Clocortolone Pivalate *(USAN, rINNM)* ⊗

CL-68; Clocortolone, Pivalate de; Clocortoloni Pivalas; Pivalato de clocortolona; SH-863. 9α-Chloro-6α-fluoro-11β,21-dihydroxy-16α-methylpregna-1,4-diene-3,20-dione 21-pivalate.

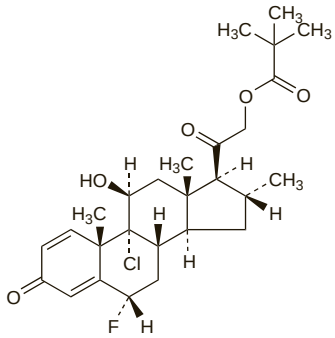
Клокортолона Пивалат

$C_{27}H_{36}ClFO_5$ = 495.0.

CAS — 4828-27-7 (clocortolone); 34097-16-0 (clocortolone pivalate).

ATC — D07AB21.

ATC Vet — QD07AB21.



Pharmacopoeias. In *US*.

USP 31 (Clocortolone Pivalate). A white to yellowish-white, odourless powder. Sparingly soluble in alcohol; soluble in acetone; freely soluble in chloroform and in dioxan; slightly soluble in ether and in benzene. Store in airtight containers. Protect from light.

Profile

Clocortolone pivalate is a corticosteroid used topically for its glucocorticoid activity (p.1490), as a 0.1% cream or ointment, in the treatment of various skin disorders. Clocortolone caproate has been used with the pivalate.

When applied topically, particularly to large areas, where the skin is broken, or under occlusive dressings, corticosteroids may be absorbed in sufficient amounts to cause systemic effects (p.1490). The effects of topical corticosteroids on the skin are described on p.1492. For recommendations concerning the correct use of corticosteroids on the skin, see p.1497.

Preparations

USP 31: Clocortolone Pivalate Cream.

Proprietary Preparations (details are given in Part 3)
Austria: Glimbal; ***Ger.:*** Kaban; Kabanimat; ***USA:*** Cloderm.

Multi-ingredient: ***Ger.:*** Corto-Tavegil†; Crino-Kaban N†; Procto-Kaban†.

Cloprednol *(BAN, USAN, rINN)* ⊗

Cloprednolum; RS-4691. 6-Chloro-11β,17α,21-trihydroxypregna-1,4,6-triene-3,20-dione.

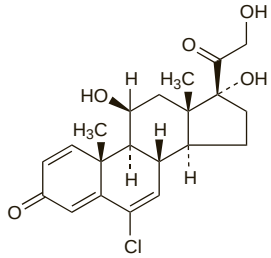
Клопреднол

$C_{21}H_{25}ClO_5$ = 392.9.

CAS — 5251-34-3.

ATC — H02AB14.

ATC Vet — QH02AB14.



Profile

Cloprednol is a corticosteroid with mainly glucocorticoid activity (p.1490); the anti-inflammatory activity of 2.5 mg of cloprednol is equivalent to about 5 mg of prednisolone. Cloprednol is given orally in various disorders for which corticosteroid therapy is helpful (p.1495), in usual doses ranging from 1.25 to 12.5 mg daily.

Preparations

Proprietary Preparations (details are given in Part 3)
Ger.: Syntestan.

Corticorelin *(rINN)* ⊗

Corticoliberin; Corticorelina; Corticoréline; Corticorelinum; Corticotrophin-releasing Hormone; Corticotropin-releasing Factor; CRF; CRH; HLC; Hormona liberadora de corticotropina.

Кортикорелин

$C_{208}H_{344}N_{60}O_{63}S_2$ = 4757.5 (human);
$C_{205}H_{339}N_{59}O_{63}S$ = 4670.3 (ovine).

CAS — 86784-80-7 (corticorelin (human)); 79804-71-0 (corticorelin (ovine)).

ATC — V04CD04.

ATC Vet — QV04CD04.

Corticorelin Triflutate *(rINNM)* ⊗

Corticorelin Trifluoroacetate; Corticoréline, Triflutate de; Corticorelini Triflutas; Triflutato de corticorelina.

Кортикорелина Трифлутат

$C_{205}H_{339}N_{59}O_{63}S.xC_2HF_3O_2$ (ovine).

CAS — 121249-14-7 (corticorelin ovine triflutate).

ATC — V04CD04.

ATC Vet — QV04CD04.

NOTE. Corticorelin Ovine Triflutate is *USAN*.

Adverse Effects

Flushing of the face, neck, and upper chest, and mild dyspnoea may follow intravenous injection of corticorelin, and last for about 3 to 5 minutes. Prolonged flushing, tachycardia, hypotension, and chest tightness have been reported after large doses.

Effects on the cardiovascular system. Loss of consciousness, lasting for 10 seconds to 5 minutes, occurred in 3 patients, 2 of whom had Cushing's disease and one who had secondary adrenal insufficiency, after intravenous injection of corticorelin 200 micrograms.[1] The 2 patients with Cushing's disease had a slight accompanying fall in blood pressure. In a fourth patient, receiving corticosteroid and thyroid hormone replacement therapy, injection of corticorelin was associated with a sharp fall in systolic blood pressure and subsequent asystole. These serious adverse effects were not noted by others[2,3] and were variously attributed to impurities,[2] high dosage,[2] vasovagal syncope,[3] or to the fact that the corticorelin used in the study was of ovine rather than human origin.[3] The authors of the original study[1] have since stated[4] that lowering of the dose from 200 micrograms given intravenously over 10 seconds to 100 micrograms over 60 seconds has stopped serious adverse effects but that ovine corticorelin was still preferred because of its longer duration of action and lower incidence of hypotensive adverse effects. There has, however, been a further report of chest pain accompanied by a fall in blood pressure in a patient receiving corticorelin at a dose of 100 micrograms.[5]

1. Hermus A, *et al.* Serious reactions to corticotropin-releasing factor. *Lancet* 1983; **i:** 776.
2. Schulte HM, *et al.* Safety of corticotropin-releasing factor. *Lancet* 1983; **i:** 1222.
3. Oppermann D. Safety of human and ovine corticotropin-releasing hormone. *Lancet* 1986; **ii:** 1031–2.
4. Hermus ARMM, *et al.* Safety of human and ovine corticotropin-releasing hormone. *Lancet* 1986; **ii:** 1032–3.
5. Paloma VC, *et al.* Chest pain after intravenous corticotropin-releasing hormone. *Lancet* 1989; **i:** 222.

Uses and Administration

Corticorelin is a polypeptide hypothalamic releasing hormone that stimulates the release of corticotropin (p.1523) from the anterior pituitary. It is used in the differential diagnosis of Cushing's syndrome (p.2344) and other adrenal disorders. Corticorelin is usually given as the triflutate, but doses are expressed in terms of corticorelin (human or ovine). A single dose of 100 micrograms, or of 1 microgram/kg, is given by intravenous injection over 30 seconds. Higher and more rapid doses have been used but may be associated with an increased risk of adverse effects (see above).

Corticorelin acetate is under investigation in cerebral oedema.

Administration. Corticorelin was well absorbed after subcutaneous injection and bioavailability was calculated to be about 60 to 70%; absorption was slower with high doses, suggesting that it may be a saturable process. Given the retention of bioactivity, the subcutaneous route was considered an attractive alternative to intravenous use.[1]

1. Angst MS, *et al.* Pharmacokinetics, cortisol release, and hemodynamics after intravenous and subcutaneous injection of human corticotropin-releasing factor in humans. *Clin Pharmacol Ther* 1998; **64:** 499–510.

Diagnosis and testing. Corticorelin may be used in the diagnosis of adrenal disorders including Cushing's syndrome (p.2344). In the initial diagnosis of Cushing's syndrome, a dexamethasone-corticorelin test may be used to identify pseudo-Cushing's conditions such as depression or alcoholism in patients with mild hypercortisolism and equivocal results on other diagnostic tests. This combination is reportedly more accurate than either alone,[1] but it is cumbersome and difficult to carry out on an ambulatory basis.[2]

When a diagnosis of ACTH-dependent Cushing's syndrome has been established, corticorelin may be used for differential diagnosis of the subtype. Patients with pituitary Cushing's syndrome have an exaggerated increase in plasma-corticotropin and plasma-cortisol concentrations in response to corticorelin, whereas those with adrenal or ectopic syndrome generally have no response.[3,4] The corticorelin stimulation test is of comparable diagnostic efficacy to the dexamethasone suppression test,[5,6] although false results have been obtained with both tests.[2,5,7] Again, a combination of the dexamethasone and corticorelin tests is reportedly more accurate than either alone.[6] The most reliable test to distinguish between pituitary and nonpituitary forms of Cushing's syndrome is to measure the difference between central and peripheral concentrations of ACTH after giving corticorelin.[2] However, this requires sampling of central (petrosal) venous blood, an invasive procedure needing considerable expertise.

1. Yanovski JA, *et al.* Corticotropin-releasing hormone stimulation following low-dose dexamethasone administration: a new test to distinguish Cushing's syndrome from pseudo-Cushing's states. *JAMA* 1993; **269:** 2232–8.
2. Raff H, Findling JW. A physiologic approach to diagnosis of the Cushing syndrome. *Ann Intern Med* 2003; **138:** 980–91.
3. Chrousos GP, *et al.* The corticotropin-releasing factor stimulation test: an aid in the evaluation of patients with Cushing's syndrome. *N Engl J Med* 1984; **310:** 622–6.
4. Newell-Price J, *et al.* Optimal response criteria for the human CRH test in the differential diagnosis of ACTH-dependent Cushing's syndrome. *J Clin Endocrinol Metab* 2002; **87:** 1640–5.
5. Hermus AR, *et al.* The corticotropin-releasing-hormone test versus the high-dose dexamethasone test in the differential diagnosis of Cushing's syndrome. *Lancet* 1986; **ii:** 540–4.
6. Nieman LK, *et al.* The ovine corticotropin-releasing hormone stimulation test and the dexamethasone suppression test in the differential diagnosis of Cushing's syndrome. *Ann Intern Med* 1986; **105:** 862–7.
7. Arnaldi G, *et al.* Diagnosis and complications of Cushing's syndrome: a consensus statement. *J Clin Endocrinol Metab* 2003; **88:** 5593–5602.

Preparations

Proprietary Preparations (details are given in Part 3)
Austria: CRH; ***Fr.:*** Stimu-ACTH; ***Ger.:*** Cortirel; CRH; ***Neth.:*** CRH; ***USA:*** Acthrel.

Corticotropin *(BAN, rINN)* ⊗

ACTH; Adrenocorticotrophic Hormone; Adrenocorticotrophin; Corticotrophin; Corticotropina; Corticotropine; Corticotropinum; Kortikotropiini; Kortikotropin.

Кортикотропин

CAS — 9002-60-2 (corticotropin); 9050-75-3 (corticotropin zinc hydroxide); 8049-55-6 (corticotropin zinc hydroxide).

ATC — H01AA01.

ATC Vet — QH01AA01.

Pharmacopoeias. In *US* as preparations for injection.

Units

5 units of porcine corticotropin for bioassay are contained in about 50 micrograms (with lactose 5 mg) in one ampoule of the third International Standard (1962).

Adverse Effects

Corticotropin stimulates the adrenals to produce cortisol (hydrocortisone) and mineralocorticoids; it therefore has the potential to produce similar adverse glucocorticoid and mineralocorticoid effects to those of the corticosteroids (see p.1490). In particular, its mineralocorticoid properties can produce marked sodium and water retention; considerable potassium loss may also occur.

Corticotropin can induce sensitisation, and severe hypersensitivity reactions, including anaphylaxis, may occur. This is generally considered to be due to the porcine component of the peptide.

Whereas corticosteroids replace endogenous cortisol (hydrocortisone) and thereby induce adrenal atrophy, corticotropin's stimulant effect induces hypertrophy. Nevertheless, the ability of the hypothalamic-pituitary-adrenal axis to respond to stress is still reduced, and abrupt withdrawal of corticotropin may result in symptoms of adrenal insufficiency (see Withdrawal, below).

◊ Reports of adverse effects in children given corticotropin for infantile spasms.

1. Riikonen R, Donner M. ACTH therapy in infantile spasms: side effects. *Arch Dis Child* 1980; **55:** 664–72.
2. Hanefeld F, *et al.* Renal and pancreatic calcification during treatment of infantile spasms with ACTH. *Lancet* 1984; **i:** 901.
3. Riikonen R, *et al.* Disturbed calcium and phosphate homeostasis during treatment with ACTH of infantile spasms. *Arch Dis Child* 1986; **61:** 671–6.
4. Perheentupa J, *et al.* Adrenocortical hyporesponsiveness after treatment with ACTH of infantile spasms. *Arch Dis Child* 1986; **61:** 750–3.

Withdrawal
Corticotropin use may depress the hypothalamic-pituitary-adrenal axis. Abrupt withdrawal of corticotropin may therefore produce adrenocortical and pituitary unresponsiveness, and therapy should be stopped gradually. An increase in corticosteroid requirements associated with the stress of infection, or accidental or surgical trauma, may also precipitate acute adrenocortical insufficiency. See also Withdrawal under Corticosteroids, p.1493.

Precautions
As for Corticosteroids, p.1493.

Phaeochromocytoma. A hypertensive crisis in a patient given intravenous tetracosactide led to the discovery of an adrenaline-secreting phaeochromocytoma in a patient.[1] It was suggested that caution should be observed when using corticotropin in patients with orthostatic hypotension in whom the diagnosis of phaeochromocytoma has not been excluded.

1. Jan T, *et al*. Epinephrine-producing pheochromocytoma with hypertensive crisis after corticotropin injection. *Am J Med* 1990; **89:** 824–5.

Interactions
Interactions seen with corticotropin are liable to be similar to those with corticosteroids (p.1494).

Uses and Administration
Corticotropin is a naturally occurring hormone of the anterior lobe of the pituitary gland. It stimulates the adrenal glands to secrete adrenocortical hormones, especially cortisol (hydrocortisone), some mineralocorticoids such as corticosterone, and, to a lesser extent, androgens. It has little effect on aldosterone secretion, which proceeds independently.

Secretion of corticotropin by the functioning pituitary gland is controlled by the release of corticorelin from the hypothalamus and is also regulated by a negative feedback mechanism involving concentrations of circulating glucocorticoids. Conditions of stress may also stimulate secretion.

Corticotropin may be used diagnostically to investigate adrenocortical insufficiency. It has also been used therapeutically in most of the conditions (with the exception of the adrenal deficiency states and adrenocortical overactivity) for which systemic corticosteroid therapy is indicated (p.1495). Such use is now fairly limited. However, corticotropin may be used in certain neurological disorders such as infantile spasms and multiple sclerosis. The synthetic polypeptide tetracosactide (p.1543), which has the same amino-acid sequence as the first 24 residues of human corticotropin, may be used as an alternative. Tosactide is another polypeptide analogue of corticotropin; it has the same sequence as the first 28 residues.

Corticotropin has been available for injection in two forms. One form is a plain injection that may be given by the subcutaneous, intramuscular, or intravenous routes. The other form is a long-acting depot preparation in which the viscosity is increased by the addition of gelatin, and which is given subcutaneously or intramuscularly; it must not be given intravenously. Individual responses to therapeutic corticotropin vary considerably and doses must be adjusted accordingly.

For *diagnostic purposes* the corticotropin test is based on the measurement of plasma-cortisol concentrations before and after injection. The plain preparation is used in doses of 10 to 25 units in 500 mL of glucose 5% infused intravenously over 8 hours.

For *therapeutic purposes* typical initial doses for the depot preparation have been about 20 to 80 units every 24 to 72 hours by the subcutaneous or the intramuscular route. As soon as possible the dosage should be reduced gradually to the minimum necessary to control symptoms.

A depot preparation of corticotropin combined with zinc hydroxide for intramuscular injection has been used in the past.

Epilepsy. The use of corticotropin in the management of infantile spasms is referred to under Epilepsy in Corticosteroids, p.1503.

Multiple sclerosis. Short-term courses of corticotropin have been used to speed recovery from acute exacerbations of multiple sclerosis (p.892) but corticosteroids, usually methylprednisolone, are now preferred.

Post-dural puncture headache. There are anecdotal reports of the relief of post-dural puncture headache by corticotropin or tetracosactide, but a controlled study of tetracosactide use found no benefit (see p.1544).

Preparations
USP 31: Corticotropin for Injection; Corticotropin Injection; Corticotropin Zinc Hydroxide Injectable Suspension; Repository Corticotropin Injection.

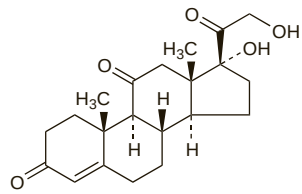
Proprietary Preparations (details are given in Part 3)
Arg.: Acthelea; ***Irl.:*** Acthar†; ***USA:*** Acthar.

Cortisone Acetate *(BANM, rINNM)* ⊗

Acetato de cortisona; Compound E Acetate; Cortisone, acétate de; Cortisoni acetas; 11-Dehydro-17-hydroxycorticosterone Acetate; Kortisonacetat; Kortison-acetát; Kortisoniasetaatti; Kortizon-acetát; Kortizono acetatas; Kortyzonu octan. 17α,21-Dihydroxypregn-4-ene-3,11,20-trione 21-acetate.

Кортизона Ацетат

$C_{23}H_{30}O_6$ = 402.5.
CAS — 53-06-5 (cortisone); 50-04-4 (cortisone acetate).
ATC — H02AB10; S01BA03.
ATC Vet — QH02AB10; QS01BA03.



(cortisone)

Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), *Jpn*, *US*, and *Viet.*
Ph. Eur. 6.2 (Cortisone Acetate). A white or almost white, crystalline powder. It shows polymorphism. Practically insoluble in water; slightly soluble in alcohol and in methyl alcohol; sparingly soluble in acetone; freely soluble in dichloromethane; soluble in dioxan. Protect from light.
USP 31 (Cortisone Acetate). A white or practically white, odourless, crystalline powder. Insoluble in water; soluble 1 in 350 of alcohol, 1 in 75 of acetone, 1 in 4 of chloroform, and 1 in 30 of dioxan. Store at a temperature of 25°, excursions permitted between 15° and 30°.

Adverse Effects, Treatment, Withdrawal, and Precautions
As for corticosteroids in general (see p.1490).

Interactions
The interactions of corticosteroids in general are described on p.1494.

Pharmacokinetics
For a brief outline of the pharmacokinetics of corticosteroids, see p.1495.

Cortisone acetate is readily absorbed from the gastrointestinal tract and the cortisone is rapidly converted in the liver to its active metabolite, hydrocortisone (cortisol). The biological half-life of cortisone itself is only about 30 minutes. Absorption of cortisone acetate from intramuscular sites is considerably slower than after oral doses.

Uses and Administration
Cortisone is a corticosteroid secreted by the adrenal cortex. It has glucocorticoid activity (p.1490), as well as appreciable mineralocorticoid activity; 25 mg of cortisone acetate is equivalent in anti-inflammatory activity to about 5 mg of prednisolone.

Cortisone acetate is rapidly effective when given orally, and more slowly by intramuscular injection.

Cortisone acetate has been used mainly for replacement therapy in adrenocortical insufficiency (p.1498), but hydrocortisone (p.1535) is generally preferred since cortisone itself is inactive and must be converted by the liver to hydrocortisone, its active metabolite; hence, in some liver disorders the activity of cortisone may be less reliable. Doses of cortisone acetate for oral replacement therapy are 12.5 to 37.5 mg daily in divided doses, with fludrocortisone if additional mineralocorticoid activity is required.

Cortisone acetate has been used in the treatment of many of the allergic and inflammatory disorders for which corticosteroid therapy is helpful (p.1495) but prednisolone or other synthetic glucocorticoids are generally preferred. Doses of cortisone acetate employed have generally ranged from about 25 to 300 mg daily by mouth or by intramuscular injection.

Preparations
BP 2008: Cortisone Tablets;
USP 31: Cortisone Acetate Injectable Suspension; Cortisone Acetate Tablets.

Proprietary Preparations (details are given in Part 3)
Austral.: Cortate; ***Belg.:*** Adreson†; ***Canad.:*** Cortone†; ***Ital.:*** Cortone; ***Neth.:*** Adreson†; ***S.Afr.:*** Cortogen†; ***UK:*** Cortisyl; ***USA:*** Cortone.

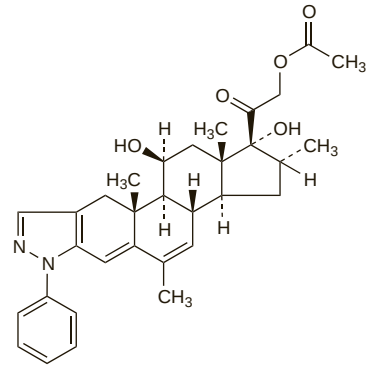
Multi-ingredient: ***Braz.:*** Corciclen; ***Spain:*** Blefarida; Gingilone.

Cortivazol *(USAN, pINN)* ⊗

Cortivazolum; H-3625; MK-650; NSC-80998. 11β,17α,21-Trihydroxy-6,16α-dimethyl-2′-phenyl-2′*H*-pregna-2,4,6-trieno[3,2-*c*]pyrazol-20-one 21-acetate.

Кортивазол

$C_{32}H_{38}N_2O_5$ = 530.7.
CAS — 1110-40-3.
ATC — H02AB17.
ATC Vet — QH02AB17.



Profile
Cortivazol is a corticosteroid with mainly glucocorticoid activity (p.1490); 300 micrograms of cortivazol is equivalent in anti-inflammatory activity to about 5 mg of prednisolone. It is given in the treatment of musculoskeletal and joint disorders by intra-articular, periarticular, or epidural injection in doses of about 1.25 to 3.75 mg, according to the size of the joint, usually at intervals of 1 to 3 weeks. It has also been given by mouth.

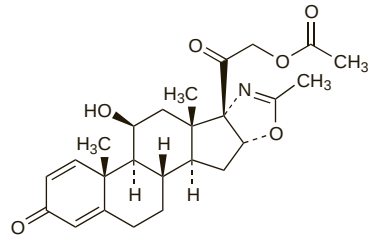
Preparations
Proprietary Preparations (details are given in Part 3)
Fr.: Altim.

Deflazacort *(BAN, USAN, rINN)* ⊗

Azacort; Deflatsakorti; Déflazacort; Deflazacortum; Deflazakort; DL-458-IT; L-5458; MDL-458; Oxazacort. 11β,21-Dihydroxy-2′-methyl-5′β*H*-pregna-1,4-dieno[17,16-*d*]oxazole-3,20-dione 21-acetate.

Дефлазакорт

$C_{25}H_{31}NO_6$ = 441.5.
CAS — 14484-47-0.
ATC — H02AB13.
ATC Vet — QH02AB13.



Profile
Deflazacort is a corticosteroid with mainly glucocorticoid activity (p.1490); 6 mg of deflazacort is reportedly equivalent in anti-inflammatory activity to about 5 mg of prednisolone (but see Action, below).

Deflazacort is used for its anti-inflammatory and immunosuppressant properties in conditions responsive to corticosteroid therapy (p.1495). It is given in initial oral doses of up to 120 mg