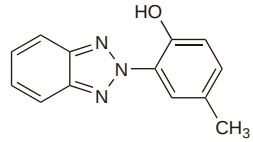
Drometrizole *(USAN, rINN)*

Drométrizol; Drometrizol; Drometrizolum. 2-(2*H*-Benzotriazol-2-yl)-*p*-cresol.

Дрометризол

$C_{13}H_{11}N_3O$ = 225.2.

CAS — 2440-22-4.



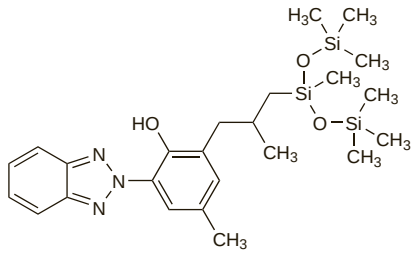
Drometrizole Trisiloxane

2-(2*H*-Benzotriazol-2-yl)-4-methyl-6-(2-methyl-3-{1,3,3,3-tetramethyl-1-[(trimethylsilyl)oxy]-1-disiloxanyl}propyl)phenol.

Дрометризола Трисилоксан

$C_{24}H_{39}N_3O_3Si_3$ = 501.8.

CAS — 155633-54-8.



NOTE. Mexoryl XL and Silatrizole are trade names that have been used for drometrizole trisiloxane.

Profile

Drometrizole trisiloxane is used as a sunscreen (p.1576). It is effective against UVA light (for definitions, see p.1580).

Preparations

Proprietary Preparations some preparations are listed in Part 3.

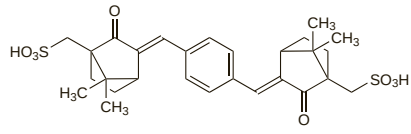
Ecamsule *(USAN, rINN)*

Ecamsul; Écamsule; Ecamsulum. (±)-(3*E*,3′*E*)-3,3′-(*p*-Phenylenedimethylidyne)bis[2-oxo-10-bornanesulfonic acid]; Terephthalylidene-3,3′-dicamphor-10,10′-disulfonic acid.

Экамсул

$C_{28}H_{34}O_8S_2$ = 562.7.

CAS — 92761-26-7.



NOTE. Mexoryl SX is a trade name that has been used for ecamsule.

Profile

Ecamsule, a camphorsulfonic acid derivative, is used as a sunscreen (p.1576). It is effective against UVA light (for definitions, see p.1580).

Preparations

Proprietary Preparations some preparations are listed in Part 3.

Efalizumab *(USAN, rINN)*

Anti-CD11a; Éfalizumab; Efalizumabum; Hu-1124. Immunoglobulin G1, anti-(human antigen CD11a)(human-mouse monoclonal hu1124 γ1-chain), disulfide with human-mouse monoclonal hu1124 light chain, dimer.

Эфализумаб

CAS — 214745-43-4.

ATC — L04AA21.

ATC Vet — QL04AA21.

Adverse Effects and Precautions

The most common adverse affects associated with efalizumab are flu-like symptoms including chills, fever, headache, myalgia, and nausea. These reactions are dose-related in both incidence and severity and usually occur within two days after the first two injections. Other adverse effects include acne, back pain, and an elevation in alkaline phosphatase concentrations. More serious adverse effects of efalizumab include arthritis, interstitial pneumonitis, hypersensitivity reactions, inflammatory polyradiculoneuropathy, and thrombocytopenia. Treatment should be stopped in patients who develop such reactions. Severe haemolytic anaemia, diagnosed 4 to 6 months after the start of efalizumab treatment, has been reported. Treatment should be stopped immediately if haemolytic anaemia occurs. Asymptomatic leucocytosis or lymphocytosis commonly occurs during treatment. Worsening of psoriasis or development of variant forms (pustular, erythrodermic, or guttate) have been reported during and after stopping efalizumab therapy.

As a result of immunosuppression, patients given efalizumab are at increased risk of infection, and might be at increased risk of developing malignancies. It should not be given to patients with pre-existing serious infection and should be used with care in patients with a history of recurring infection or malignancy. Response to vaccines may also be reduced and acellular, live, and live-attenuated vaccines should not be given during efalizumab treatment.

Assessment of the platelet count is advised before starting therapy and monthly during early treatment. Frequency of monitoring may be decreased with ongoing treatment.

Incidence of adverse effects. The safety data from 13 controlled and open-label studies of efalizumab in psoriasis have been analysed.[1] During the first 12 weeks of therapy the most common events in patients treated with efalizumab were headache, fever, chills, nausea, vomiting, or myalgia, starting within 48 hours of dosing. In 4 controlled studies that included 1620 patients treated with efalizumab and 715 with placebo, about a third of efalizumab-treated patients reported headache, while chills, nausea, and pain occurred in around 10%, and fever and myalgia in about 8%. These events usually occurred with the first 1 or 2 doses of efalizumab but by the third and subsequent doses the incidence was similar to that in the placebo group. Atypical or unusual worsening of psoriasis, and the development of variant forms, particularly guttate psoriasis, were reported in 3.2% of patients treated with efalizumab; other forms included psoriatic erythroderma, inverse psoriasis, palmoplantar psoriasis, and pustular psoriasis. In 5 studies of extended therapy for 13 to 60 weeks (1115 patients treated for 13 to 24 weeks and 228 for 60 weeks) the rate of adverse effects remained low, there was no new pattern of serious adverse effects, and there was no evidence of cumulative toxicity. An analysis of infection risk found similar rates of mild to moderate and serious infections in patients treated with either efalizumab or placebo. Nevertheless, efalizumab should not be used in patients with pre-existing serious infection. Anti-efalizumab antibodies were found in 67 of 1063 patients, but there was no apparent effect on efficacy, safety, or pharmacodynamics.

There have been infrequent reports of new onset or recurrent severe arthritis, including psoriatic arthritis, in patients treated with efalizumab. Separate analyses[1,2] of pooled study data both found that the incidence of arthropathy events was low (less than 4%) and similar for patients treated with either efalizumab or placebo. However, there was some suggestion[2] that patients with a history of arthropathy and those who have a poor clinical response to efalizumab may be at higher risk.

1. Papp KA, *et al.* Safety of efalizumab in patients with moderate to severe chronic plaque psoriasis: review of clinical data. *J Cutan Med Surg* 2005; **9:** 313–23.
2. Pincelli C, *et al.* The incidence of arthropathy adverse events in efalizumab-treated patients is low and similar to placebo and does not increase with long-term treatment: pooled analysis of data from phase III clinical trials of efalizumab. *Arch Dermatol Res* 2006; **298:** 329–38.

Carcinogenicity. Efalizumab is an immunosuppressant and as such might increase the risk of malignancy. An analysis[1] of pooled data from clinical studies that included 2980 patients given efalizumab found 51 patients (1.7%) with 67 malignancies. Most cases were of non-melanoma skin cancer (51 cases in 35 patients) and it was found that many had risk factors for skin cancer. Other cases included 3 lymphomas, 12 solid tumours at various sites, and 1 malignant melanoma. However, when compared with patients given placebo and data from 2 external cohorts of psoriasis patients (to allow for the increased risk of skin cancers seen in psoriasis patients compared with the general population) there was no evidence that efalizumab increased the risk of developing a malignancy. Nevertheless, further data are needed to determine whether efalizumab has any long-term effect on the development of malignancies.

1. Leonardi CL, *et al.* A review of malignancies observed during efalizumab (Raptiva) clinical trials for plaque psoriasis. *Dermatology* 2006; **213:** 204–14.

Effects on the blood. Thrombocytopenia has been described in 6 patients given efalizumab.[1] In 5 cases it started 8 to 12 weeks after starting weekly efalizumab. In all cases the platelet counts recovered quickly after efalizumab was stopped; in 5 cases corticosteroids were also given. In another case a woman presented with pancytopenia 4 weeks after starting efalizumab therapy.[2] Efalizumab was stopped and the patient treated with granulocyte colony-stimulating factor, normal immunoglobulin, oral prednisone, platelet transfusion, and darbepoetin alfa. Cell counts returned to normal limits within 4 weeks.

1. Warkentin TE, Kwon P. Immune thrombocytopenia associated with efalizumab therapy for psoriasis. *Ann Intern Med* 2005; **143:** 761–3.
2. Tom WL, *et al.* Efalizumab-induced autoimmune pancytopenia. *Br J Dermatol* 2006; **155:** 1045–7.

Interactions

For a warning concerning the use of live vaccines in patients receiving efalizumab see Adverse Effects and Precautions, above.

Pharmacokinetics

Peak plasma concentrations of efalizumab are reached about 1 to 2 days after subcutaneous injection, with a bioavailability of about 50%. Steady state is reached at week 4 of weekly dosing. Efalizumab is metabolised by intracellular degradation. It is cleared by non-linear saturable elimination and the time to elimination after the last dose is about 25 days.

◊ References.

1. Mortensen DL, *et al.* Pharmacokinetics and pharmacodynamics of multiple weekly subcutaneous efalizumab doses in patients with plaque psoriasis. *J Clin Pharmacol* 2005; **45:** 286–98.
2. Sun Y-N, *et al.* Population pharmacokinetics of efalizumab (humanized monoclonal anti-CD11a antibody) following long-term subcutaneous weekly dosing in psoriasis subjects. *J Clin Pharmacol* 2005; **45:** 468–76.
3. Joshi A, *et al.* An overview of the pharmacokinetics and pharmacodynamics of efalizumab: a monoclonal antibody approved for use in psoriasis. *J Clin Pharmacol* 2006; **46:** 10–20.

Uses and Administration

Efalizumab is a humanised monoclonal antibody that binds to human CD11a on leucocytes to inhibit the activation of T-lymphocytes. It is used for the treatment of chronic moderate to severe plaque psoriasis (p.1583) in patients aged 18 years and over. Efalizumab is given by subcutaneous injection. The initial dose is 700 micrograms/kg, followed by a weekly dose of 1 mg/kg; a single dose should not exceed 200 mg. Treatment is given for 12 weeks, then continued in those who have responded.

◊ References.

1. Lebwohl M, *et al.* A novel targeted T-cell modulator, efalizumab, for plaque psoriasis. *N Engl J Med* 2003; **349:** 2004–13.
2. Gordon KB, *et al.* Efalizumab for patients with moderate to severe plaque psoriasis: a randomized controlled trial. *JAMA* 2003; **290:** 3073–80. Correction. *ibid.* 2004; **291:** 1070.
3. Menter A, *et al.* Efficacy and safety observed during 24 weeks of efalizumab therapy in patients with moderate to severe plaque psoriasis. *Arch Dermatol* 2005; **141:** 31–8.
4. Leonardi CL, *et al.* Extended efalizumab therapy improves chronic plaque psoriasis: results from a randomized phase III trial. *J Am Acad Dermatol* 2005; **52:** 425–33.
5. Wellington K, Perry CM. Efalizumab. *Am J Clin Dermatol* 2005; **6:** 113–20.
6. Jordan JK. Efalizumab for the treatment of moderate to severe plaque psoriasis. *Ann Pharmacother* 2005; **39:** 1476–82.
7. Menter A, *et al.* Long-term management of plaque psoriasis with continuous efalizumab therapy. *J Am Acad Dermatol* 2006; **54** (suppl 1): S182–S188.
8. Dubertret L, *et al.* Clinical experience acquired with the efalizumab (Raptiva) (CLEAR) trial in patients with moderate-to-severe plaque psoriasis: results from a phase III international randomized, placebo-controlled trial. *Br J Dermatol* 2006; **155:** 170–81.

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Raptiva; ***Austral.:*** Raptiva; ***Braz.:*** Raptiva; ***Canad.:*** Raptiva; ***Cz.:*** Raptiva; ***Denm.:*** Raptiva; ***Fin.:*** Raptiva; ***Fr.:*** Raptiva; ***Ger.:*** Raptiva; ***Gr.:*** Raptiva; ***Hong Kong:*** Raptiva; ***Irl.:*** Raptiva; ***Ital.:*** Raptiva; ***Malaysia:*** Raptiva; ***Mex.:*** Raptiva; ***Neth.:*** Raptiva; ***Norw.:*** Raptiva; ***NZ:*** Raptiva; ***Port.:*** Raptiva; ***Singapore:*** Raptiva; ***Spain:*** Raptiva; ***Swed.:*** Raptiva; ***Switz.:*** Raptiva; ***UK:*** Raptiva; ***USA:*** Raptiva.

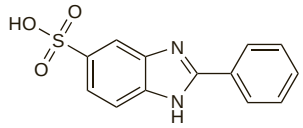
Ensulizole *(USAN, rINN)*

Ensulizol; Ensulizolum; Phenylbenzimidazole Sulphonic Acid. 2-Phenyl-1*H*-benzimidazole-5-sulphonic acid.

Энсулизол

$C_{13}H_{10}N_2O_3S$ = 274.3.

CAS — 27503-81-7.



NOTE. Eusolex 232 and Neo-Heliopan Hydro are trade names that have been used for ensulizole.

Pharmacopoeias. In *US.*

USP 31 (Ensulizole). A white to ivory-coloured, odourless powder. Practically insoluble in water and in oily solvents; soluble in alcohol; its salts are freely soluble in water. Store in airtight containers at a temperature of 8° to 15°.

Profile

Ensulizole is used topically as a sunscreen (p.1576). It is effective against UVB light (for definitions, see p.1580).

Preparations

Proprietary Preparations some preparations are listed in Part 3.

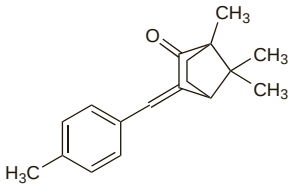
Enzacamene *(USAN, rINN)*

Enzacamène; Enzacameno; Enzacamenum; Methyl Benzylidene Camphor; 3-(4-Methylbenzylidene)bornan-2-one; 3-(4-Methylbenzylidene)camphor. 1,7,7-Trimethyl-3-[(4-methylphenyl)methylene]bicyclo[2.2.1]heptan-2-one.

Энзакамен

$C_{18}H_{22}O$ = 254.4.

CAS — 36861-47-9 (D,L-form); 38102-62-4 (form unspecified).



NOTE. Eusolex 6300, Neo-Heliopan MBC, and Parsol 5000 are trade names that have been used for enzacamene.

Pharmacopoeias. In *US.*

USP 31 (Enzacamene). A white, fine crystalline powder. M.p. between 66° and 68°. Practically insoluble in water; freely soluble in alcohol; very soluble in chloroform. Store in airtight containers.

Profile

Enzacamene is a camphor derivative used as a sunscreen (p.1576). It is effective against UVB light (for definitions, see p.1580).

Preparations

Proprietary Preparations numerous preparations are listed in Part 3.

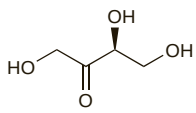
Erythrulose

DL-Glycero-tetrulose. 1,3,4-Trihydroxy-2-butanone.

Эритрулаза

$C_4H_8O_4$ = 120.1.

CAS — 40031-31-0 (DL-erythrulose); 496-55-9 (D-erythrulose); 533-50-6 (L-erythrulose).



Profile

Application to the skin of preparations containing L-erythrulose slowly produces a brown coloration similar to that caused by exposure to the sun, probably due to a reaction with the amino acids of the skin. It is often used with dihydroxyacetone (p.1594) in artificial suntan preparations. Recommended concentrations are up to 5% when used alone or up to 4% with dihydroxyacetone.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: Braz.: Sunmax Autobronzeador; ***UK:*** ViTicolor.

Etretinate *(BAN, USAN, rINN)*

Etretinaatti; Etretinat; Étrétinate; Etretinato; Etretinatum; Ro-10-9359. Ethyl 3-methoxy-15-apo-ϕ-caroten-15-oate; Ethyl (*all-trans*)-9-(4-methoxy-2,3,6-trimethylphenyl)-3,7-dimethylnona-2,4,6,8-tetra-enoate.

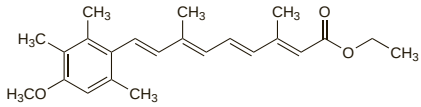
Этретинат

$C_{23}H_{30}O_3$ = 354.5.

CAS — 54350-48-0.

ATC — D05BB01.

ATC Vet — QD05BB01.



Adverse Effects and Precautions

As for Isotretinoin, p.1599.

Donation of blood should be avoided for at least 2 years after cessation of treatment. The period of time during which pregnancy must be avoided after stopping treatment has not been determined; detectable plasma-etretinate concentrations have been reported nearly 3 years after the last dose.

◊ In addition to the references cited below, further references to the adverse effects of etretinate can be found in Isotretinoin, p.1599, under Effects on the Blood, Cardiovascular System, Eyes, Liver, Musculoskeletal System, Serum Lipids, and the Skin, as well as under Vasculitic Syndromes.

Carcinogenicity. A report of 2 patients who developed lymphomas while receiving etretinate[1] prompted a report of 3 other malignancies in patients taking etretinate.[2]

1. Woll PJ, *et al.* Lymphoma in patients taking etretinate. *Lancet* 1987; **ii:** 563–4.
2. Harrison PV. Retinoids and malignancy. *Lancet* 1987; **ii:** 801.

Effects on the kidneys. Rare cases of impaired renal function associated with etretinate have been described.[1,2] In one report[1] it was also noted that in manufacturer-sponsored studies the mean serum-creatinine concentration had been raised in patients receiving etretinate.

1. Horber FF, *et al.* Impaired renal function and hypercalcaemia associated with etretinate. *Lancet* 1984; **ii:** 1093.
2. Cribier B, *et al.* Renal impairment probably induced by etretinate. *Dermatology* 1992; **185:** 266–8.

Oedema. A report of generalised oedema after treatment with etretinate.[1] Five other cases had been reported in the literature and rechallenge in 4 patients had provoked a recurrence. Generalised oedema as part of the capillary leak syndrome has been reported with acitretin (p.1586).

1. Allan S, Christmas T. Severe edema associated with etretinate. *J Am Acad Dermatol* 1988; **19:** 140.

Pregnancy. For further information on the teratogenicity of etretinate, see under Acitretin, p.1586.

Interactions

As for Isotretinoin, p.1602.

Anticoagulants. Etretinate has been reported to reduce the therapeutic efficacy of *warfarin* (see p.1430).

Antiepileptics. Etretinate was ineffective and none of its characteristic mucocutaneous adverse effects occurred in a patient with pityriasis rubra pilaris who was already taking *carbamazepine* and *valproate* for epilepsy. However, there was a clinical response after the carbamazepine had been withdrawn, suggesting that it may have reduced the bioavailability or increased the metabolism of etretinate.[1]

1. Mohammed KN. Unresponsiveness to etretinate during anticonvulsant therapy. *Dermatology* 1992; **185:** 79.

Antineoplastics. The risk of developing hepatotoxicity may be increased when etretinate is used with *methotrexate* (see Retinoids, p.748).

Hormonal contraceptives. For discussion of the potential interactions of retinoids with oral hormonal contraceptives, and the effect this might have on contraceptive choice during retinoid treatment, see p.2068.

Pharmacokinetics

The mean bioavailability of etretinate is about 40% after oral doses but there is a large interindividual variation. Absorption can be increased if taken with milk or fatty food. Etretinate undergoes significant first-pass metabolism and plasma concentrations of the active carboxylic acid metabolite, acitretin (p.1586), may be detected before those of the parent drug; acitretin may itself be metabolised to etretinate (see p.1586). Both etretinate and acitretin are extensively bound to plasma protein. Etretinate appears to accumulate in adipose tissue after repeated dosing and has a prolonged elimination half-life of about 120 days; detectable serum concentrations have been observed up to 3 years after stopping therapy. Up to 75% of a dose is excreted in the faeces mainly as unchanged drug. Etretinate is also excreted in the urine as metabolites. Etretinate crosses the placenta. Although it is not known whether etretinate is distributed into breast milk, this would be expected because of its lipophilicity; acitretin, a metabolite of etretinate, has been found in breast milk when it was given to a lactating woman (see p.1586).

◊ References.

1. Lucek RW, Colburn WA. Clinical pharmacokinetics of the retinoids. *Clin Pharmacokinet* 1985; **10:** 38–62.
2. DiGiovanna JJ, *et al.* Etretinate: persistent serum levels after long-term therapy. *Arch Dermatol* 1989; **125:** 246–51.
3. Larsen FG. Pharmacokinetics of etretinate and acitretin with special reference to treatment of psoriasis. *Acta Derm Venereol (Stockh)* 1994; **190** (suppl): 1–33.
4. Wiegand UW, Chou RC. Pharmacokinetics of acitretin and etretinate. *J Am Acad Dermatol* 1998; **39** (suppl): S25–S33.

Uses and Administration

Etretinate is a retinoid and is a derivative of tretinoin (p.1618). It has been given orally for the treatment of severe, extensive psoriasis that has not responded to other treatment, especially generalised and palmo-plantar pustular psoriasis. It has also been used in severe congenital ichthyosis, severe Darier's disease (keratosis follicularis) as well as other disorders of keratinisation, and oral lichen planus. Acitretin (p.1586) is now preferred to etretinate.

Therapy is generally started at doses of 0.75 to 1 mg/kg daily in divided oral doses. A maximum dose of 1.5 mg/kg daily should not be exceeded (some licensed product information has suggested a maximum of 75 mg daily). Erythrodermic psoriasis may respond to lower initial doses of 250 micrograms/kg daily, increased at weekly intervals by 250 micrograms/kg daily until optimal response occurs. After the initial response, generally after 8 to 16 weeks of therapy, maintenance doses of 500 to 750 micrograms/kg daily have been given. Therapy should be stopped once lesions have sufficiently resolved.

◊ References.

1. Magis NLJ, *et al.* The treatment of psoriasis with etretinate and acitretin: a follow up of actual use. *Eur J Dermatol* 2000; **10:** 517–21.
2. Katugampola RP, Finlay AY. Oral retinoid therapy for disorders of keratinization: single-centre retrospective 25 years' experience on 23 patients. *Br J Dermatol* 2006; **154:** 267–76.

Preparations

Proprietary Preparations (details are given in Part 3)

Jpn: Tigason.

Fumaric Acid

Acidum Fumaricum; Allomalenic Acid; Boletic Acid; E297; Fumárico, ácido; Kwas fumarowy. *trans*-Butenedioic acid.

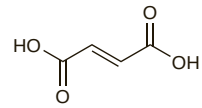
Фумаровая Кислота

$C_2H_2(CO_2H)_2$ = 116.1.

CAS — 110-17-8 (fumaric acid); 624-49-7 (dimethyl fumarate).

ATC — D05AX01.

ATC Vet — QD05AX01.



Pharmacopoeias. In *Pol.* Also in *USNF.*

USNF 26 (Fumaric Acid). White, odourless granules or crystalline powder. Slightly soluble in water and in ether; soluble in alcohol; very slightly soluble in chloroform.

Profile

Fumaric acid and some of its derivatives have been used in the treatment of psoriasis and other skin disorders.

Fumaric acid is also used as an acidifier and flavouring agent in foods.

Skin disorders. Fumaric acid, its sodium salts, and derivatives such as dimethyl fumarate, monoethyl fumarate (ethyl hydrogen fumarate), and octil hydrogen fumarate have been used, both topically and systemically, in the treatment of psoriasis (p.1583) and other skin disorders. Dimethyl fumarate appears to be the most active compound given orally but combination with various salts of monoethyl fumarate has been claimed to improve efficacy.[1-6] However, there have been reports of acute renal failure associated with treatment and the German Federal Office of Health has expressed the opinion that the available evidence did not establish the value of fumaric acid derivatives in psoriasis or other skin disorders.[7] A subsequent retrospective analysis of 41 patients who received fumaric acid esters orally, for between 1 and 14 years, suggested that these drugs might be effective,[8] and a later review suggested that they may be of value in refractory psoriasis.[9] Reported adverse effects in the earlier analysis[8] were generally mild, with only 1 case of elevated serum creatinine; however, lymphocytopenia was noted in 76% of patients and treatment consequently stopped in 4 patients. Other adverse effects with oral therapy have included disturbances of liver func-