Malignant neoplasms. Retinoids such as isotretinoin have been studied in the treatment of various neoplastic or preneoplastic disorders. Although oral tretinoin is used for remission induction in acute promyelocytic leukaemia (see p.1619), other retinoids do not have an established role in the treatment of cancer. There may, however, be a place for the use of retinoids in the chemoprevention of some malignancies.

There has been particular interest in the potential for retinoids to prevent the formation of *skin cancers* (p.672) in patients at increased risk. Maintenance immunosuppression may increase the incidence of pre-malignant and malignant skin lesions in solid organ transplant recipients; large numbers of lesions can develop and tend to be more aggressive than those in the general population.[1] Although there has been some investigation in cardiac transplant recipients, most case reports and some small studies have involved renal transplant patients. Oral acitretin has been reported to reduce the number of actinic keratoses and reduce the development of new basal and squamous cell carcinomas in these patients.[1-4] Other patients at increased risk of skin cancers who may benefit from prophylactic retinoid therapy include those with xeroderma pigmentosum and naevoid basal cell carcinoma syndrome; oral isotretinoin, rather than acitretin, has been tried in such patients.[5] Retinoids might also be considered in others who have already developed nonmelanoma skin cancers, such as those with conditions requiring maintenance immunosuppression, chronic lymphocytic leukaemia or non-Hodgkin's lymphoma, severe photodamage of the skin, and those with squamous cell carcinoma at high risk of metastasis or that has already metastasised.[5]

Since retinoids suppress rather than cure skin cancer, rebound occurs when the retinoid is stopped and long-term therapy is needed. There is some concern about the risks of such long-term use, particularly on plasma lipids and bone, and monitoring has been recommended.[1,4,5] The mucocutaneous adverse effects that commonly occur can affect patient acceptance during long-term use; mucocutaneous effects may be more severe with isotretinoin, but hair loss may be more extensive with acitretin.[4,5] Gradual dose escalation to an effective dose can be used to minimise these mucocutaneous effects. One example using isotretinoin starts with a dose of 250 micrograms/kg on alternate days for a month, increased to 250 micrograms/kg daily for the second month, then to 500 micrograms/kg daily for the third month; the dose is then adjusted as tolerated.[5] As there are risks of teratogenicity with retinoids, isotretinoin is preferred for women of child-bearing potential because of its shorter half-life.[4,5] For acitretin doses that have been used, see p.1586.

Topical application of retinoids has also been tried for chemoprevention of skin cancers. Topical tretinoin has been used on actinic keratoses in organ transplant recipients, but results have been mixed and may depend on dose. If squamous cell carcinomas are present, however, systemic retinoids should be considered.[3]

Retinoids have been studied in the chemoprevention of primary disease recurrence and second primary tumours after treatment for *squamous cell carcinoma of the head and neck* (p.666) but results have been mixed and limited by resistance and toxicity.[6] A large placebo-controlled study[7] has also reported that low-dose oral isotretinoin (30 mg daily for 3 years with an additional 4 years of follow-up) did not reduce the rate of second primary tumours or death in patients who had been treated for early stage head and neck squamous cell carcinoma. There has also been some interest in the use of retinoids, given orally (isotretinoin) or topically (isotretinoin or tretinoin), in the management of *oral leucoplakia*, which can be pre-malignant (see under Bleomycin, p.688). However, despite reports of beneficial response, relapse frequently occurs on stopping retinoid therapy.[6,8]

Oral isotretinoin has been studied as continuation therapy in children with high-risk *neuroblastoma* that had responded to intensive chemotherapy. One study[9] found improved survival with 6 cycles of isotretinoin given for 14 days of each 28-day cycle. However, another study[10] using a lower dose given daily for 4 years or until relapse found no additional benefit from isotretinoin.

1. Kovach BT, *et al.* Systemic strategies for chemoprevention of skin cancers in transplant recipients. *Clin Transplant* 2005; **19:** 726–34.
2. Chen K, *et al.* Oral retinoids for the prevention of skin cancers in solid organ transplant recipients: a systematic review of randomized controlled trials. *Br J Dermatol* 2005; **152:** 518–23.
3. Neuhaus IM, Tope WD. Practical retinoid chemoprophylaxis in solid organ transplant recipients. *Dermatol Ther* 2005; **18:** 28–33.
4. Campbell RM, DiGiovanna JJ. Skin cancer chemoprevention with systemic retinoids: an adjunct in the management of selected high-risk patients. *Dermatol Ther* 2006; **19:** 306–14.
5. Otley CC, *et al.* Chemoprevention of nonmelanoma skin cancer with systemic retinoids: practical dosing and management of adverse effects. *Dermatol Surg* 2006; **32:** 562–8.
6. Smith W, Saba N. Retinoids as chemoprevention for head and neck cancer: where do we go from here? *Crit Rev Oncol Hematol* 2005; **55:** 143–52.
7. Khuri FR, *et al.* Randomized phase III trial of low-dose isotretinoin for prevention of second primary tumors in stage I and II head and neck cancer patients. *J Natl Cancer Inst* 2006; **98:** 441–50.
8. Gorsky M, Epstein JB. The effect of retinoids on premalignant oral lesions: focus on topical therapy. *Cancer* 2002; **95:** 1258–64.
9. Matthay KK, *et al.* Treatment of high-risk neuroblastoma with intensive chemotherapy, radiotherapy, autologous bone marrow transplantation, and 13-cis-retinoic acid. *N Engl J Med* 1999; **341:** 1165–73.
10. Kohler JA, *et al.* A randomized trial of 13-cis retinoic acid in children with advanced neuroblastoma after high-dose therapy. *Br J Cancer* 2000; **83:** 1124–7.

Skin disorders. Apart from its established role in the treatment of acne (above), isotretinoin has been tried in many other skin disorders not responding to usual therapy.[1,2] Clinical responses to oral isotretinoin have been reported[1] in small numbers of patients with anogenital warts (p.1584), rosacea (p.1583), and lichen planus (p.1580). Benefit has also been reported for keratinisation disorders such as Darier's disease[2] (p.1578), ichthyosis[1,2] (p.1580), and pityriasis rubra pilaris.[1,2] Isotretinoin is less effective than other retinoids for psoriasis[1] (p.1583). Oral isotretinoin may be used for chemoprevention of skin cancers (see Malignant Neoplasms, above).

Topical isotretinoin has been used to reduce some of the signs of photoageing[3] (p.1581).

1. Akyol M, Özçelik S. Non-acne dermatologic indications for systemic isotretinoin. *Am J Clin Dermatol* 2005; **6:** 175–84.
2. Sehgal VN, *et al.* Isotretinoin – unapproved indications/uses and dosage: a physician's reference. *Int J Dermatol* 2006; **45:** 772–7.
3. Stratigos AJ, Katsambas AD. The role of topical retinoids in the treatment of photoaging. *Drugs* 2005; **65:** 1061–72.

Preparations

BP 2008: Isotretinoin Capsules; Isotretinoin Gel;
USP 31: Isotretinoin Capsules.

Proprietary Preparations (details are given in Part 3)
Arg.: Atlacne; Curacne; Isotrex; Retinide; Roaccutan; Scheritonin†; Zonatian; ***Austral.:*** Accure; Isohexal; Isotrex; Oratane; Roaccutane; ***Austria:*** Cicutan; Isocutan†; Isosol; Lurantal; Roaccutan; ***Belg.:*** Isosupra Lidose; Roaccutane; ***Braz.:*** Acnil; Cecnoin; Isoacne†; Isoface; Isotrex; Lurantal; Roacutan; ***Canad.:*** Accutane; Clarus; Isotrex†; ***Chile:*** Acnotin; Isotrex; Lisacne†; Piplex; Roacnetan; ***Cz.:*** Aknenormin; Curacne; Isotretin; Isotrex†; Roaccutane; Stiefel Acne Gel; ***Denm.:*** Accutin; Dermaoral†; Isotrex; Roaccutan; ***Fin.:*** Roaccutan; ***Fr.:*** Contracne; Curacne; Procuta; Roaccutane; ***Ger.:*** Aknefug Iso; Aknenormin; Isoderm; Isotret; Isotrex; Roaccutan; ***Gr.:*** A-Cnotren; Accuran; Acnogen; Aknesil; Curacne; Derminoin†; Flitrion; Inotrin; Isodermal; Isogeni†; Isoskin; Isotroin; Lyotret; Noitron; Noroseptan; Novacne; Opridan; Policano; Reducar; Roaccutane; Stiefotrex; Trecifan; Tretin; ***Hong Kong:*** Acnotin; Isotrex; Oratane†; Roaccutane; ***Hung.:*** Aknenormin; Isotrex; Roaccutan; Sotret; Tretinak; ***India:*** Acutret†; Isotroin; ***Irl.:*** Isotrex; Roaccutane; ***Israel:*** Curatane; Isotrex; Roaccutane; ***Ital.:*** Aisoskin; Isotrex; Roaccutan; ***Malaysia:*** Acnotin; Isotrex; Nimegen; Oratane; Roaccutane; ***Mex.:*** Isoface; Isotrex; Neotrex; Oratane; Roaccutan; Sotrexe; ***Neth.:*** Roaccutane; ***NZ:*** Isotane; Isotrex; Oratane; Roaccutane†; ***Philipp.:*** Acnetrex; Isotrex; Roaccutane; ***Pol.:*** Aknenormin; Curacne; Isotrex; Izotek; Roaccutane; Tretinex; ***Port.:*** Isdiben; Isoprotil; Isotrex; Orotrex; Roaccutan†; ***S.Afr.:*** Acnetane; Isotrex; Oratane; Roaccutane; ***Singapore:*** Acnotin; Isotrex; Nimegen; Oratane; Roaccutane; ***Spain:*** Acnemin; Dercutane; Farmacne; Flexresan; Isdiben; Iso Estedi†; Isotrex; Roacutan; ***Switz.:*** Curakne; Liderma; Roaccutane; Tretinac; ***Thai.:*** Acnotin; Isotane; Isotrex; Proacne; Roaccutane; Sotret; ***Turk.:*** Roaccutane; ***UK:*** Isotrex; Roaccutane; ***USA:*** Accutane; Amnesteem; Claravis; Sotret; ***Venez.:*** Cuticlin; Isoface; Isotrex†; Roaccutan.

Multi-ingredient: ***Austria:*** Isotrex; Isotrexin; ***Braz.:*** Isotrexin; Isotrexol; ***Cz.:*** Isotrexin; ***Fr.:*** Antibiotrex; ***Ger.:*** Isotrexin; ***Hung.:*** Isotrexin; ***Irl.:*** Isotrexin; ***Ital.:*** Isotrexin; ***Pol.:*** Isotrexin; ***Port.:*** Isotrexin; ***Singapore:*** Isotrexin; ***Spain:*** Isotrex Eritromicina; ***Thai.:*** Isotrexin; ***UK:*** Isotrexin.

Keluamid

Keluamida.

Келуамид

Profile
Keluamid has keratolytic properties and has been used in topical preparations for the treatment of seborrhoeic dermatitis and other scaling skin disorders.

Preparations
Proprietary Preparations (details are given in Part 3)
Arg.: Kelual; ***Fr.:*** Kelual.

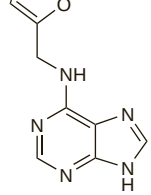
Multi-ingredient: ***Arg.:*** Kelual Zinc; ***Fr.:*** Kelual DS; Kelual Zinc; Kertyol-S.

Kinetin

N^6-Furfuryladenine; 6-Furfurylaminopurine.

Кинетин

$C_{10}H_9N_5O$ = 215.2.
CAS — 525-79-1.



NOTE. The name kinetin has also been used as a proprietary name for hyaluronidase (p.2321).

Profile
Kinetin is a plant growth hormone that has been promoted in products for the management of photodamaged skin and hyperpigmentation but good evidence of efficacy appears to be lacking.

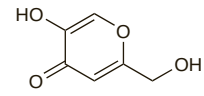
Preparations
Proprietary Preparations (details are given in Part 3)
Arg.: Kinerase†; ***Braz.:*** Kinerase; ***Hong Kong:*** Kinerase; ***Malaysia:*** Kinerase†; ***Mex.:*** Kinerase; ***Singapore:*** Kinerase; ***USA:*** Kinerase.

Kojic Acid

Kójico, ácido. 5-Hydroxy-2-hydroxymethyl-4-pyrone.

Койевая Кислота

$C_6H_6O_4$ = 142.1.
CAS — 501-30-4.



Profile
Kojic acid is reported to inhibit melanin production and is used in topical preparations for the treatment of hyperpigmentation disorders (p.1582). Kojic acid is also used as a food additive.

◊ References.

1. Lim JT. Treatment of melasma using kojic acid in a gel containing hydroquinone and glycolic acid. *Dermatol Surg* 1999; **25:** 282–4.

Preparations
Proprietary Preparations (details are given in Part 3)
Chile: Unitone 4.

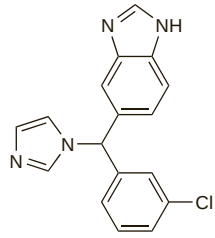
Multi-ingredient: ***Arg.:*** Cellskinlab Phyto Spot; Melasoft†; Neoquin; ***Braz.:*** Melani-D Maos; ***Chile:*** Alastik†; D 4†; Neostrata; Phyto Spot; Primacy Phyto +†; ***Mex.:*** Nova Derm; ***Port.:*** Despigmentante; Fade Cream†.

Liarozole *(BAN, rINN)*

Liarozol; Liarozolum. (±)-5-(*m*-Chloro-α-imidazol-1-ylbenzyl)benzimidazole.

Лиарозол

$C_{17}H_{13}ClN_4$ = 308.8.
CAS — 115575-11-6; 145858-51-1.



Liarozole Fumarate *(BANM, USAN, rINNM)*

Fumarato de liarozol; Liarozole, Fumarate de; Liarozoli Fumaras; R-85246.

Лиарозола Фумарат

$2C_{17}H_{13}ClN_4,3C_4H_4O_4$ = 965.7.
CAS — 145858-52-2.

Liarozole Hydrochloride *(BANM, USAN, rINNM)*

Hidrocloruro de liarozol; Liarozole, Chlorhydrate de; Liarozoli Hydrochloridum; R-75251.

Лиарозола Гидрохлорид

$C_{17}H_{13}ClN_4$, HCl = 345.2.
CAS — 145858-50-0.

Profile
Liarozole, an imidazole analogue, increases plasma and cutaneous retinoic acid concentrations through inhibition of cytochrome P450 isoenzymes involved in retinoic acid catabolism. It is under investigation for the management of ichthyoses and psoriasis.

◊ References.

1. Bhushan M, *et al.* Oral liarozole in the treatment of palmoplantar pustular psoriasis: a randomized, double-blind, placebo-controlled study. *Br J Dermatol* 2001; **145:** 546–53.
2. Lucker GPH, *et al.* Topical liarozole in ichthyosis: a double-blind, left-right comparative study followed by a long-term open maintenance study. *Br J Dermatol* 2005; **152:** 566–9.
3. Verfaille CJ, *et al.* Oral liarozole vs. acitretin in the treatment of ichthyosis: a phase II/III multicentre, double-blind, randomized, active-controlled study. *Br J Dermatol* 2007; **156:** 965–73.