6. Pericin M, Trüeb RM. Topical immunotherapy of severe alopecia areata with diphenylcyclopropenone: evaluation of 68 cases. *Dermatology* 1998; **196:** 418–21.
7. Cotellessa C, *et al.* The use of topical diphenylcyclopropenone for the treatment of extensive alopecia areata. *J Am Acad Dermatol* 2001; **44:** 73–6.
8. Wiseman MC, *et al.* Predictive model for immunotherapy of alopecia areata with diphencyprone. *Arch Dermatol* 2001; **137:** 1063–8.
9. van der Steen PHM, *et al.* Topical immunotherapy for alopecia areata: re-evaluation of 139 cases after an additional follow-up period of 19 months. *Dermatology* 1992; **184:** 198–201.

Warts. Diphencyprone has been tried in the treatment of recalcitrant warts. The successful treatment of digital or plantar warts in 42 of 60 patients has been described.[1] The patients were initially sensitised with a 2% topical solution of diphencyprone in acetone, then the warts treated every 1 to 4 weeks with solutions ranging from 0.01 to 6%. In another series,[2] diphencyprone in a paraffin ointment was effective in the clearance of palmar, plantar, palmoplantar, and periungual warts in 135 of 154 patients. A concentration of diphencyprone 2% was used for the initial sensitisation, and concentrations of 0.5 to 4% were used for treatment once every 3 weeks. After initial sensitisation with diphencyprone 2% in acetone, a preparation of diphencyprone with salicylic acid in white soft paraffin applied every night as tolerated was reported to be successful in 44 of 50 patients treated for palmoplantar warts.[3] The concentration of diphencyprone in the ointment ranged from 0.01 to 0.2%, and the concentration of salicylic acid was 15%.

1. Buckley DA, *et al.* Recalcitrant viral warts treated by diphencyprone immunotherapy. *Br J Dermatol* 1999; **141:** 292–6.
2. Upitis JA, Krol A. The use of diphenylcyclopropenone in the treatment of recalcitrant warts. *J Cutan Med Surg* 2002; **6:** 214–17.
3. Armour K, Orchard D. Treatment of palmoplantar warts with a diphencyprone and salicylic acid ointment. *Australas J Dermatol* 2006; **47:** 182–5.

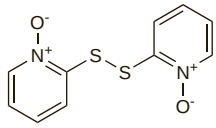
Dipyrithione *(USAN, rINN)*

Bispiriyon; Bispyrithione; Dipiritiona; Dipyrithionum; OMDS; Piriyon Disülfit; Pyrithione Disulfide. 2,2′-Dithiodipyridine 1,1′-dioxide.

Дипиритион

$C_{10}H_8N_2O_2S_2$ = 252.3.

CAS — 3696-28-4.



Profile

Dipyrithione is reported to have antibacterial and antifungal properties and is included in preparations for the treatment of dandruff.

Preparations

Proprietary Preparations (details are given in Part 3)

Turk.: Perkapil.

Multi-ingredient: ***Canad.:*** Dan-Tar Plus; Polytar AF; ***Switz.:*** Crimanex.

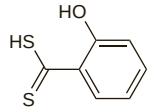
Dithiosalicylic Acid

Ditiosalicílico, ácido. 2-Hydroxybenzenecarbodithioic acid.

Дитиосалициловая Кислота

$C_7H_6OS_2$ = 170.3.

CAS — 527-89-9.



Profile

Dithiosalicylic acid has been used in multi-ingredient preparations used topically for the treatment of acne and seborrhoeic dermatitis.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Ital.:*** Sacnel.

Dithranol *(BAN, rINN)*

Anthralin; Antralin; Dioxyanthranol; Dithranolum; Ditranol; Ditranoli; Ditranolis. 1,8-Dihydroxyanthrone; 1,8-Dihydroxy-9(10*H*)-anthracenone.

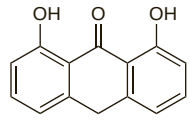
Дитранол

$C_{14}H_{10}O_3$ = 226.2.

CAS — 1143-38-0 (dithranol); 16203-97-7 (dithranol triacetate).

ATC — D05AC01.

ATC Vet — QD05AC01.



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

Ph. Eur. 6.2 (Dithranol). A yellow or brownish-yellow, crystalline powder. Practically insoluble in water; slightly soluble in alcohol; sparingly soluble in acetone; soluble in dichloromethane; dissolves in dilute solutions of alkali hydroxides. Protect from light.

USP 31 (Anthralin). A yellowish-brown, odourless, crystalline powder. Insoluble in water; slightly soluble in alcohol, in ether, and in glacial acetic acid; soluble in acetone, in chloroform, in benzene, and in solutions of alkali hydroxides. The filtrate from a suspension in water is neutral to litmus. Store at a temperature of 8° to 15° in airtight containers. Protect from light.

Stability. The stability of dithranol has been studied in a number of bases and vehicles.[1-4] The weaker preparations of dithranol may be less stable.[1,3,4] Salicylic acid is included in dithranol preparations as an antoxidant and its inclusion in pastes also containing zinc oxide prevents their discoloration due to the inactivation of dithranol by zinc oxide.[5] However, zinc oxide or starch can be omitted from dithranol pastes without loss of effectiveness provided stiffness is maintained.[5] Addition of ascorbic or oxalic acid may improve dithranol's stability in '*Unguentum Merck*' but salicylic acid appears to be ineffective.[1] The effect of salicylic acid on the instability of dithranol in yellow soft paraffin is variable[1,2] and its inclusion has been questioned as it can be irritant and percutaneous absorption can be significant.[1] Dithranol is relatively stable in white soft paraffin.[1]

The application of any type of heat and contact with metal spatulas should be avoided during the manufacture of dithranol pastes[6] and if milling facilities are not available dithranol can be incorporated into Lassar's paste by dissolving it first in chloroform.[5]

1. Green PG, *et al.* The stability of dithranol in various bases. *Br J Dermatol* 1985; **113** (suppl 29): 26.
2. Lee RLH. Stability of dithranol (anthralin) in various vehicles. *Aust J Hosp Pharm* 1987; **17:** 254–8.
3. Hiller C, *et al.* How stable is dithranol? An investigation into the degradation of different dithranol formulations. *Pharm Pract* 1995; **5:** 428–31.
4. Thoma K, Holzmann C. Stabilization of dithranol in topical formulations. *Acta Pharm Hung* 1998; **68:** 313–21.
5. Comaish S, *et al.* Factors affecting the clearance of psoriasis with dithranol (anthralin). *Br J Dermatol* 1971; **84:** 282–9.
6. *PSGB Lab Report P/79/1* 1979.

Adverse Effects and Precautions

Dithranol may cause a burning sensation especially on perilesional skin. Patients with fair skin may be more sensitive than those with dark skin. It is irritant to the eyes and mucous membranes. Use on the face, skin flexures, and genitals should be avoided. Hands should be washed after use.

Dithranol should not be used for acute or pustular psoriasis or on inflamed skin. It stains skin, hair, some fabrics, plastics, and enamel. Staining of bathroom ware may be less of a problem with creams than ointments. Stains on skin and hair slowly disappear on cessation of treatment.

Handling. Dithranol is a powerful irritant and should be kept away from the eyes and tender parts of the skin.

Uses and Administration

Dithranol is used in the treatment of subacute and chronic psoriasis, usually in one of two ways.

Conventional treatment is commonly started with an ointment or paste containing 0.1% dithranol (0.05% in very fair patients) applied for a few hours; the strength is gradually increased as necessary to 0.5%, occasionally to 1%, and the duration of contact extended to overnight periods or longer. The preparation is sparingly and accurately applied to the lesions only. If, on initial treatment, lesions spread or excessive irritation occurs, the concentration of dithranol or the frequency of application should be reduced; if necessary, treatment should be stopped. After each treatment period the patient should bathe or shower to remove any residual dithranol.

For *short-contact therapy* dithranol is usually applied in a soft basis to the lesions for up to 60 minutes daily, before being washed off. As with conventional treatment the strength used is gradually increased from 0.1 to 2% but strengths up to 5% have been used. Surrounding unaffected skin may be protected by white soft paraffin.

Treatment for psoriasis should be continued until the skin is entirely clear. Intermittent courses may be needed to maintain the response. Treatment schedules often involve coal tar and UV irradiation (preferably UVB) before the application of dithranol (see below). Salicylic acid is included in many topical preparations of dithranol.

A cream containing dithranol triacetate has been used similarly to dithranol in conventional treatment of psoriasis.

Alopecia. Dithranol cream (0.5 to 1%) applied for 20 to 60 minutes to the scalp and then washed off, has been found to be of benefit in the treatment of alopecia areata (p.1577). However, at least 6 months of treatment may be required for a cosmetically acceptable result.[1] The response rate has, however, been difficult to evaluate because of the small number of reports, and although it has been widely prescribed for limited patchy alopecia areata, some guidelines conclude that there is no convincing evidence of efficacy.[2]

1. Meidan VM, Touitou E. Treatments for androgenetic alopecia and alopecia areata: current options and future prospects. *Drugs* 2001; **61:** 53–69.
2. MacDonald Hull SP, *et al.* British Association of Dermatologists. Guidelines for the management of alopecia areata. *Br J Dermatol* 2003; **149:** 692–9. Also available at: http://www.bad.org.uk/healthcare/guidelines/Alopecia_Areata.pdf (accessed 27/09/07)

Psoriasis. Dithranol used alone or with coal tar, (with or without ultraviolet light), continues to be one of the drugs of first-line treatment for psoriasis (p.1583). It is particularly suited to the treatment of stable chronic plaque psoriasis but unlike coal tar, is irritant to healthy skin and care is required to ensure that it is only applied to lesions. Treatment with dithranol is therefore more feasible when the plaques are large, or few in number. Use with coal tar may help to reduce the irritant effects of dithranol without affecting efficacy. Traditional treatment with dithranol is time consuming and more suitable for use on hospital inpatients. Dithranol formulated in stiff preparations such as Lassar's paste to minimise spreading to perilesional skin is left on overnight covered with a suitable dressing and washed off the next day. Treatment is usually started with a concentration of 0.1% (0.05% in fair-skinned patients) and gradually increased according to the response and irritation produced. Cream formulations may be less effective but are more suitable for domestic use. Short-contact therapy in which concentrations of up to 5% of dithranol are applied daily for up to 1 hour is more suitable for use on an outpatient basis and there appears to be little reduction in efficacy; irritation and staining may also be reduced.

Dithranol is also used with UVB phototherapy and there have been many modifications of the original Ingram's regimen in which dithranol is applied after bathing in a tar bath and exposure to ultraviolet light. Inpatient stays of up to 3 weeks may be required but long periods of remission can be obtained.

Reviews.

1. Mahrle G. Dithranol. *Clin Dermatol* 1997; **15:** 723–37.

Preparations

BP 2008: Dithranol Cream; Dithranol Ointment; Dithranol Paste;
USP 31: Anthralin Cream; Anthralin Ointment.

Proprietary Preparations (details are given in Part 3)

Austral.: Dithrocream†; Micanol†; ***Austria:*** Micanol; ***Belg.:*** Micanol†; ***Canad.:*** Anthraforte; Anthranol; Anthrascalp; Micanol†; ***Denm.:*** Micanol†; ***Fin.:*** Micanol†; ***Ger.:*** Micanol; ***Hong Kong:*** Micanol†; ***India:*** Psorinol; ***Indon.:*** Anthramed; ***Irl.:*** Dithrocream; Micanol†; ***Israel:*** Dithrocream; Micanol; ***Ital.:*** Psoriderm; Timicolid†; ***Neth.:*** Psoricreme; Psoristick; ***Norw.:*** Micanol; ***NZ:*** Micanol; ***Port.:*** Micanol; ***S.Afr.:*** Anthranol; ***Spain:*** Micanol; ***Swed.:*** Micanol; ***Thai.:*** Micanol†; ***UK:*** Dithrocream; Micanol; ***USA:*** Anthra-Derm†; Dritho-Scalp; Drithocreme†; Psoriatec.

Multi-ingredient: ***Austral.:*** Dithrasal; ***Fr.:*** Anaxeryl; ***Ger.:*** Psoradexan; Psoralon MT; ***Hong Kong:*** Dithrasal; ***India:*** Derobin Skin; ***Singapore:*** Dithrasal; ***Spain:*** Lapices Epiderm Metadier; ***Turk.:*** Psoraks; ***UK:*** Psorin.

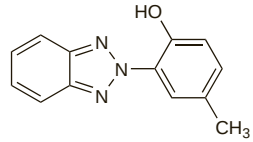
Drometrizole *(USAN, rINN)*

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

Дрометризол

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

CAS — 2440-22-4.



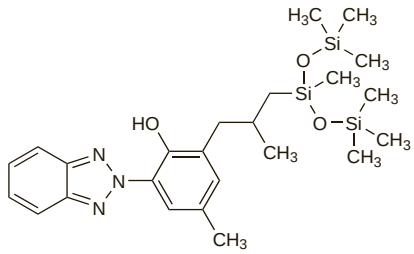
Drometrizole Trisiloxane

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.

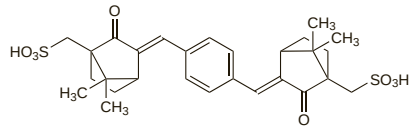
Ecamsule *(USAN, rINN)*

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.