin-resistant, and some strains of meticillin-resistant *Staph. aureus* are also resistant to clindamycin. In some countries and institutions there is evidence of an increase in resistance amongst the *B. fragilis* group to about 25% of strains or more. Resistance to clindamycin by anaerobes has also been reported in 10 to 20% of *Clostridium* spp. other than *C. perfringens*, 8% of peptostreptococci, 9% of *Fusobacterium* spp., and 11% of *Prevotella* strains.

Action. References suggesting that clindamycin may reduce microbial adherence and enhance phagocytosis by its effects on bacterial slime (glycocalyx)[1-3] and that its antibacterial effects may be independent of plasma concentrations.[4,5]

1. Veringa EM, *et al.* Enhancement of opsonophagocytosis of Bacteroides spp by clindamycin in subinhibitory concentrations. *J Antimicrob Chemother* 1981; **23:** 577–87.
2. Veringa EM, *et al.* The role of glycocalyx in surface phagocytosis of Bacteroides spp, in the presence and absence of clindamycin. *J Antimicrob Chemother* 1989; **23:** 711–20.
3. Khardori N, *et al.* Effect of subinhibitory concentrations of clindamycin and trospectomycin on the adherence of Staphylococcus epidermidis in an in vitro model of vascular catheter colonization. *J Infect Dis* 1991; **164:** 108–13.
4. Xue IB, *et al.* Variation in postantibiotic effect of clindamycin against clinical isolates of Staphylococcus aureus and implications for dosing of patients with osteomyelitis. *Antimicrob Agents Chemother* 1996; **40:** 1403–7.
5. Klepser ME, *et al.* Bactericidal activity of low-dose clindamycin administered at 8- and 12-hour intervals against Staphylococcus aureus, Streptococcus pneumoniae, and Bacteroides fragilis. *Antimicrob Agents Chemother* 1997; **41:** 630–5.

Resistance. Although there is usually cross-resistance between clindamycin and macrolides (above), a resistance pattern has been identified that results in streptococcal resistance to macrolides while retaining susceptibility to clindamycin.[1]

1. Sutcliffe J, *et al.* Streptococcus pneumoniae and Streptococcus pyogenes resistant to macrolides but sensitive to clindamycin: a common resistance pattern mediated by an efflux system. *Antimicrob Agents Chemother* 1996; **40:** 1817–24.

Pharmacokinetics

About 90% of a dose of clindamycin hydrochloride is absorbed from the gastrointestinal tract; concentrations of 2 to 3 micrograms/mL occur within 1 hour after a 150-mg oral dose, with average concentrations of about 700 nanograms/mL after 6 hours. After doses of 300 and 600 mg, peak plasma concentrations of 4 and 8 micrograms/mL, respectively, have been reported. Absorption is not significantly diminished by food in the stomach but the rate of absorption may be reduced. Clindamycin palmitate hydrochloride is rapidly hydrolysed on oral use to free clindamycin.

After parenteral use, the biologically inactive clindamycin phosphate is also hydrolysed to clindamycin. When the equivalent of 300 mg of clindamycin is injected intramuscularly, a mean peak plasma concentration of 6 micrograms/mL occurs within 3 hours; 600 mg gives a peak concentration of 9 micrograms/mL. In children, peak concentrations may occur within 1 hour. When the same doses are infused intravenously, peak concentrations of 7 and 10 micrograms/mL occur by the end of infusion.

Small amounts of clindamycin may be absorbed after topical application to the skin; bioavailability from topical preparations of the hydrochloride and phosphate (the former in an extemporaneous formulation) has been reported to be about 7.5% and 2% respectively.

About 5% of a dose may be absorbed systemically from an intravaginal cream formulation; absorption from vaginal pessaries is reported to be about 30%.

Clindamycin is widely distributed in body fluids and tissues, including bone, but it does not reach the CSF in significant concentrations. It diffuses across the placenta into the fetal 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 preterm neonates and in patients with severe renal impairment.

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

AIDS patients. Clindamycin was reported to have higher bioavailability, lower plasma clearance, and a lower volume of distribution in patients with AIDS than in healthy subjects.[1] This may partly be explained by increased binding to plasma proteins.[2]

Although it is generally considered that penetration of clindamycin into the CSF is insignificant, parasiticidal CSF concentrations against *Toxoplasma gondii* were achieved with intravenous clindamycin in patients with AIDS.[3]

1. Gatti G, *et al.* Comparative study of bioavailabilities and pharmacokinetics of clindamycin in healthy volunteers and patients with AIDS. *Antimicrob Agents Chemother* 1993; **37:** 1137–43.
2. Flaherty JF, *et al.* Protein binding of clindamycin in sera of patients with AIDS. *Antimicrob Agents Chemother* 1996; **40:** 1134–8.
3. Gatti G, *et al.* Penetration of clindamycin and its metabolite N-demethylclindamycin into cerebrospinal fluid following intravenous infusion of clindamycin phosphate in patients with AIDS. *Antimicrob Agents Chemother* 1998; **42:** 3014–17.

Uses and Administration

Clindamycin is a lincosamide antibacterial that is a chlorinated derivative of lincomycin. It is a mainly bacteriostatic drug used in the treatment of serious anaerobic infections, notably due to *Bacteroides fragilis*. Clindamycin is also used for some Gram-positive infections due to pneumococci, staphylococci, and streptococci. However, because of its potential for causing pseudomembranous colitis (see Adverse Effects, above) it is usually used only when alternative drugs are unsuitable.

Amongst the conditions that it may be used to treat are liver abscess, actinomycosis, biliary-tract infections, staphylococcal bone and joint infections, the carrier state of diphtheria, endophthalmitis, gas gangrene, various gynaecological infections including bacterial vaginosis, endometritis, and pelvic inflammatory disease (the latter two with an aminoglycoside), intra-abdominal infections including secondary peritonitis, streptococcal pharyngitis (usually to treat the carrier state), serious respiratory-tract infections including empyema and pneumonia (especially lung abscess), septicaemia, and skin and soft-tissue infections involving heavy colonisation with streptococci or anaerobes such as necrotising fasciitis. Clindamycin is also used as part of a multidrug regimen in the treatment of anthrax. It is used in the prophylaxis of endocarditis in penicillin-allergic patients, in the prevention of perinatal streptococcal infections, and with other drugs for the prophylaxis of surgical infection. It may be used as part of a multi-drug regimen for the treatment of inhalation and gastrointestinal anthrax.

For details of these bacterial infections and their treatment, see under Choice of Antibacterial, p.162.

Clindamycin is also applied topically in the treatment of acne (p.1577) and rosacea (below).

Clindamycin has some antiprotozoal actions, and has been used, usually with other antiprotozoals, in various infections (see below) including babesiosis, malaria, and toxoplasmosis. It may also be used with primaquine in the treatment of pneumocystis pneumonia (below).

Clindamycin is given **orally** as capsules containing the hydrochloride or as oral liquid preparations containing the palmitate hydrochloride. The capsules should be taken with a glass of water. Doses are expressed in terms of the base; 1.1 g of clindamycin hydrochloride and 1.6 g of clindamycin palmitate hydrochloride are each equivalent to about 1 g of clindamycin. The usual adult oral dose is 150 to 300 mg every 6 hours; in severe infections the dose may be increased to 450 mg every 6 hours.

Clindamycin is given **parenterally** as the phosphate by intramuscular injection or by intermittent or continuous intravenous infusion over 10 minutes to 1 hour. Doses are again expressed in terms of the base; 1.2 g of clindamycin phosphate is equivalent to about 1 g of clindamycin. For intravenous use, the concentration of clindamycin in diluent for infusion should not exceed 18 mg/mL and the rate of infusion should be not more

than 30 mg/minute. Not more than 1.2 g should be given as a single one-hour infusion, and not more than 600 mg should be given as a single intramuscular injection.

The usual parenteral dose is the equivalent of 0.6 to 1.2 g of clindamycin daily in divided doses; in severe infections the dose may be increased to 2.7 g daily and up to 4.8 g daily may be given intravenously in life-threatening situations.

For *prophylaxis* in adult patients at risk of developing endocarditis and who cannot be given a penicillin, an oral dose of clindamycin 600 mg, given 1 hour before procedures such as dental extractions under local or no anaesthesia, has been suggested. For high-risk patients undergoing dental procedures involving general anaesthesia and who cannot be given a penicillin, clindamycin 300 mg given intravenously over at least 10 minutes, at induction or 15 minutes before the procedure, has been suggested. However in the UK the *BNF* and NICE now suggest that such prophylaxis is unnecessary (see p.168).

For details of doses in children, including infants and adolescents, see below.

Topical formulations containing clindamycin phosphate equivalent to 1% of clindamycin are used for the treatment of acne. The hydrochloride may be applied similarly, but systemic absorption may be greater (see Pharmacokinetics, above). Clindamycin phosphate is also available in combination preparations with benzoyl peroxide and tretinoin.

Clindamycin phosphate may be given **intravaginally** as pessaries or as a 2% cream for the treatment of bacterial vaginosis; the equivalent of about 100 mg of clindamycin is given at night for 3 to 7 days.

Administration. A number of studies have suggested that a parenteral regimen of clindamycin 600 mg three times daily is as effective as giving the same dose four times daily,[1] or as giving 900 mg three times daily.[2,3]

1. Buchwald D, *et al.* Effect of hospitalwide change in clindamycin dosing schedule on clinical outcome. *Rev Infect Dis* 1989; **11:** 619–24.
2. Chin A, *et al.* Cost analysis of two clindamycin dosing regimens. *DICP Ann Pharmacother* 1989; **23:** 980–3.
3. Chatwani A, *et al.* Clindamycin dosage scheduling for acute pelvic infection. *Am J Obstet Gynecol* 1990; **163:** 240.

SUBCONJUNCTIVAL ROUTE. It has been suggested, should periocular use of clindamycin be necessary, that the injection solution can be given in doses of 15 to 50 mg by subconjunctival injection.[1]

1. Moorfields Eye Hospital NHS Foundation Trust. *Pharmacists Handbook 2006*. London: Moorfields Pharmaceuticals, 2006.

Administration in children. The usual oral dose for infants and children under 12 years of age is the equivalent of 3 to 6 mg/kg of clindamycin every 6 hours. In the UK, the *BNFC* suggests that neonates aged under 14 days may be given this dose every 8 hours and children aged 1 month and over but weighing less than 10 kg should be given a minimum dose of 37.5 mg every 8 hours; children over 12 years of age may be given the usual adult dose (see above).

The usual parenteral dose for infants and children aged from 1 month to 12 years is the equivalent of 15 to 25 mg/kg of clindamycin daily in 3 or 4 divided doses; in severe infections the dose may be increased to 40 mg/kg daily and a minimum dose of 300 mg daily should be given regardless of body-weight. Children over 12 years of age may be given the usual adult dose (see above). In the USA, it is also licensed for parenteral use in those aged under 1 month and 15 to 20 mg/kg daily may be given in 3 or 4 divided doses. It should be borne in mind that some parenteral formulations contain benzyl alcohol which may cause fatal 'gasping syndrome' in neonates (see p.1632).

For the treatment of staphylococcal lung infection in children aged from 1 month to 18 years with cystic fibrosis, the *BNFC* recommends oral doses of 5 to 7 mg/kg (to a maximum of 600 mg) every 6 hours.

For children's doses in babesiosis, malaria, and toxoplasmosis, see below.

Babesiosis. Clindamycin, given with quinine, both for 7 to 10 days, is recommended by some experts in the USA[1,2] for the treatment of babesiosis (p.823) caused by *Babesia microti*. Dosage regimens include:

- clindamycin 1.2 g intravenously twice daily, with quinine 650 mg three or four times daily by mouth
- clindamycin 300 to 600 mg intravenously every 6 hours, with quinine as above
- clindamycin 600 mg orally three times daily, with quinine as above

Children may be given clindamycin 20 to 40 mg/kg daily intravenously or by mouth in 3 or 4 divided doses with quinine 25 mg/kg daily by mouth in 3 divided doses, both for 7 to 10 days.

1. Abramowicz M, ed. *Drugs for parasitic infections*. 1st ed. New Rochelle NY: The Medical Letter, 2007.
2. Wormser GP, *et al.* The clinical assessment, treatment, and prevention of Lyme disease, human granulocytic anaplasmosis, and babesiosis: clinical practice guidelines by the Infectious Diseases Society of America. *Clin Infect Dis* 2006; **43:** 1089–1134. Correction. *ibid.* 2007; **45:** 941. Also available at: http://www.journals.uchicago.edu/doi/pdf/10.1086/508667 (accessed 11/08/08)

Malaria. Quinine sulfate plus follow-on treatment with doxycycline, tetracycline, or clindamycin are recommended regimens for the treatment of chloroquine-resistant falciparum malaria (p.594) in non-endemic malaria areas. Doxycycline is generally preferred because it can be given once daily. However, tetracyclines are contra-indicated in children under 8 years of age and in pregnant women, who may be given clindamycin. Clindamycin is given in the usual *adult* dose of 20 mg/kg daily in 3 divided doses (or 450 mg 3 times daily) for 7 days with quinine sulfate 600 to 650 mg 3 times daily for 3 to 7 days, both orally.[1-5] Parenteral quinine (or quinidine) plus follow-on treatment with a tetracycline or clindamycin may be used for severe falciparum malaria in both endemic and non-endemic malaria areas.[2-5] Patients unable to tolerate oral treatment may begin follow-on therapy intravenously.[2,3]

In the UK[5] public health authorities recommend that *children* be given clindamycin at a dose of 7 to 13 mg/kg 3 times daily for 7 days; US[2] public health authorities recommend giving 20 mg/kg daily in 3 divided doses.

1. Abramowicz M, ed. *Drugs for parasitic infections*. 1st ed. New Rochelle NY: The Medical Letter, 2007.
2. CDC. Treatment guidelines: treatment of malaria (guidelines for clinicians) (issued 28th June 2004, updated 6th March 2007). Available at: http://www.cdc.gov/malaria/pdf/clinicalguidance.pdf (accessed 28/03/07)
3. British Infection Society. Algorithm for initial assessment and management of malaria in adults (issued February 2007). Available at: http://www.britishinfectionsociety.org/documents/MalariaAlgorithm07.pdf (accessed 20/06/07)
4. WHO. *Guidelines for the treatment of malaria*. Geneva: WHO, 2006. Available at: http://www.who.int/malaria/docs/TreatmentGuidelines2006.pdf (accessed 28/03/07)
5. Lalloo DG, *et al.* HPA Advisory Committee on Malaria Prevention in UK Travellers. UK malaria treatment guidelines. *J Infect* 2007; **54:** 111–21.

Pneumocystis pneumonia. Clindamycin may be used with primaquine as an alternative to co-trimoxazole for the **treatment** of pneumocystis pneumonia (p.521). In the USA, some experts[1,2] recommend giving clindamycin 600 to 900 mg intravenously, or 300 to 450 mg orally, every 6 to 8 hours with primaquine 15 to 30 mg by mouth once daily, both for 21 days. In the UK the *BNF* suggests giving clindamycin 600 mg every 8 hours with primaquine 30 mg daily, both by mouth, for mild to moderate disease (but notes that this combination is associated with considerable toxicity).

A meta-analysis[3] of literature published between January 1975 to August 1999 found that, when compared with other salvage agents (such as atovaquone, co-trimoxazole, eflornithine, pentamidine, and trimetrexate), clindamycin with primaquine was the most effective regimen in patients unresponsive to conventional treatment. The authors also concluded that this latter regimen was effective as primary treatment of mild to moderately severe disease and suggested that it had fewer adverse effects than co-trimoxazole.

Clindamycin with primaquine is not normally recommended for **prophylaxis** although there are reports of it being tried.[4] A retrospective examination[5] of the records of patients who had received prophylaxis found that clindamycin with primaquine was less effective than co-trimoxazole or dapsone, although this could have been due in part to underdosing.

1. Abramowicz M, ed. *Drugs for parasitic infections*. 1st ed. New Rochelle NY: The Medical Letter, 2007.
2. CDC. Treating opportunistic infections among HIV-infected adults and adolescents: recommendations from CDC, the National Institutes of Health, and the HIV Medicine Association/Infectious Diseases Society of America. *MMWR* 2004; **53** (RR-15): 1–112. Also available at: http://www.cdc.gov/mmwr/PDF/RR/RR5315.pdf (accessed 14/05/07) Correction. *MMWR* 2005; **54:** 311. [dose of amphotericin B/flucytosine for C. neoformans meningitis] Also available at: http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5412a10.htm (accessed 14/05/07)
3. Smego RA, *et al.* A meta-analysis of salvage therapy for Pneumocystis carinii pneumonia. *Arch Intern Med* 2001; **161:** 1529–33.
4. Kay R, DuBois RE. Clindamycin/primaquine therapy and secondary prophylaxis against Pneumocystis carinii pneumonia in patients with AIDS. *South Med J* 1990; **83:** 403–4.
5. Barber BA, *et al.* Clindamycin/primaquine as prophylaxis for Pneumocystis carinii pneumonia. *Clin Infect Dis* 1996; **23:** 718–22.

Rosacea. Topical clindamycin[1] has improved inflammatory episodes of rosacea (p.1583), although other features of the skin disorder may not respond. A small study[2] showed that once-daily application of clindamycin 1% plus benzoyl peroxide 5% was effective in the treatment of moderate to severe rosacea.

1. Wilkin JK, DeWitt S. Treatment of rosacea: topical clindamycin versus oral tetracycline. *Int J Dermatol* 1993; **32:** 65–7.
2. Breneman D, *et al.* Double-blind, randomized, vehicle-controlled clinical trial of once-daily benzoyl peroxide/clindamycin topical gel in the treatment of patients with moderate to severe rosacea. *Int J Dermatol* 2004; **43:** 381–7.

Toxoplasmosis. Clindamycin with pyrimethamine has been used for the treatment and secondary prophylaxis (chronic maintenance) of toxoplasmosis (p.826) instead of the more usual treatment with pyrimethamine plus sulfadiazine, in patients unable to tolerate sulfonamides; folinic acid is also given to counteract the megaloblastic anaemia associated with pyrimethamine. In adult patients with AIDS and toxoplasmic encephalitis, clindamycin 600 mg every 6 hours orally or intravenously for at least 6 weeks, then maintenance therapy with 300 to 450 mg every 6 to 8 hours by mouth, has been recommended in the USA.[1] Children may be given clindamycin 5 to 7.5 mg/kg 4 times daily by mouth or intravenously for at least 6 weeks, followed by chronic maintenance therapy.[2]

Other studies found acute therapy with pyrimethamine and clindamycin, 600 mg 4 times daily by mouth[3] or 1200 mg every 6 hours intravenously,[4] to be as effective as pyrimethamine and sulfadiazine, but oral maintenance therapy with pyrimethamine and clindamycin 300 mg 4 times daily was less effective than pyrimethamine and sulfadiazine at preventing relapses in a population followed for 3 years or more.[3] Clindamycin with fluorouracil produced beneficial responses in a study involving 16 patients.[5]

In contrast, another study, comparing clindamycin alone (in lower oral doses—300 mg twice daily) with pyrimethamine alone for prophylaxis of toxoplasmic encephalitis, reported an unacceptably high incidence of adverse effects with clindamycin, which forced premature termination of the clindamycin arm—see AIDS under Precautions, above.

1. CDC. Treating opportunistic infections among HIV-infected adults and adolescents: recommendations from CDC, the National Institutes of Health, and the HIV Medicine Association/Infectious Diseases Society of America. *MMWR* 2004; **53** (RR-15): 1–112. Also available at: http://www.cdc.gov/mmwr/PDF/RR/RR5315.pdf (accessed 14/05/07) Correction. *MMWR* 2005; **54:** 311. [dose of amphotericin B/flucytosine for C. neoformans meningitis] Also available at: http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5412a10.htm (accessed 14/05/07)
2. CDC. Treating opportunistic infections among HIV-exposed and infected children: recommendations from CDC, the National Institutes of Health, and the Infectious Diseases Society of America. *MMWR* 2004; **53** (RR-14): 1–63. Also available at: http://www.cdc.gov/mmwr/PDF/RR/RR5314.pdf (accessed 14/05/07)
3. Katlama C, *et al.* Pyrimethamine-clindamycin vs pyrimethamine-sulphadiazine as acute and long-term therapy for toxoplasmic encephalitis in patients with AIDS. *Clin Infect Dis* 1996; **22:** 268–75.
4. Dannemann B, *et al.* Treatment of toxoplasmic encephalitis in patients with AIDS: a randomized trial comparing pyrimethamine plus clindamycin to pyrimethamine plus sulfadiazine. *Ann Intern Med* 1992; **116:** 33–43.
5. Dhiver C, *et al.* 5-Fluoro-uracil-clindamycin for treatment of cerebral toxoplasmosis. *AIDS* 1993; **7:** 143–4.

Preparations

BP 2008: Clindamycin Capsules; Clindamycin Injection;
USP 31: Clindamycin for Injection; Clindamycin Hydrochloride Capsules; Clindamycin Hydrochloride Oral Solution; Clindamycin Injection; Clindamycin Palmitate Hydrochloride for Oral Solution; Clindamycin Phosphate Gel; Clindamycin Phosphate Topical Solution; Clindamycin Phosphate Topical Suspension; Clindamycin Phosphate Vaginal Cream; Clindamycin Phosphate Vaginal Inserts.

Proprietary Preparations (details are given in Part 3)

Arg.: Acnestop; Clidan; Clindacin; Clindalaf; Clindopax; Clintopic; Dalacin C; Dalacin ST; Dalacin†; Naxoclinda; Torgyn; ***Austral.:*** Cleocin; Clindatech; Dalacin C; Dalacin T; Dalacin V; ***Austria:*** Cleocin; Clidam†; Clindac; Dalacin; Lanacine; ***Belg.:*** Dalacin; Dalacin C; Zindaclin; ***Braz.:*** Anaerocid; Clinagel; Clindacin†; Clindacne; Clindamin C; Clindarix; Dalacin C; Dalacin T; Dalacin V; ***Canad.:*** Clindets; Dalacin C; Dalacin T; Dalacin Vaginal; ***Chile:*** Clidets; Cluvax; Daclin; Dalacin; Dalacin C; Dalacin T; Dalacin V; Dermabel; Divanon; Lexis†; ***Cz.:*** Dalacin; Dalacin C; Dalacin T; Klimicin; Zindaclin; ***Denm.:*** Dalacin; ***Fin.:*** Dalacin; Klindagol; ***Fr.:*** Dalacine; Dalacine T; Zindacline; ***Ger.:*** Aclinda†; Basocin; Clin-Sanorania; Clinda; Clinda-saar; Clindabeta; Clindahexal; Clindastad; Dentomycin; Jutaclin; Sobelin; Turimycin; Zindaclin; ***Gr.:*** Arfarel; Borophen; Botamycin-N; Clidacin; Climycen; Clindagel; Dalacin C; Edason†; Fouch; Lindasol†; Paradis; Sotomycin; Toliken; Upderm; Vagiclin; Veldom; Velkaderm; Ygielle; ***Hong Kong:*** Claribel; Clinac; Clindatech; Dalacin C; Dalacin T; Delta T; Feminosan†; Qualiclinda; Topicil†; ***Hung.:*** Dalacin; Dalacin C; Dalacin T; Klimicin; ***India:*** Clindac A; Dalacin; Dalcap; ***Indon.:*** Albiotin; Anerocid; Biodasin; Cindala; Climadan; Clinbercin; Clindexcin; Clinidac; Clinika; Clinium; Clinjos; Clinmas; Comdasin; Dacin; Daclin; Dalacin C; Ethidan; Indanox; Lando; Librodan; Lindacyn; Lindan; Mediklin; Niladacin; Nufaclind; Opiclam; Probiotin; Prolic; Zumatic; ***Irl.:*** Dalacin; Dalacin C; Dalacin T; Zindaclin; ***Israel:*** Dalacin C; Dalacin Vaginal; Dalagis T; Zindaclin; ***Ital.:*** Cleocin; Dalacin C; Dalacin T; ***Malaysia:*** C-Mycin†; Clindac; Dalacin C; Dalacin T; T3Mycin; Tidact; Topicil; Zindaclin; ***Mex.:*** Ancine; Apomiclin; Biodaclin; Cigmadil; Clendazaf; Clidets; Clinamsa; Clindazyn; Cutaclin; Dalacin C; Dalacin T; Dalacin V; Dalatina; Dalatina V; Damiclin; Destralina; Feisclin; Galecin; Indamid; Klyndaken; Lindacil; Lisiken; Losertrin; Trexen; Ulmicy; ***Neth.:*** Dalacin C; Dalacin T; ***Norw.:*** Dalacin; ***NZ:*** Clinac†; Dalacin C; Dalacin T†; Topicil; ***Philipp.:*** Anerocin; Clindal; Clindatech; Cliz; Dalacin C; Inprosyn-HP; Lincyn; Myclin; Tidact; Zindal; ***Pol.:*** Clindacin; Clindacne; Clindo; Dalacin C; Dalacin T; Klimicin; Klindacin T; Zindaclin; ***Port.:*** Clincina; Dalacin C; Dalacin T; Dalacin V; Zindaclin; ***Rus.:*** Clindacin (Клиндацин); Dalacin (Далацин); Dalacin C (Далацин Ц)†; Klimicin (Климицин); ***S.Afr.:*** Clindac; Clindahexal; Dalacin C; Dalacin T; Dalacin VC; ***Singapore:*** C-Mycin†; Climadan†; Clindagel; Clindatech; Dalacin C; Dalacin T; T3Mycin; Tidact; Topicil; Zindaclin; ***Spain:*** Clinwas; Dalacin; Zindaclin; ***Swed.:*** Dalacin; ***Switz.:*** Dalacin C; Dalacin T; Dalacin V; ***Thai.:*** Chinacin-T; Clindalin; Clindavid; Clinott; Dacin-F; Dalacin C; Dalacin T; Klimicin; Klindan; Klinna; Lacin; Rosil; ***Turk.:*** Cleocin T; Clin; Klindan; Klindaver; Klinoksin; Klitopsin; Meneklin; ***UK:*** Dalacin; Dalacin C; Dalacin T; Zindaclin; ***USA:*** Cleoc-

in; Cleocin T; Clindagel; ClindaMax; Clindesse; Clindets; Evoclin; ***Venez.:*** Bioclindax; Clindaval; Clindox; Clinfol; Dalacin; Felisep†.

Multi-ingredient: ***Arg.:*** Clindacur; Clindoxyl; CP-Acne; Dermaclean; Duo Clindacin; Ovogin; Perclin; Torgyn Duo; ***Austral.:*** Duac; ***Austria:*** Clindoxyl; ***Braz.:*** Clindoxyl; ***Canad.:*** Benzaclin; Clindoxyl; ***Chile:*** Indoxyl; Klina; ***Cz.:*** Duac; ***Ger.:*** Copal; ***Gr.:*** Indoxyl; ***Hong Kong:*** Duac; ***India:*** Deriva-C; ***Indon.:*** Benzolac Cl; Climadan; Medi-Klin TR; ***Irl.:*** Duac; ***Mex.:*** Benzaclin; Clindapack; Femisan; Gynoclin-V; Indoxyl; Trexen Duo; ***Neth.:*** Duac; ***NZ:*** Duac; ***Pol.:*** Duac; ***Port.:*** Duac; ***Spain:*** Duac; ***Swed.:*** Duac; ***Turk.:*** Cleocin; ***UK:*** Duac Once Daily; ***USA:*** Benzaclin; Duac; Ziana.

Clioquinol *(BAN, rINN)*

Chinoform; Chloroiodoquine; Cliochinolum; Clioquinolum; Iodochlorhydroxyquin; Iodochlorhydroxyquinoline; Kliochinol; Kliokinol; Kliokinoli; Kliokvinolis; PBT-1; Quiniodochlor. 5-Chloro-7-iodoquinolin-8-ol.

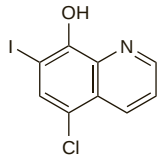
Клиохинол

C_9H_5ClINO = 305.5.

CAS — 130-26-7.

ATC — D08AH30; D09AA10; G01AC02; P01AA02; S02AA05.

ATC Vet — QD08AH30; QD09AA10; QG01AC02; QS02AA05.



Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), and *US.*

Ph. Eur. 6.2 (Clioquinol). An almost white, light yellow, brownish-yellow, or yellowish-grey powder. Practically insoluble in water; very slightly soluble or slightly soluble in alcohol; sparingly soluble in dichloromethane. Protect from light.

USP 31 (Clioquinol). A voluminous, spongy, yellowish-white to brownish-yellow powder having a slight characteristic odour. It darkens on exposure to light. Practically insoluble in water; soluble 1 in 3500 of alcohol, 1 in 120 of chloroform, and 1 in 4500 of ether; soluble in hot ethyl acetate and in hot glacial acetic acid. Store in airtight containers. Protect from light.

Adverse Effects and Precautions

Clioquinol may rarely cause iodism in sensitive patients. Local application of clioquinol in ointments or creams may occasionally cause severe irritation or hypersensitivity and there may be cross-sensitivity with other halogenated hydroxyquinolines.

Clioquinol stains clothing and linen yellow on contact and may stain the skin and discolour fair hair.

Clioquinol given by mouth has been associated with severe neurotoxicity. In Japan, the epidemic development of subacute myelo-opticoneuropathy (SMON) in the 1960s was associated with the ingestion of normal or high doses of clioquinol for prolonged periods, and the sale of clioquinol and related hydroxyquinolines was subsequently banned there. Symptoms of SMON are principally those of peripheral neuropathy, including optic atrophy, and myelopathy. Abdominal pain and diarrhoea often precede neurological symptoms, such as paraesthesias in the legs progressing to paraplegia in some patients, and loss of visual acuity sometimes leading to blindness. A characteristic green pigment, a chelate of clioquinol with iron, is often seen on the tongue and in the urine and faeces. Cerebral disturbances, including confusion and retrograde amnesia, have also been reported. Although many patients improved when clioquinol was withdrawn, others had residual disablement.

It was suggested that the Japanese epidemic might be due to genetic susceptibility, but a few similar cases of SMON associated with clioquinol or related hydroxyquinoline derivatives, such as broxyquinoline or diiodohydroxyquinoline have been reported from other countries. Oral preparations of clioquinol have now been banned in most countries.

Hypersensitivity. Clioquinol is classified as a contact allergen which can commonly cause sensitisation, especially when applied to eczematous skin; chlorquinaldol can also cause sensitisation, although less frequently.[1] It is important to include clioquinol and chlorquinaldol in routine patch testing since the clinical reaction may be relatively mild and sensitivity easily missed, particularly in the presence of a corticosteroid which suppresses or attenuates the reaction.

1. Anonymous. Skin sensitisers in topical corticosteroids. *Drug Ther Bull* 1986; **24:** 57–9.

Topical application. Absorption of clioquinol through the skin has been noted on topical application.[1,2] The Committee on Drugs of the American Academy of Pediatrics[3] considered that there was a potential risk of toxicity to infants and children from clioquinol and diiodohydroxyquinoline applied topically. Since alternative effective preparations are available for dermatitis, the Committee recommended that products containing either of these compounds should not be used.

1. Fischer T, Hartvig P. Skin absorption of 8-hydroxyquinolines. *Lancet* 1977; **i:** 603.
2. Stohs SJ, *et al.* Percutaneous absorption of iodochlorhydroxyquin in humans. *J Invest Dermatol* 1984; **82:** 195–8.
3. Kauffman RE, *et al.* Clioquinol (iodochlorhydroxyquin, Vioform) and iodoquinol (diiodohydroxyquin): blindness and neuropathy. *Pediatrics* 1990; **86:** 797–8.

Uses and Administration

Clioquinol is a halogenated hydroxyquinoline with antibacterial and antifungal activity and is used in creams and ointments, usually containing 3%, in the treatment of skin infections. It is applied with a corticosteroid in inflammatory skin conditions complicated by bacterial or fungal infections. It is also used in ear drops for otitis externa. The treatment of bacterial and of fungal skin infections is described on p.194 and p.521 respectively.

For a discussion of the risks from topical application of clioquinol, see Adverse Effects and Precautions, above.

Clioquinol was formerly given by mouth in the treatment of intestinal amoebiasis. It was also formerly used for the prophylaxis and treatment of traveller's diarrhoea and similar infections but was of doubtful value. Oral preparations have now been withdrawn because of neurotoxicity (see Adverse Effects and Precautions, above). However, clioquinol by mouth has been investigated for its action as a chelator of copper and zinc in the treatment of Alzheimer's disease (see below).

Alzheimer's disease. A systematic review[1] to evaluate the efficacy of metal protein attenuating compounds, such as clioquinol, for the treatment of cognitive impairment due to Alzheimer's disease, evaluated only one small randomised controlled study comparing clioquinol and placebo; no significant differences were found. Further studies with clioquinol have now been stopped, but studies are on-going with a successor compound, PBT2.

1. Sampson E, *et al.* Metal protein attenuating compounds for the treatment of Alzheimer's disease. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2008 (accessed 14/05/08).

Preparations

BP 2008: Betamethasone and Clioquinol Cream; Betamethasone and Clioquinol Ointment; Hydrocortisone and Clioquinol Cream; Hydrocortisone and Clioquinol Ointment;
USP 31: Clioquinol and Hydrocortisone Cream; Clioquinol and Hydrocortisone Ointment; Clioquinol Cream; Clioquinol Ointment; Compound Clioquinol Topical Powder.

Proprietary Preparations (details are given in Part 3)

Ger.: Linola-sept; ***Hung.:*** Linola-sept†; ***India:*** Dermoquinol; Entero-Quinol; Entrozyme Plain; ***Mex.:*** Bagton; Bionder-C; Cortifung-C; Lasalar-Y Simple; Luzolona Simple; Nolil; Quindoleina†; Vioformo; ***Port.:*** Quinodermil†.

Multi-ingredient: ***Arg.:*** Betnovate-C; Locorten Vioformo†; Quadriderm†; ***Austral.:*** Hydroform; Locacorten Vioform; Quinaband†; ***Austria:*** Betnovate-C; Locacorten Vioform; ***Belg.:*** Betnelan-VC†; Locacortene Vioforme†; ***Braz.:*** Betnovate-Q; Cremederme; Dreniformio; Hidrocorte; Locorten Vioformio; Permut; Policderms; Predmicin; Quadriderm; Quadrikin; Quadrilon; Quadriplus; Qualiderm; Tetraderm; Vioformio-Hidrocortisona; ***Canad.:*** Locacorten Vioform; Phenoris; Vioform-Hydrocortisone; ***Cz.:*** Lorinden C†; Prednisolon J†; ***Denm.:*** Betnovat med Chinoform; Celeston med Chinoform; Locacorten Vioform; Synalar med Chinoform; ***Fin.:*** Bemetson-K; Betnovat-C; Celestoderm cum Chinoform†; Locacorten Vioform; ***Fr.:*** Diprosept†; Locacortene Vioforme; ***Ger.:*** Locacorten Vioform; ***Gr.:*** Betnovate-C; Myco-Synalar; ***Hong Kong:*** Betnovate-C†; Clobeta-G; Dermafacte; Quadriderm; ***Hung.:*** Lorinden C; Prednisolon J; ***India:*** Beclate-C; Betnederm C; Betnovate-C; Cortoquinol; Fourderm; Millicorten-Vioform; Polyderm†; Quiss; ***Indon.:*** Benoson V; Krimbeson; Viohydrocort; Visancort; ***Irl.:*** Betnovate-C; Synalar C†; Vioform-Hydrocortisone; ***Israel:*** Betnovate-C; Topicorten V; ***Ital.:*** Diproform; Locorten; Locorten Vioformio; ***Mex.:*** Bentix; Cetoquina Y; Clio-Betnovate; Cliooderm-H; Contefur†; Cortifung-Y; Cortilona Compuesta; Dealan; Diprosone Y; Ditayod; Farmacorti YC; Fluccinol C†; Flunal†; Lasalar-Y; Luzolona Y; Sebryl; Sebryl Plus; Sebstopp; Solfurol; Sultroquin†; Suyodil; Synalar C; Taliviform†; Topsyn-Y; Trilor†; Ultracortin; Vioformo-Cort; Yderm; Yodozona; ***Neth.:*** Locacorten Vioform; ***Norw.:*** Betnovat med Chinoform; Synalar med Chinoform; ***NZ:*** Betnovate-C; Locorten Vioform; ***Philipp.:*** Aplosyn C; Betnovate-C; Dermalin; Diproform; Quadriderm; Quadrotopic; ***Pol.:*** Betnovate-C; Lorinden C; Viosept; ***Port.:*** Betnovate-C; Dexaval V; Locorten Vioformio†; Quinodermil-AS; ***Rus.:*** Dermosolon (Дермозолон); Lorinden C (Лоринден С); ***S.Afr.:*** Betnovate-C; Cortoderm-C; Locacorten Vioform; Quadriderm; Synalar C; ***Singapore:*** Dermanol-C; Hydroderm-C; Quadriderm†; ***Spain:*** Cuatroderm; Menaderm Clio; Menaderm Otologico; Synobel†; ***Swed.:*** Betnovat med Chinoform; Celeston valerat med chinoform; Locacorten Vioform; ***Switz.:*** Betnovate-C; Quadriderm; ***Thai.:*** Banocin; Beta-C; Betnovate-C; Betosone-CE; Chlorotracin; Endothalyl; Genquin; ***Turk.:*** Betnovate-C; Locacortene Vioform; Prednol-A; ***UK:*** Betnovate-C; Locorten Vioform; Quinaband†; Synalar C; Vioform-Hydrocortisone; ***USA:*** I + I-F; Corque; Hysone; ***Venez.:*** Dermosupril C; Diproformo; Locorten Vioformo; Neo-Synalar con Yodoclorohidroxiquina†; Propioformo†; Quadriderm; Tridetarmon; Vio Celestoderm†.

Clofazimine *(BAN, USAN, rINN)*

B-663; Clofazimina; Clofaziminum; G-30320; Klofatsimiini; Klofatzimin; Klofazimin; Klofaziminas; NSC-141046. 3-(4-Chloroanilino)-10-(4-chlorophenyl)-2,10-dihydro-2-phenazin-2-ylideneisopropylamine.

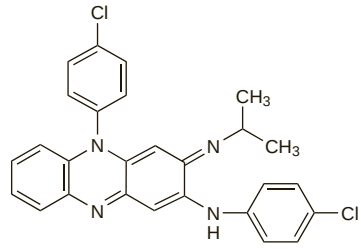
Клофазимин

$C_{27}H_{22}Cl_2N_4$ = 473.4.

CAS — 2030-63-9.

ATC — J04BA01.

ATC Vet — QJ04BA01.



Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), *Int.*, and *US.*

Ph. Eur. 6.2 (Clofazimine). A fine reddish-brown powder. It exhibits polymorphism. Practically insoluble in water; very slightly soluble in alcohol; soluble in dichloromethane.

USP 31 (Clofazimine). Dark red crystals. Practically insoluble in water; sparingly soluble in alcohol, in acetone, and in ethyl acetate; soluble in chloroform and in benzene. Store in airtight containers. Protect from light.

Adverse Effects

Adverse effects to clofazimine are dose related, the most common being red to brown discoloration of the skin especially on areas exposed to sunlight; leprotic lesions may become mauve to black. These changes are more noticeable in light-skinned people and may limit its acceptance. The conjunctiva and cornea may also show some signs of red to brown pigmentation. The generalised discoloration may take months to years to disappear after stopping therapy. Discoloration of hair, tears, sweat, sputum, breast milk, urine, and faeces may occur, as may nail discoloration with high doses of 300 mg daily. Severe depression related to skin discoloration has been reported rarely.

Gastrointestinal effects are uncommon for doses of clofazimine less than 100 mg daily and usually are not severe. Symptoms of nausea, vomiting, and abdominal pain experienced shortly after the start of treatment may be due to direct irritation of the gastrointestinal tract and such symptoms usually disappear on dose reduction. Use of doses of 300 mg daily or more for several months sometimes produces abdominal pain, diarrhoea, weight loss, gastrointestinal bleeding, and in severe cases the small bowel may become oedematous and symptoms of bowel obstruction may develop. This may be due to deposition of crystals of clofazimine in the wall of the small bowel and in the mesenteric lymph nodes. Crystal deposition may also occur in other organs including the liver and spleen and there have been rare reports of splenic infarction. Symptoms usually regress on withdrawal of treatment although fatalities have been reported.

Clofazimine may produce a dryness of the skin and ichthyosis as well as decreased sweat production and rashes. Pruritus, acneiform eruptions, and photosensitivity reactions have also been reported.

Eye irritation and decreased tear production may occur.

Headache, drowsiness, dizziness, taste disorders, and elevation of blood glucose levels have been reported rarely.

Incidence of adverse effects. The incidence of adverse effects was reviewed in 65 patients[1] who were receiving, or had received, clofazimine in weekly doses of either 700 mg or less as antimycobacterial therapy, or more than 700 mg as anti-inflammatory therapy. Length of treatment ranged from 1 to 83 months. Adverse effects on the skin included discoloration (20% of patients), pigmentation (64.6%), dry skin (35.4%), and pruritus (5%). Ocular adverse effects were conjunctival pigmentation (49.2%), subjective dimness of vision (12.3%), and dry eyes, burning, and other ocular irritation (24.6%). Gastrointestinal adverse effects included abdominal pain (33.8%), nausea (9.2%), diarrhoea (9.2%), and weight loss, vomiting, or loss of appetite (13.8%). The different dose regimens for antimycobacterial therapy or anti-inflammatory effect had similar incidences of adverse effects. Skin pigmentation in 8 patients disappeared on average 8.5 months after stopping therapy with clofazimine, the maximum time required being one year. Adverse effects of clofazimine were considered to be well tolerated.

In another report covering 540 patients receiving clofazimine 100 mg on alternate days or 300 mg daily, the most common adverse effect was skin pigmentation, which occurred in 77.8% of