Because of potential teratogenicity lenalidomide use is restricted in women of child-bearing potential, see also under Thalidomide, p.2397.

Interactions

Lenalidomide may increase peak plasma concentrations of digoxin. Epoetins or other drugs that increase the risk of thrombosis should be used with caution in patients taking lenalidomide.

Pharmacokinetics

Lenalidomide is rapidly absorbed with maximum plasma concentrations occurring between about 0.6 and 1.5 hours after an oral dose. Giving lenalidomide with food may reduce plasma concentrations but not the extent of absorption. Binding to plasma proteins is about 30%. About two-thirds of a dose is eliminated unchanged through the kidneys. The elimination half-life is about 3 hours after a 5 mg-dose; half-life increases with dose. Clearance decreases proportionally with renal function.

Uses and Administration

Lenalidomide is an analogue of thalidomide (p.2397) that has immunomodulatory and antiangiogenic properties. It is given orally for the treatment of patients with transfusion-dependent anaemia due to myelodysplastic syndromes (p.654) associated with certain abnormalities of chromosome 5 (deletion 5q abnormalities). The recommended initial dose is 10 mg daily. Lenalidomide is also used orally with dexamethasone for the treatment of patients with multiple myeloma (p.658) who have received at least one prior therapy. The recommended starting dose of lenalidomide is 25 mg daily, given for 21 days of a 28-day cycle. The recommended oral dose of dexamethasone is 40 mg daily on days 1 to 4, days 9 to 12, and days 17 to 20 of each 28-day cycle, for the first 4 cycles, and then 40 mg daily on days 1 to 4 of each 28-day cycle thereafter.

Lenalidomide is associated with significant neutropenia and thrombocytopenia, and dosage is adjusted according to haematological toxicity.

◊ References.

1. List A, *et al.* Efficacy of lenalidomide in myelodysplastic syndromes. *N Engl J Med* 2005; **352:** 549–57.
2. Anderson KC. Lenalidomide and thalidomide: mechanisms of action—similarities and differences. *Semin Hematol* 2005; **42** (suppl 4): S3–S8.
3. Hideshima T, *et al.* Current therapeutic uses of lenalidomide in multiple myeloma. *Expert Opin Invest Drugs* 2006; **15:** 171–9.
4. List A, *et al.* Myelodysplastic Syndrome-003 Study Investigators. Lenalidomide in the myelodysplastic syndrome with chromosome 5q deletion. *N Engl J Med* 2006; **355:** 1456–65.
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6. Rao KV. Lenalidomide in the treatment of multiple myeloma. *Am J Health-Syst Pharm* 2007; **64:** 1799–1807.
7. Lacy MQ, *et al.* Long-term results of response to therapy, time to progression, and survival with lenalidomide plus dexamethasone in newly diagnosed myeloma. *Mayo Clin Proc* 2007; **82:** 1179–84.
8. Dimopoulos M, *et al.* Multiple Myeloma (010) Study Investigators. Lenalidomide plus dexamethasone for relapsed or refractory multiple myeloma. *N Engl J Med* 2007; **357:** 2123–32.
9. Weber DM, *et al.* Multiple Myeloma (009) Study Investigators. Lenalidomide plus dexamethasone for relapsed multiple myeloma in North America. *N Engl J Med* 2007; **357:** 2133–42.
10. Chanan-Khan AA, Cheson BD. Lenalidomide for the treatment of B-cell malignancies. *J Clin Oncol* 2008; **26:** 1544–52.

Administration in renal impairment. Lenalidomide is eliminated mainly via the kidneys as unchanged drug. Clearance decreases as renal function decreases, prolonging the elimination half-life and increasing exposure to the drug. A study recommended that dose adjustments be made for patients with creatinine clearance (CC) less than 50 mL/minute; a 40% reduction to 60% of the starting dose was recommended for these patients. For those with CC less than 30 mL/minute, the reduced dose should be given at extended dosing intervals. About 30% of circulating lenalidomide was removed by a 4-hour session of haemodialysis.[1]

UK licensed product information makes the following recommendations at the start of oral therapy for patients with multiple myeloma and renal impairment:

- mild renal impairment (CC greater than or equal to 50 mL/minute): 25 mg once daily (full dose)
- moderate renal impairment (CC from 30 mL/minute to less than 50 mL/minute): 10 mg once daily. This dose may be increased to 15 mg once daily after 2 cycles if the patient is not responding to treatment, but is tolerating lenalidomide
- severe renal impairment (CC less than 30 mL/minute, not requiring dialysis): 15 mg every other day
- end-stage renal disease (CC less than 30 mL/minute, requiring dialysis): 15 mg, three times weekly, after dialysis

1. Chen N, *et al.* Pharmacokinetics of lenalidomide in subjects with various degrees of renal impairment and in subjects on hemodialysis. *J Clin Pharmacol* 2007; **47:** 1466–75.

Preparations

Proprietary Preparations (details are given in Part 3)
Cz.: Revlimid; ***Fr.:*** Revlimid; ***Port.:*** Revlimid; ***UK:*** Revlimid; ***USA:*** Revlimid.

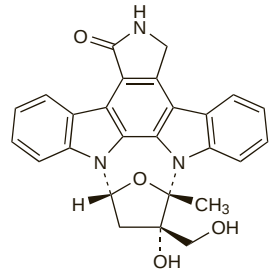
Lestaurtinib *(USAN, rINN)*

A-154475.0; CEP-701; KT-5555; Lestaurtinibum; SP-924. (9*S*,10*S*,12*R*)-10-Hydroxy-10-(hydroxymethyl)-9-methyl-2,3,9,10,11,12-hexahydro-1*H*-9,12-epoxydiindolo[1,2,3-*fg*:3′,2′,1′-*kl*]pyrrolo[3,4-*i*][1,6]benzodiazocin-1-one.

Лестауртиниб

$C_{26}H_{21}N_3O_4$ = 439.5.

CAS — 111358-88-4.



Profile

Lestaurtinib is a tyrosine kinase inhibitor that is under investigation for the treatment of acute myeloid leukaemia.

Letrozole *(BAN, USAN, rINN)* ⊗

CGS-20267; Letrotsoli; Letrozol; Létrozole; Letrozolum. 4,4′-(1*H*-1,2,4-Triazol-1-ylmethylene)dibenzonitrile.

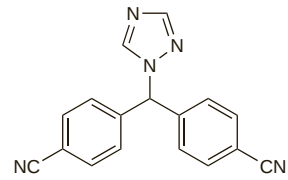
Летрозол

$C_{17}H_{11}N_5$ = 285.3.

CAS — 112809-51-5.

ATC — L02BG04.

ATC Vet — QL02BG04.



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

Ph. Eur. 6.2 (Letrozole). A white or yellowish, crystalline powder. Practically insoluble in water; sparingly soluble in methyl alcohol; freely soluble in dichloromethane.

USP 31 (Letrozole). A white to yellowish, crystalline powder. Practically insoluble in water; slightly soluble in alcohol; freely soluble in dichloromethane. Store in airtight containers.

Adverse Effects and Precautions

As for Anastrozole, p.681.

Effects on the musculoskeletal system. Postmenopausal women with primary breast cancer were reported to have significant decreases in bone mineral density at the hip and lumbar spine after 24 months of letrozole therapy.[1]

1. Perez EA, *et al.* Effect of letrozole versus placebo on bone mineral density in women with primary breast cancer completing 5 or more years of adjuvant tamoxifen: a companion study to NCIC CTG MA.17. *J Clin Oncol* 2006; **24:** 3629–35.

Effects on the skin. Toxic epidermal necrolysis, attributed to letrozole, has been reported in a patient with breast cancer who was also receiving dexamethasone and omeprazole.[1] She had been switched from tamoxifen to letrozole a few weeks before the reaction occurred.

1. Chia WK, *et al.* Toxic epidermal necrolysis in patient with breast cancer receiving letrozole. *Lancet Oncol* 2006; **7:** 184–5.

Interactions

Tamoxifen. In a study[1] of postmenopausal women with breast cancer, the addition of tamoxifen reduced letrozole plasma concentrations by a mean of about 38%, but the effect of letrozole on hormone concentrations was unchanged. The mechanism and possible clinical effect of this interaction are unknown.

1. Dowsett M, *et al.* Impact of tamoxifen on the pharmacokinetics and endocrine effects of the aromatase inhibitor letrozole in postmenopausal women with breast cancer. *Clin Cancer Res* 1999; **5:** 2338–43.

Pharmacokinetics

Letrozole is rapidly and completely absorbed from the gastrointestinal tract. About 60% of letrozole in the circulation is bound to plasma protein, mainly albumin. Most of an oral dose is slowly metabolised to an inactive carbinol metabolite, which is then excreted as the glucuronide in the urine. Letrozole has a terminal elimination half-life of about 2 days.

Uses and Administration

Letrozole is a selective nonsteroidal inhibitor of the aromatase (oestrogen synthetase) system, similar to anastrozole (p.681). It is used in the treatment of advanced or locally advanced breast cancer (p.661) in postmenopausal women. It may be given as neoadjuvant (pre-operative) therapy to those with localised hormone-receptor positive disease, to allow subsequent breast-conserving surgery. Letrozole is also used for the adjuvant treatment of postmenopausal women with hormone receptor-positive early breast cancer; treatment is generally given for 5 years or until tumour relapse occurs, although optimal duration of therapy is unknown. In postmenopausal women given 5 years of adjuvant tamoxifen for early breast cancer, letrozole may be used as extended adjuvant therapy; treatment should continue for 4 years or until tumour relapse occurs, although optimal duration of therapy is unknown. The usual dose is 2.5 mg daily by mouth.

◊ References.

1. Mouridsen H, *et al.* Superior efficacy of letrozole versus tamoxifen as first-line therapy for postmenopausal women with advanced breast cancer: results of a phase III study of the International Letrozole Breast Cancer Group. *J Clin Oncol* 2001; **19:** 2596–2606.
2. Buzdar A, *et al.* Phase III, multicenter, double-blind, randomized study of letrozole, an aromatase inhibitor, for advanced breast cancer versus megestrol acetate. *J Clin Oncol* 2001; **19:** 3357–66.
3. Ellis MJ, *et al.* Letrozole is more effective neoadjuvant endocrine therapy than tamoxifen for ErbB-1- and/or ErbB-2-positive, estrogen receptor-positive primary breast cancer: evidence from a phase III randomized trial. *J Clin Oncol* 2001; **19:** 3808–16.
4. Goss PE, *et al.* A randomized trial of letrozole in postmenopausal women after five years of tamoxifen therapy for early-stage breast cancer. *N Engl J Med* 2003; **349:** 1793–1802.
5. Simpson D, *et al.* Letrozole: a review of its use in postmenopausal women with breast cancer. *Drugs* 2004; **64:** 1213–30.
6. Goss PE, *et al.* Randomized trial of letrozole following tamoxifen as extended adjuvant therapy in receptor-positive breast cancer: updated findings from NCIC CTG MA.17. *J Natl Cancer Inst* 2005; **97:** 1262–71.
7. The Breast International Group (BIG) 1-98 Collaborative Group. A comparison of letrozole and tamoxifen in postmenopausal women with early breast cancer. *N Engl J Med* 2005; **353:** 2747–57.
8. Scott LJ, Keam SJ. Letrozole: in postmenopausal hormone-responsive early-stage breast cancer. *Drugs* 2006; **66:** 353–62.
9. Gelmon K. Prescribing extended adjuvant letrozole. *Breast* 2007; **16:** 446–55.
10. Goss PE, *et al.* Late extended adjuvant treatment with letrozole improves outcome in women with early-stage breast cancer who complete 5 years of tamoxifen. *J Clin Oncol* 2008; **26:** 1948–55.
11. Muss HB, *et al.* Efficacy, toxicity, and quality of life in older women with early-stage breast cancer treated with letrozole or placebo after 5 years of tamoxifen: NCIC CTG intergroup trial MA.17. *J Clin Oncol* 2008; **26:** 1956–64.

Administration in hepatic impairment. Licensed product information in the UK and USA states that no dosage adjustment of letrozole is required for patients with mild to moderate hepatic impairment (Child-Pugh category A and B). While letrozole is contra-indicated in the UK in severe hepatic impairment (Child-Pugh category C), in the USA, it is recommended that the dose of letrozole be reduced by 50% in those patients with cirrhosis and severe hepatic impairment; the recommended dose for these patients is 2.5 mg given every other day.

Infertility. Letrozole has been investigated[1-4] as an adjunct to assisted reproduction technologies in the management of infertility (p.2080). However, concerns about this unlicensed use have been raised by the Canadian manufacturer (*Novartis, Canad.*) because of the potential for maternal and fetal toxicity, and fetal malformations:[5] licensed product information contra-indicates the use of letrozole in premenopausal women, and there have