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 opacify 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 λKB7/λHFL1 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.

1. Robson MC, *et al.* Sequential cytokine therapy for pressure ulcers: clinical and mechanistic response. *Ann Surg* 2000; **231:** 600–11.
2. Payne WG, *et al.* Long-term outcome study of growth factor-treated pressure ulcers. *Am J Surg* 2001; **181:** 81–6.
3. 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.
4. 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; Tretinoinas; Trétinoïne; Tretinoinum; Tretynoina; Vitamin A Acid; Vitamina A ácida. *all-trans*-Retinoic acid; 15-Apo-β-caroten-15-oic acid; 3,7-Dimethyl-9-(2,6,6-trimethylcyclohex-1-enyl)nona-2,4,6,8-*all-trans*-tetraenoic acid.

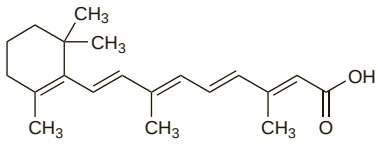
Третиноин

$C_{20}H_{28}O_2$ = 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.[1] However, other studies refuted this[2] and evidence indicates that topical tretinoin is not carcinogenic in humans.

1. Epstein JH. Chemicals and photocarcinogenesis. *Australas J Dermatol* 1977; **18:** 57–61.
2. 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.[1-3] In other cases,[2,4] 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.[5]

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

1. 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.
2. 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 leukemia. *Leuk Lymphoma* 2003; **44:** 1433–7.
3. Levin M-D, *et al.* Acute renal cortex necrosis caused by arterial thrombosis during treatment for acute promyelocytic leukemia. *Haematologica* 2003; **88:** ECR21. Available at: http://www.haematologica.org/cgi/reprint/88/6/ECR21.pdf (accessed 28/07/08)
4. Torromeo C, *et al.* Intraventricular thrombosis during all-trans retinoic acid treatment in acute promyelocytic leukemia. *Leukemia* 2001; **15:** 1311–13.
5. 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;[1] 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.

1. 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.[1]

1. 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.[1-5] 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;[3] an 8-year-old girl developed ulcers 5 days after finishing a course of tretinoin.[6]

Sweet's syndrome (acute febrile neutrophilic dermatosis) has been reported in at least 12 patients treated with oral tretinoin for acute promyelocytic leukaemia.[7] 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[8] 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.

1. 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.
2. Charles KS, *et al.* Scrotal ulceration during all-trans retinoic (ATRA) therapy for acute promyelocytic leukaemia. *Clin Lab Haematol* 2000; **22:** 171–4.
3. Fukuno K, *et al.* Genital ulcers during treatment with ALL-trans retinoic acid for acute promyelocytic leukemia. *Leuk Lymphoma* 2003; **44:** 2009–13.
4. Gettinger S, *et al.* Scrotal ulceration during all-trans-retinoic acid therapy for acute promyelocytic leukemia. *J Clin Oncol* 2004; **22:** 4648–9.
5. Shimizu D, *et al.* Scrotal ulcers arising during treatment with all-trans retinoic acid for acute promyelocytic leukemia. *Intern Med* 2005; **44:** 480–3.
6. 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.
7. Astudillo L, *et al.* Sweet's syndrome associated with retinoic acid syndrome in a patient with promyelocytic leukemia. *Ann Hematol* 2002; **81:** 111–14.
8. 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.[1] 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[2,3] 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).

1. Frankel SR, *et al.* The "retinoic acid syndrome" in acute promyelocytic leukemia. *Ann Intern Med* 1992; **117:** 292–6.
2. Fenaux P, De Botton S. Retinoic acid syndrome: recognition, prevention and management. *Drug Safety* 1998; **18:** 273–9.
3. 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[1-4] of congenital abnormalities in infants born to mothers who used tretinoin topically before and during pregnancy, studies involving a

total of 415 women[5-7] showed no increased risk for major congenital disorders in infants who had been exposed in the first trimester.

As a characteristic pattern of fetal malformation has been described with the use of oral retinoids, particularly isotretinoin (see p.1601), licensed product information warns that oral tretinoin is contra-indicated during pregnancy and that conception should be avoided for at least one month after the end of treatment. Nevertheless, the outcomes of up to 20 cases have been reviewed,[8,9] in which a course of tretinoin was generally given in the second or third trimester for promyelocytic leukaemia; some women were also given cytotoxic chemotherapy. There were reports of transient pulmonary and cardiac complications in some infants, but no congenital malformations were described. In one case[10] tretinoin was started in the first trimester and continued throughout the pregnancy to avoid the use of cytotoxic chemotherapy. The small-for-date infant was born by caesarean section at week 32 with jaundice and respiratory distress syndrome, which both resolved within 11 days. At 15 months of age the infant had normal growth and development.

1. Camera G, Pregliasco P. Ear malformation in baby born to mother using tretinoin cream. *Lancet* 1992; **339:** 687.
2. Lipson AH, *et al.* Multiple congenital defects associated with maternal use of topical tretinoin. *Lancet* 1993; **341:** 1352–3.
3. Navarre-Belhassen C, *et al.* Multiple congenital malformations associated with topical tretinoin. *Ann Pharmacother* 1998; **32:** 505–6.
4. Colley SMJ, *et al.* Topical tretinoin and fetal malformations. *Med J Aust* 1998; **168:** 467.
5. Jick SS, *et al.* First trimester topical tretinoin and congenital disorders. *Lancet* 1993; **341:** 1181–2.
6. Shapiro L, *et al.* Safety of first-trimester exposure to topical tretinoin: prospective cohort study. *Lancet* 1997; **350:** 1143–4.
7. Loureiro KD, *et al.* Minor malformations characteristic of the retinoic acid embryopathy and other birth outcomes in children of women exposed to topical tretinoin during early pregnancy. *Am J Med Genet* 2005; **136A:** 117–21.
8. Giagounidis AAN, *et al.* Acute promyelocytic leukemia and pregnancy. *Eur J Haematol* 2000; **64:** 267–71.
9. Consoli U, *et al.* Acute promyelocytic leukemia during pregnancy: report of 3 cases. *Int J Hematol* 2004; **79:** 31–6.
10. Simone MD, *et al.* All-trans retinoic acid (ATRA) administration during pregnancy in relapsed acute promyelocytic leukemia. *Leukemia* 1995; **9:** 1412–13.

Skin fragility. As with other retinoids (see under Isotretinoin, p.1602) the use of depilatory products should be avoided in patients treated with tretinoin. Erosions of the skin occurred in 2 patients after the use of wax depilation on facial areas also being treated topically with tretinoin.[1]

1. Goldberg NS, Zalka AD. Retin-A and wax epilation. *Arch Dermatol* 1989; **125:** 1717.

Interactions

As for Isotretinoin, p.1602.

Tretinoin is metabolised by the hepatic cytochrome P450 isoenzyme system, therefore there is a potential for interaction between oral tretinoin and inhibitors or inducers of these enzymes.

Antifibrinolytics. Thrombotic events have occurred in patients being treated with tretinoin and *tranexamic acid* (see Effects on the Cardiovascular System, above). Licensed product information for tretinoin used in the treatment of acute promyelocytic leukaemia advises caution when it is given with drugs such as *aminocaproic acid*, *aprotinin*, and tranexamic acid, particularly in the first month of treatment.

Minoxidil. For the effect of tretinoin on the percutaneous absorption of minoxidil, see p.1342.

Pharmacokinetics

After oral doses tretinoin is well absorbed from the gastrointestinal tract, and peak plasma concentrations are obtained after 1 to 2 hours. Oral bioavailability is about 50%. Minimal systemic absorption occurs after topical application. Tretinoin is highly bound to plasma proteins. It undergoes metabolism in the liver by the cytochrome P450 isoenzyme system. Metabolites include isotretinoin, 4-oxo-*trans*-retinoic acid, and 4-oxo-*cis*-retinoic acid. The terminal elimination half-life of tretinoin is 0.5 to 2 hours. Tretinoin is excreted in the bile and the urine. There is some evidence that tretinoin induces its own metabolism.

◊ References.

1. Regazzi MB, *et al.* Clinical pharmacokinetics of tretinoin. *Clin Pharmacokinet* 1997; **32:** 382–402.

Uses and Administration

Tretinoin is a retinoid and is the acid form of vitamin A (p.1971).

Tretinoin is used primarily in the topical treatment of **acne vulgaris** when comedones, papules, and pustules predominate. It appears to stimulate mitosis and turnover of follicular epithelial cells and reduce their cohesiveness thereby facilitating the extrusion of existing comedones and preventing the formation of new ones. It also appears to have a thinning effect on the stratum corneum. Tretinoin is applied as a cream, gel, or alcoholic solution, usually containing 0.01 to 0.1%. The skin should be cleansed to remove excessive oiliness and dried before applying tretinoin lightly, once or twice daily according to response and irritation; some patients may require less frequent applications. Other topical preparations (including skin moisturisers) should not be applied at the same time as tretinoin is applied, and caution is required if other local irritants are used concurrently. There may be apparent exacerbations of the acne during early treatment and a therapeutic response may not be evident for 6 to 8 weeks. When the condition has resolved maintenance therapy should be less frequent.

Preparations containing 0.02 or 0.05% tretinoin are available for the treatment of mottled hyperpigmentation, roughness, and fine wrinkling of **photodamaged skin**. It is applied once daily at night. Effects may not be seen until about 6 months after starting treatment.

Tretinoin is also used to induce remission in acute promyelocytic **leukaemia**. A daily dose of 45 mg/m^2 is given orally in 2 divided doses with food. Treatment is continued until 30 days after complete remission or 90 days of treatment have been given, whichever occurs first. Dose reduction has been recommended in hepatic or renal impairment (see below).

For the use of tretinoin in children, see below.

A liposomal formulation of tretinoin for intravenous use is under investigation in T-cell non-Hodgkin's lymphoma, and acute and chronic leukaemia.

Administration in children. Although topical tretinoin is not licensed for infantile acne in the UK, the *BNFC* suggests that it may be used under specialist supervision.

The use of oral tretinoin to induce remission in acute promyelocytic leukaemia (see Malignant Neoplasms, below) in children has been studied.[1-3] Although there is less experience than in adults, a similar dosage regimen of 45 mg/m^2 daily (see also above) has been used in children ranging in age from 1 to 16 years. Dose reduction should be considered if severe toxicity, particularly intractable headache, occurs. Although a lower dose of 25 mg/m^2 daily might reduce neurotoxicity[2,3] the two doses have not been directly compared.

1. de Botton S, *et al.* Outcome of childhood acute promyelocytic leukemia with all-trans-retinoic acid and chemotherapy. *J Clin Oncol* 2004; **22:** 1404–12.
2. Testi AM, *et al.* GIMEMA-AIEOP AIDA protocol for the treatment of newly diagnosed acute promyelocytic leukemia (APL) in children. *Blood* 2005; **106:** 447–53.
3. Ortega JJ, *et al.* Treatment with all-trans retinoic acid and anthracycline monochemotherapy for children with acute promyelocytic leukemia: a multicenter study by the PETHEMA Group. *J Clin Oncol* 2005; **23:** 7632–40.

Administration in hepatic and renal impairment. Although dosage adjustment has not been studied in patients with hepatic or renal impairment, licensed UK product information suggests that oral doses of tretinoin for acute promyelocytic leukaemia should be reduced to 25 mg/m^2 daily.

There is a report[1] of 2 patients who required dialysis during tretinoin treatment for acute promyelocytic leukaemia and who achieved remission; one was given a dose of 20 mg/m^2 daily in 2 divided doses and the other received 35 mg/m^2 daily in 3 divided doses.

1. Takitani K, *et al.* Pharmacokinetics of all-trans retinoic acid in acute promyelocytic leukemia patients on dialysis. *Am J Hematol* 2003; **74:** 147–8.

Malignant neoplasms. Tretinoin differentiation therapy has become the established treatment for acute promyelocytic leukaemia (APL), a subtype of acute myeloid leukaemia (p.652). Tretinoin is effective in APL because the characteristic chromosomal abnormalities result in an abnormal retinoic acid receptor. When given *orally*, it has produced complete remissions in more than 90% of patients.[1-4] However, the duration of remission is short unless consolidation, usually with an anthracycline- and cytarabine-based regimen, is given concurrently or subsequently. The combination of tretinoin and chemotherapy has been shown to result in improved survival compared with chemotherapy alone.[1,5,6] Prolonged maintenance therapy including intermittent tretinoin also appears to reduce the rate of relapse.[6] Although benefit has been reported with continuous tretinoin maintenance[7] this is generally considered to lead to resistance.[8] A life-threatening syndrome has developed in some patients who have received oral tretinoin for APL (see Retinoic Acid Syndrome, under Adverse Effects, above). Children seem particularly sensitive to the adverse effects of oral tretinoin on the CNS (see also Effects on the Eyes, and Administration in Children, above). A lipid-based *intravenous* formulation of tretinoin is under investigation for the treatment of APL.

Tretinoin has also been tried for *topical* chemoprevention in patients at increased risk of skin cancers, and in the management of oral leucoplakia (see Malignant Neoplasms under Isotretinoin, p.1603).

1. Avvisati G, Tallman MS. All-trans retinoic acid in acute promyelocytic leukaemia. *Best Pract Res Clin Haematol* 2003; **16:** 419–32.
2. de Botton S, *et al.* Outcome of childhood acute promyelocytic leukemia with all-trans-retinoic acid and chemotherapy. *J Clin Oncol* 2004; **22:** 1404–12.
3. Ortega JJ, *et al.* Treatment with all-trans retinoic acid and anthracycline monochemotherapy for children with acute promyelocytic leukemia: a multicenter study by the PETHEMA Group. *J Clin Oncol* 2005; **23:** 7632–40.
4. Testi AM, *et al.* GIMEMA-AIEOP AIDA protocol for the treatment of newly diagnosed acute promyelocytic leukemia (APL) in children. *Blood* 2005; **106:** 447–53.
5. Tallman MS, *et al.* Acute promyelocytic leukemia: evolving therapeutic strategies. *Blood* 2002; **99:** 759–67.
6. Tallman MS, Nabhan C. Management of acute promyelocytic leukemia. *Curr Oncol Rep* 2002; **4:** 381–9.
7. Tallman MS, *et al.* All-trans retinoic acid in acute promyelocytic leukemia: long-term outcome and prognostic factor analysis from the North American Intergroup protocol. *Blood* 2002; **100:** 4298–4302.
8. Fenaux P, *et al.* A randomized comparison of all transretinoic acid (ATRA) followed by chemotherapy and ATRA plus chemotherapy and the role of maintenance therapy in newly diagnosed acute promyelocytic leukemia. *Blood* 1999; **94:** 1192–1200.

Skin disorders. Topical treatment with tretinoin has been tried with varying success in a wide range of cutaneous conditions. Its use in acne (p.1577) is well established. Some benefit has also been reported in rosacea[1] (p.1583), in keratinisation disorders such as Darier's disease (p.1578), and in pigmentation disorders (p.1582) such as chloasma.[2] Healing of diabetic foot ulcers (see Diabetic Complications, p.433) was improved in a small placebo-controlled study of topical tretinoin.[3] The 0.05% solution was applied topically for 10 minutes of every day for 4 weeks.

Topical tretinoin is used to improve some of the signs of photoageing (p.1581). Studies have found that tretinoin can improve fine facial wrinkling, with some reduction in coarse wrinkles, tactile roughness, sallowness, irregular pigmentation, and actinic lentigines.[4-6] Tretinoin appears to prevent and repair collagen damage and reduce epidermal melanin content; there is also increased epidermal proliferation and thickening, compaction of the stratum corneum, and deposition of mucinous material.[5] The previous suggestion that skin irritation might be the mechanism behind tretinoin's effects on photodamaged skin has not been supported by clinical study.[4,5] It can take up to 4 months of treatment for a response to develop and the maximum response can be reached between 8 and 12 months. Continued use is necessary to maintain the effect of tretinoin, although it may be used less often.[5,6]

1. Ertl GA, *et al.* A comparison of the efficacy of topical tretinoin and low-dose oral isotretinoin in rosacea. *Arch Dermatol* 1994; **130:** 319–24.
2. Griffiths CEM, *et al.* Topical tretinoin (retinoic acid) improves melasma: a vehicle-controlled, clinical trial. *Br J Dermatol* 1993; **129:** 415–21.
3. Tom WL, *et al.* The effect of short-contact topical tretinoin therapy for foot ulcers in patients with diabetes. *Arch Dermatol* 2005; **141:** 1373–7.
4. Griffiths CEM. The role of retinoids in the prevention and repair of aged and photoaged skin. *Clin Exp Dermatol* 2001; **26:** 613–18.
5. Stratigos AJ, Katsambas AD. The role of topical retinoids in the treatment of photoaging. *Drugs* 2005; **65:** 1061–72.
6. Singh M, Griffiths CEM. The use of retinoids in the treatment of photoaging. *Dermatol Ther* 2006; **19:** 297–305.

Preparations

BP 2008: Tretinoin Gel; Tretinoin Solution;
USP 31: Tretinoin Cream; Tretinoin Gel; Tretinoin Topical Solution.

Proprietary Preparations (details are given in Part 3)
Arg.: A Acido; Dorpiel; Eurotretin; Locacid; Lotioblanc; Neotretin; Niterey; Retacnyl; Reticne; Retin-A; Tretinoderm; Vesanoid; Vitanol-A†; ***Austral.:*** Retin-A; ReTrieve; Stieva-A; Vesanoid; ***Austria:*** Eudyna; Retin-A; Vesanoid; ***Belg.:*** Retinova†; Vesanoid; ***Braz.:*** Retacnyl†; Retin-A; Retinova; Vesanoid; Vitacid; Vitanol-A; ***Canad.:*** Rejuva-A; Renova; Retin-A; Retisol-A; Stieva-A; Vesanoid; ***Chile:*** Dermodan; Retacnyl; Retin-A; Stieva-A; Vesanoid; ***Cz.:*** Airol; Locacid; Retin-A; Vesanoid; ***Denm.:*** Retinova; ***Fin.:*** Avitcid; Vesanoid; ***Fr.:*** Effederm; Ketrel; Locacid; Retacnyl; Retin-A; Retinova†; Retitop†; Vesanoid; ***Ger.:*** Airol; Cordes VAS; Vesanoid; ***Gr.:*** Airol; Vesanoid; ***Hong Kong:*** Acta; Alten†; Locacid†; Quali-A; Retacnyl†; Retin-A; ReTrieve; Stieva-A; Vesanoid; Vitamin A Acid; ***Hung.:*** Vesanoid†; ***India:*** Eudyna; ***Indon.:*** Eudyna; Jeraklin; Melavita; Nuface; Retin-A; Skinovit; Tracne; Trentin; Vitacid; ***Irl.:*** Retin-A; Vesanoid; ***Israel:*** Airol; Locacid; Retavit; Retin-A; Vesanoid; ***Ital.:*** Airol; Retin-A; Vesanoid; ***Malaysia:*** Alten; Renova†; Retacnyl; Retin-A; Stieva-A; T3 Actin; Tretinon; ***Mex.:*** Acnil; Arretin; Biovitol-C; Epitrel; Queratal; Reacel-A; Ret-A-Pres; Retacnyl; Retin-A; Stieva-A; Tocoderm; Vesanoid; ***Neth.:*** Acid A Vit; Vesanoid; ***Norw.:*** Aberela; ***NZ:*** Retin-A; Retinova; Vesanoid; ***Philipp.:*** Airol; Derm A; Retacnyl; Retin-A; Stieva-A; Vesanoid; ***Pol.:*** Arretin; Atrederm; Locacid; Retin-A; Vesanoid; ***Port.:*** Ketrel; Locacid; Retin-A; Vesanoid; Vitacid†; ***Rus.:*** Vesanoid (Весаноид); ***S.Afr.:*** Ilotycin-A; Renova; Retacnyl; Retin-A; Vesanoid; ***Singapore:*** Alten; Retacnyl; Retin-A; Retinova; ReTrieve; Stieva-A; Vesanoid†; ***Spain:*** Dermojuventus; Retinova†; Retirides; Vesanoid; Vitanol; ***Swed.:*** Aberela; Retinova; ***Switz.:*** Airol; Retin-A; Vesanoid; ***Thai.:*** A-Tinic†; Renova; Retacnyl; Retin-A; Stieva-A; Vesanoid; ***Turk.:*** Acnelyse; Retino; Vesanoid; ***UK:*** Retin-A; Retinova†; Vesanoid; ***USA:*** Atralin; Avita; Renova; Retin-A; Tretin-X; Vesanoid; ***Venez.:*** Betarretin; Retacnyl; Retinei†; Tretinax; Vesanoid.

Multi-ingredient: ***Arg.:*** Acneout; Hidrosam T; Kitacne AR†; Melasmax; Puraloe; Stievamycin; Tratacne; Tri-Luma; Verrugard; ***Austria:*** Keratosis forte; ***Braz.:*** Tri-Luma; Vitacid Plus; ***Canad.:*** Solage†; Stievamycin; ***Chile:***

Dermodan Plus; Erylik; Stievamycin; Tri-Luma; ***Cz.:*** Aknemycin Plus; ***Fin.:*** Wicaran; ***Fr.:*** Erylik; ***Ger.:*** Aknemycin Plus; Balisa VAS; Carbamid + VAS; Clinesfar†; Pigmanorm; Ureotop + VAS; ***Hong Kong:*** Dermabaz†; Erylik; Tri-Luma; ***Hung.:*** Verra-med; ***Indon.:*** Medi-Klin TR; ***Israel:*** Aknemycin Plus; ***Ital.:*** Psorinase†; ***Malaysia:*** Aknemycin Plus; Tri-Luma; ***Mex.:*** Stievamycin; Tri-Luma; ***Philipp.:*** Tri-Luma; ***Pol.:*** Aknemycin Plus; ***Singapore:*** Aknemycin Plus; Tri-Luma; ***Spain:*** Acnisdin Retinoico; Loderm Retinoico; ***Switz.:*** Carbamide + VAS; Pigmanorm; Sebo-Psor; Verra-med; ***Thai.:*** Tri-Luma; ***UK:*** Aknemycin Plus; ***USA:*** Solage; Tri-Luma; Ziana; ***Venez.:*** Tri-Luma.

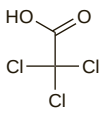
Trichloroacetic Acid

Acide Trichloracétique; Acidum trichloraceticum; Acidum Trichloroaceticum; Kwas trichlorooctowy; Kyselina trichloroctová; Trichloracetic Acid; Trichloracto rūgštis; Trichloressigsäure; Tricloroacético, ácido; Trikloorietikkahappo; Triklorättiksyra; Triklórecetsav.

Трихлоруксусная Кислота

$C_2HCl_3O_2$ = 163.4.

CAS — 76-03-9.



Pharmacopoeias. In *Eur.* (see p.vii).

Ph. Eur. 6.2 (Trichloroacetic Acid). A very deliquescent white or almost white crystalline mass or colourless crystals. Very soluble in water, in alcohol, and in dichloromethane. Store in airtight containers.

Adverse Effects and Treatment

As for Hydrochloric Acid, p.2322.

Uses and Administration

Trichloroacetic acid is caustic and astringent. When used as an escharotic for warts it is applied as a strong solution; a range of concentrations have been used including 50% and 80%. The surrounding areas of skin should be protected. Trichloroacetic acid has also been used for the removal of tattoos and in cosmetic surgery for chemical peeling of the skin.

Tattoo removal. References to the use of trichloroacetic acid in the removal of tattoos.

1. Hall-Smith P, Bennett J. Tattoos: a lasting regret. *BMJ* 1991; **303:** 397.

Warts. References to the use of trichloroacetic acid in the treatment of genital warts (p.1584).

1. Godley MJ, *et al.* Cryotherapy compared with trichloroacetic acid in treating genital warts. *Genitourin Med* 1987; **63:** 390–2.
2. Davis AJ, Emans SJ. Human papilloma virus infection in the pediatric and adolescent patient. *J Pediatr* 1989; **115:** 1–9.
3. Boothby RA, *et al.* Single application treatment of human papillomavirus infection of the cervix and vagina with trichloroacetic acid: a randomized trial. *Obstet Gynecol* 1990; **76:** 278–80.
4. Abdullah AN, *et al.* Treatment of external genital warts comparing cryotherapy (liquid nitrogen) and trichloroacetic acid. *Sex Transm Dis* 1993; **20:** 344–5.

Preparations

Proprietary Preparations (details are given in Part 3)
Hong Kong: AccuPeel†; ***Ital.:*** CL tre; Verrupor; ***Singapore:*** AccuPeel†; ***USA:*** Tri-Chlor.

Multi-ingredient: ***Spain:*** Callicida Brum†; ***Turk.:*** IL-33.

Trioxysalen *(rINN)*

NSC-71047; 4,5′,8-Trimethylpsoralen; Trioksisaleeni; Trioxisalen; Trioxisaleno; Trioxsalen *(USAN)*; Trioxysalène; Trioxysalenum. 2,5,9-Trimethyl-7*H*-furo[3,2-*g*][1]benzopyran-7-one.

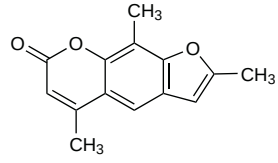
Триоксизален

$C_{14}H_{12}O_3$ = 228.2.

CAS — 3902-71-4.

ATC — D05AD01; D05BA01.

ATC Vet — QD05AD01; QD05BA01.



Pharmacopoeias. In *US.*

USP 31 (Trioxsalen). A white to off-white or greyish, odourless, crystalline solid. Practically insoluble in water; soluble 1 in 1150 of alcohol, 1 in 84 of chloroform, 1 in 43 of dichloromethane, and 1 in 100 of methyl isobutyl ketone. Protect from light.

Profile

Trioxysalen, a psoralen, is a photosensitiser used similarly to methoxsalen in photochemotherapy or PUVA therapy (p.1606).

Trioxysalen is used in idiopathic vitiligo to enhance pigmentation or increase the tolerance to sunlight in selected patients. In vitiligo an oral dose of 10 mg daily is given 2 to 4 hours before exposure to sunlight or ultraviolet radiation; prolonged therapy may be necessary. To increase tolerance to sunlight a dose of 10 mg daily is given 2 hours before exposure; treatment should not be continued for longer than 14 days.

Trioxysalen may also be used topically in the PUVA treatment of psoriasis.

◊ References.

1. Snellman E, Rantanen T. Concentration-dependent phototoxicity in trimethylpsoralen bath psoralen ultraviolet A. *Br J Dermatol* 2001; **144:** 490–4.

Preparations

USP 31: Trioxsalen Tablets.

Proprietary Preparations (details are given in Part 3)
Arg.: Trisoralen†; ***Fin.:*** Tripsor; ***Gr.:*** Trisolaren; ***Hong Kong:*** Puvadin†; ***India:*** Neosoralen†; ***Malaysia:*** Puvadin†.

Urea ⊗

Carbamida; Carbamide; E927b; Karbamid; Karbamidi; Močovina; Mocznik; Üre; Urée; Ureia; Urėja; Ureum. Carbonic acid diamide.

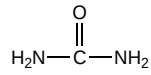
Карбамид; Мочевина

$NH_2.CO.NH_2$ = 60.06.

CAS — 57-13-6.

ATC — B05BC02; D02AE01.

ATC Vet — QB05BC02; QD02AE01.



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

Ph. Eur. 6.2 (Urea). Transparent, slightly hygroscopic, crystals or a white or almost white, crystalline powder. Very soluble in water; soluble in alcohol; practically insoluble in dichloromethane. Store in airtight containers.

USP 31 (Urea). Colourless or white, practically odourless, prismatic crystals, or white crystalline powder or pellets. May gradually develop a slight odour of ammonia on prolonged standing. Soluble 1 in 1.5 of water, 1 in 10 of alcohol, and 1 in 1 of boiling alcohol; practically insoluble in chloroform and in ether. Solutions are neutral to litmus. Store at a temperature of 25°, excursions permitted between 15° and 30°.

Incompatibility. Urea can cause haemolysis when mixed with blood and should never be added to whole blood for transfusion or given through the same set by which blood is being infused.

Adverse Effects and Precautions

As for Mannitol, p.1330. Urea should also be used with caution in liver impairment as blood-ammonia concentrations can rise, and should be avoided in liver failure.

Urea is reported to be more irritant than mannitol, and intravenous use may cause venous thrombosis or phlebitis at the site of injection; extravasation may cause sloughing or necrosis. Only large veins should be used for infusion, and urea should not be infused into veins of the lower limbs of elderly patients. Extreme care is essential to prevent accidental extravasation of urea infusions.

Rapid intravenous injection of solutions of urea can cause haemolysis; the risk is reduced by using glucose or invert sugar solutions as diluent. Urea should not be mixed with whole blood.

Topical applications may be irritant to sensitive skin.

Infants and neonates. High plasma-urea concentrations have been reported[1,2] in neonates after topical application of emollient creams containing urea. Since there was no evidence of dehydration[2,3] absorption of urea through the skin was the likely cause. Raised plasma-urea concentrations have been reported[4] in infants with erythematous skin conditions who had not been treated with urea cream and this was attributed to dehydration due to increased insensible water loss through the damaged skin.

1. Beverley DW, Wheeler D. High plasma urea concentrations in collodion babies. *Arch Dis Child* 1986; **61:** 696–8.
2. Oudesluys-Murphy AM, van Leeuwen M. High plasma urea concentrations in collodion babies. *Arch Dis Child* 1987; **62:** 212.
3. Beverley DW, Wheeler D. High plasma urea concentration in babies with lamellar ichthyosis. *Arch Dis Child* 1986; **61:** 1245–6.
4. Garty BZ. High plasma urea concentration in babies with lamellar ichthyosis. *Arch Dis Child* 1986; **61:** 1245.

Pregnancy. There have been reports of women suffering coagulopathy associated with urea treatment given for termination of pregnancy.[1,2]

1. Grundy MFB, Craven ER. Consumption coagulopathy after intra-amniotic urea. *BMJ* 1976; **2:** 677–8.
2. Burkman RT, *et al.* Coagulopathy with midtrimester induced abortion: association with hyperosmolar urea administration. *Am J Obstet Gynecol* 1977; **127:** 533–6.

Pharmacokinetics

Urea is fairly rapidly absorbed from the gastrointestinal tract but causes gastrointestinal irritation. Urea is distributed into extracellular and intracellular fluids including lymph, bile, CSF, and blood. It is reported to cross the placenta, and penetrate the eye. It is excreted unchanged in the urine.

Uses and Administration

Urea promotes hydration and is mainly applied topically in the treatment of ichthyosis and hyperkeratotic skin disorders (p.1580). Used intravenously it has osmotic diuretic properties similar to mannitol (p.1331) and has been used in the treatment of acute increases in intracranial pressure (p.1181), due to cerebral oedema, and to decrease intra-ocular pressure in acute glaucoma (p.1873), but has been largely superseded by mannitol. Urea has also been given intra-amniotically for the termination of pregnancy (p.2004).

When applied topically urea has hydrating and keratolytic properties. In the management of ichthyosis and other dry skin disorders it is applied in creams or lotions containing 5 to 25% urea; higher concentrations of 30% and 40% have also been used in severe cases. A preparation containing 40% may be used for nail destruction.

For the reduction of raised intracranial or intra-ocular pressure, urea is given intravenously, as an infusion of a 30% solution in glucose 5 or 10% or invert sugar 10%, at a rate not exceeding 4 mL/minute, in a dose of 0.5 to 1.5 g/kg to a maximum of 120 g daily. Doses used in children are based on the same regimen, but see also below. Rebound increases in intracranial and intra-ocular pressure may occur after about 12 hours.

Solutions of urea 40 to 50% have been given by intra-amniotic injection for the termination of pregnancy.

Urea labelled with carbon-13 (p.2277) is used in the *in vivo* diagnosis of *Helicobacter pylori* infection (see Peptic Ulcer Disease, p.1702). The test involves collecting a breath sample before and after oral ingestion of a single dose of ^{13}C-urea. *H. pylori* produces urease which hydrolyses the urea to carbon dioxide and ammonia; therefore, an excess of carbon-13-labelled carbon dioxide in the sample, compared with a baseline sample, indicates infection. Doses of ^{13}C-urea include 50 mg, 75 mg, or 100 mg depending on the kit being used. Urea labelled with the radionuclide carbon-14 (p.2053) is also used in a urea breath test for *H. pylori* detection.

Administration in children. For the reduction of raised intracranial or intra-ocular pressure in children, urea is given intravenously in dosage regimens similar to those used in adults (see above). However, for children under 2 years of age, a dose of 100 mg/kg may be adequate.

Breath test kits containing ^{13}C-urea for the diagnosis of *Helicobacter pylori* infection are available for children. However, the *BNFC* states that the appropriateness of testing in children has not been established, and that endoscopy with biopsy is more accurate than *in vivo* breath testing, which is frequently unreliable in children.

Preparations

BP 2008: Urea Cream;
USP 31: Urea for Injection.

Proprietary Preparations (details are given in Part 3)
Arg.: Hidroplus; Keratopic; Lociherp; Nutralcon; Optiwhite†; Ureadin; Urecrem; Uremol; Xerobase; ***Austral.:*** Aquacare; Hamilton Skin Therapy; Nutraplus; Urecare; Urederm; ***Austria:*** Nubral; ***Braz.:*** Emoderm; Hidrapel Plus; Nutraplus; Ureadin; ***Canad.:*** Dermaflex; Ultra Mide; Uree; Uremol; Urisec; ***Chile:*** Ayr con urea; Ayr-5; Hyderm; Nutraplus†; Uramol; Ureadin 10 and 20; ***Cz.:*** Elacutan; Excipial U; Linola Urea; ***Fin.:*** Fenuril; ***Fr.:*** Anti-Dessechement; Charlieu Topic†; Ictyoderm†; Nutraplus; Sedagel; ***Ger.:*** Balisa; Basodexan; Elacutan; Eucerin Salbe†; Hyanit N; Linola Urea; Nubral; Onychomal; Sebexol cum urea; Ureotop; ***Hong Kong:*** Balneum Intensiv; Carmol; Caruderma; Euderm; Nutraplus†; Urecare; Urederm; ***Hung.:*** Linola Urea; ***Indon.:*** Calmuderm; Carmed; Moisderm; Soft U Derm; Urederm; ***Ital.:*** Aquadrate; Nutraplus; ***Ital.:*** Dermal Care; ***Jpn:*** Keratinamin; ***Malaysia:*** Balneum Intensiv; Euderm†; Nutraplus; UO; Urecare†; ***Mex.:***