

**Profile**

Titanium dioxide has an action on the skin similar to that of zinc oxide (p.1621) and has similar uses. Titanium peroxide and titanium salicylate are used with titanium dioxide for nappy rash. Titanium dioxide reflects ultraviolet light and is used as a physical sunscreen (p.1576). It is also an ingredient of some cosmetics. It is used to pigment and opacity hard gelatin capsules and tablet coatings and as a delustring agent for regenerated cellulose and other man-made fibres. Specially purified grades may be used in food colours.

**Preparations**

**BP 2008:** Titanium Ointment.

**Proprietary Preparations** numerous preparations are listed in Part 3.

**Trafermin** (USAN, rINN)

CAB-2001; Trafermina; Trafermine; Traferminum. 2-155-Basic fibroblast growth factor (human clone  $\lambda$ KB7/ $\lambda$ HFL1 precursor reduced).

Трафермин

CAS — 131094-16-1.

**Profile**

Trafermin is a human recombinant basic fibroblast growth factor (b-FGF) that promotes tissue granulation and the formation of new blood vessels. It is used as a topical liquid spray for the treatment of burns and intractable skin ulcers.

## ◇ References.

- Robson MC, *et al.* Sequential cytokine therapy for pressure ulcers: clinical and mechanistic response. *Ann Surg* 2000; **231**: 600–11.
- Payne WG, *et al.* Long-term outcome study of growth factor-treated pressure ulcers. *Am J Surg* 2001; **181**: 81–6.
- Ichioka S, *et al.* The positive experience of using a growth factor product on deep wounds with exposed bone. *J Wound Care* 2005; **14**: 105–9.
- Motomura H, *et al.* Aggressive conservative therapy for refractory ulcer with diabetes and/or arteriosclerosis. *J Dermatol* 2006; **33**: 353–9.

**Preparations**

**Proprietary Preparations** (details are given in Part 3)

**Jpn:** Fiblast.

**Tretinoin** (BAN, USAN, rINN)

Ácido retinoico; NSC-122758; Retinoic Acid; Tretinoiini; Tretinoína; Tretinoínas; Trétinoine; Tretinoinum; Tretinoína; Vitamin A Acid; Vitamina A ácida. *all-trans*-Retinoic acid; 15-Apo- $\beta$ -caroten-15-*oic* acid; 3,7-Dimethyl-9-(2,6,6-trimethylcyclohex-1-enyl)nona-2,4,6,8-*all-trans*-tetraenoic acid.

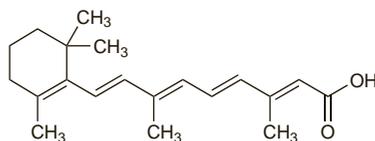
Третиноин

$C_{20}H_{28}O_2 = 300.4$ .

CAS — 302-79-4.

ATC — D10AD01; L01XX14.

ATC Vet — QD10AD01; QL01XX14.



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

**Ph. Eur. 6.2** (Tretinoin). A yellow or light orange crystalline powder. Practically insoluble in water; slightly soluble in alcohol; soluble in dichloromethane. It is sensitive to light, heat, and air, especially in solution. Store in airtight containers at a temperature not exceeding 25°. Protect from light. The contents of an opened container should be used as soon as possible and any unused portion should be protected by an atmosphere of an inert gas.

**USP 31** (Tretinoin). A yellow to light-orange crystalline powder. Insoluble in water; slightly soluble in alcohol and in chloroform. Store in airtight containers, preferably under an atmosphere of an inert gas. Protect from light.

**Adverse Effects**

Tretinoin is a skin irritant. Topical application may cause transitory stinging and a feeling of warmth, and in normal use it produces some erythema, dryness, pruritus, and peeling similar to that of mild sunburn. Sensitive individuals may experience oedema, blistering, and crusting of the skin. Excessive application can cause severe erythema, peeling, and discomfort with

no increase in efficacy. Photosensitivity may occur. Temporary hypopigmentation and hyperpigmentation have been reported.

Oral doses of tretinoin may produce similar adverse effects to those of isotretinoin (see p.1599). Adverse cardiovascular effects have also been reported; the most common were arrhythmias, flushing, hypotension, hypertension, and heart failure. Less common events were cardiac arrest, myocardial infarction, cardiomegaly, heart murmur, ischaemia, stroke, myocarditis, pericarditis, pulmonary hypertension, and secondary cardiomyopathy. A potentially life-threatening 'retinoic acid syndrome' (see below) has been described after oral use.

**Carcinogenicity.** Studies in *mice* suggested that tretinoin could enhance photocarcinogenesis.<sup>1</sup> However, other studies refuted this<sup>2</sup> and evidence indicates that topical tretinoin is not carcinogenic in humans.

- Epstein JH. Chemicals and photocarcinogenesis. *Australas J Dermatol* 1977; **18**: 57–61.
- Epstein JH. All-trans-retinoic acid and cutaneous cancers. *J Am Acad Dermatol* 1986; **15**: 772–8.

**Effects on the blood.** Transient and asymptomatic thrombocytosis has been reported with the use of oral tretinoin, see under Isotretinoin, p.1599.

**Effects on the cardiovascular system.** Tretinoin given for induction remission rapidly improves the coagulopathy associated with acute promyelocytic leukaemia, but there are associated reports of arterial and venous thromboembolism. In a number of cases the combination of tretinoin with an antifibrinolytic drug such as tranexamic acid may have increased the risk of thrombosis.<sup>1–3</sup> In other cases,<sup>2,4</sup> thrombosis occurred in the absence of tranexamic acid and appeared to be related to the retinoic acid syndrome (below). An assessment of 124 patients, including 11 who developed thrombosis, found that the expression of particular phenotypic and genotypic features of leukaemic cells may indicate an increased risk of thrombotic events in patients given tretinoin.<sup>5</sup>

For reports associated with other retinoids, see under Isotretinoin, p.1600.

- Brown JE, *et al.* All-trans retinoic acid (ATRA) and tranexamic acid: a potentially fatal combination in acute promyelocytic leukaemia. *Br J Haematol* 2000; **110**: 1010–12.
- Goldschmidt N, *et al.* Extensive splenic infarction, deep vein thrombosis and pulmonary emboli complicating induction therapy with all-trans-retinoic acid (ATRA) for acute promyelocytic leukaemia. *Leuk Lymphoma* 2003; **44**: 1433–7.
- Levin M-D, *et al.* Acute renal cortex necrosis caused by arterial thrombosis during treatment for acute promyelocytic leukaemia. *Haematologica* 2003; **88**: ECR21. Available at: <http://www.haematologica.com/cgi/reprint/88/6/ECR21.pdf> (accessed 28/07/08)
- Torromeo C, *et al.* Intraventricular thrombosis during all-trans retinoic acid treatment in acute promyelocytic leukemia. *Leukemia* 2001; **15**: 1311–13.
- Breccia M, *et al.* Occurrence of thrombotic events in acute promyelocytic leukemia correlates with consistent immunophenotypic and molecular features. *Leukemia* 2007; **21**: 79–83.

**Effects on the eyes.** Papilloedema, retinal haemorrhage and visual changes as a result of benign intracranial hypertension have been associated with oral tretinoin;<sup>6</sup> children appear to be particularly sensitive. For further information about oral retinoids, including tretinoin, causing benign intracranial hypertension, see Effects on the Eyes under Isotretinoin, p.1600.

- Mahmoud HH, *et al.* Tretinoin toxicity in children with acute promyelocytic leukaemia. *Lancet* 1993; **342**: 1394–5.

**Effects on the musculoskeletal system.** For reports of myositis occurring in patients receiving oral tretinoin, see under Isotretinoin, p.1600.

**Effects on the nervous system.** Neurotoxicity (ataxia, dysarthria, and headache) has been reported in a woman with liver impairment using topical tretinoin 0.025% for acne.<sup>1</sup>

- Bernstein AL, Leventhal-Rochon JL. Neurotoxicity related to the use of topical tretinoin (Retin-A). *Ann Intern Med* 1996; **124**: 227–8.

**Effects on the skin.** Painful scrotal ulcers, often accompanied by fever, have occurred in men receiving oral tretinoin for acute promyelocytic leukaemia.<sup>1–5</sup> The appearance of the ulcers ranged from days 9 to 30 of the tretinoin course and improved after it was stopped (either at complete remission or because of the ulceration or other adverse effects). Management of the ulcers often included an intravenous or topical corticosteroid and in some cases an antibacterial ointment. Genital ulcers have also been reported in 2 women;<sup>3</sup> an 8-year-old girl developed ulcers 5 days after finishing a course of tretinoin.<sup>6</sup>

Sweet's syndrome (acute febrile neutrophilic dermatosis) has been reported in at least 12 patients treated with oral tretinoin for acute promyelocytic leukaemia.<sup>7</sup> In some cases there was also systemic involvement affecting muscle, kidneys, and lungs, and in a few cases patients also had retinoic acid syndrome (below). Most patients responded to systemic corticosteroid treatment and in some cases the course of tretinoin therapy could be continued

as a result. There has also been a report<sup>8</sup> of Sweet's syndrome with myalgia and arthralgia in a child treated with oral tretinoin for acute myeloid leukaemia.

Details of other skin reactions to oral and topical retinoids, including tretinoin, are described under Isotretinoin, p.1601.

- Mori A, *et al.* Scrotal ulcer occurring in patients with acute promyelocytic leukemia during treatment with all-trans retinoic acid. *Oncol Rep* 1999; **6**: 55–8.
- Charles KS, *et al.* Scrotal ulceration during all-trans retinoic acid (ATRA) therapy for acute promyelocytic leukaemia. *Clin Lab Haematol* 2000; **22**: 171–4.
- Fukuno K, *et al.* Genital ulcers during treatment with ALL-trans retinoic acid for acute promyelocytic leukemia. *Leuk Lymphoma* 2003; **44**: 2009–13.
- Gettinger S, *et al.* Scrotal ulceration during all-trans-retinoic acid therapy for acute promyelocytic leukemia. *J Clin Oncol* 2004; **22**: 4648–9.
- Shimizu D, *et al.* Scrotal ulcers arising during treatment with all-trans retinoic acid for acute promyelocytic leukemia. *Intern Med* 2005; **44**: 480–3.
- Ünal S, *et al.* Genital ulcers after treatment with all-trans-retinoic acid in a child with acute promyelocytic leukemia. *Pediatr Hematol Oncol* 2005; **22**: 357–9.
- Astudillo L, *et al.* Sweet's syndrome associated with retinoic acid syndrome in a patient with promyelocytic leukemia. *Ann Hematol* 2002; **81**: 111–14.
- Al-Saad K, *et al.* Sweet syndrome developing during treatment with all-trans retinoic acid in a child with acute myelogenous leukemia. *J Pediatr Hematol Oncol* 2004; **26**: 197–9.

**Retinoic acid syndrome.** A syndrome consisting primarily of fever and respiratory distress developed in 9 of 35 patients between 2 and 21 days after starting induction therapy with oral tretinoin for suspected acute promyelocytic leukaemia.<sup>1</sup> Other symptoms included weight gain, oedema of the lower extremities, pleural or pericardial effusions, and episodic hypotension. Symptoms were life-threatening in 5 patients, 3 of whom subsequently died of multi-system failure. Leucocytosis was frequently, although not invariably, associated with development of the syndrome. Experience showed that early treatment with high-dose corticosteroids should be given to these patients irrespective of the leucocyte count. There have also been a few reports of thrombosis occurring with the retinoic acid syndrome (see Effects on the Cardiovascular System, above).

Reviews<sup>2,3</sup> of this syndrome, known as the 'retinoic acid syndrome', reported that it occurs in about 25% of patients with acute promyelocytic leukaemia treated with tretinoin and that the median time to onset is 10 to 12 days after the start of treatment; the severity of the syndrome varies greatly. A high leucocyte count at diagnosis or a rapidly-increasing count on initiation of therapy appears to increase the likelihood of the syndrome occurring. Close monitoring of leucocyte counts and clinical signs is recommended; high-dose intravenous corticosteroids, and possibly antineoplastic drugs, should be given if symptoms appear or the leucocyte count increases rapidly.

A similar syndrome has been reported in patients with acute promyelocytic leukaemia treated with arsenic trioxide (see p.2260). A capillary leak syndrome, similar to retinoic acid syndrome, has also been described with acitretin (see p.1586).

- Frankel SR, *et al.* The "retinoic acid syndrome" in acute promyelocytic leukemia. *Ann Intern Med* 1992; **117**: 292–6.
- Fenaux P, De Botton S. Retinoic acid syndrome: recognition, prevention and management. *Drug Safety* 1998; **18**: 273–9.
- Larson RS, Tallman MS. Retinoic acid syndrome: manifestations, pathogenesis, and treatment. *Best Pract Res Clin Haematol* 2003; **16**: 453–61.

**Vasculitic syndromes.** For a report of vasculitis associated with oral tretinoin, see under Isotretinoin, p.1601.

**Precautions**

Contact of tretinoin with the eyes, mouth, or other mucous surfaces should be avoided. It should not be applied to eczematous, sunburnt, or abraded skin and the effects of other topical treatment, especially with keratolytics, should be allowed to subside before topical use of tretinoin. Exposure to UV light and excessive exposure to sunlight should be avoided.

Absorption does not seem to occur to any great extent with topical use. Nevertheless, because of teratogenicity in *animal* studies and isolated cases of congenital abnormalities (see below), licensed product information suggests that the use of topical tretinoin should be avoided during pregnancy. It is not known whether tretinoin is distributed into breast milk, and it should therefore be used topically with caution in breast-feeding mothers.

When tretinoin is given by mouth the precautions described under isotretinoin (see p.1601) should be adopted. Oral tretinoin is contra-indicated in pregnancy and in breast-feeding mothers.

**Pregnancy.** Although there have been isolated reports<sup>1–4</sup> of congenital abnormalities in infants born to mothers who used tretinoin topically before and during pregnancy, studies involving a