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.

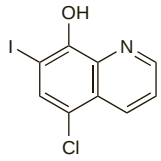
Клиохинол

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.

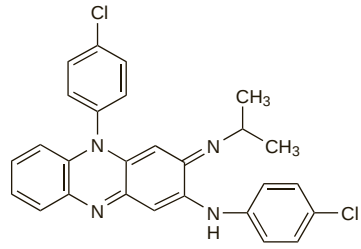
Клофазимин

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