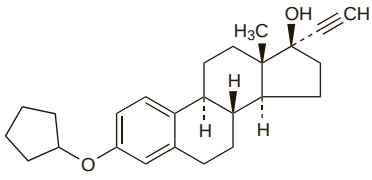
Quinestrol *(BAN, USAN, rINN)*

17α-Ethinyloestradiol 3-cyclopentyl Ether; Quinestrolum; W-3566. 3-Cyclopentyloxy-19-nor-17α-pregna-1,3,5(10)-trien-20-yn-17β-ol.

Хинэстрол

$C_{25}H_{32}O_2$ = 364.5.

CAS — 152-43-2.



Pharmacopoeias. In *Chin.*

Profile

Quinestrol is a synthetic oestrogen that has a prolonged duration of action and is metabolised to ethinylestradiol (p.2101). Quinestrol has been given orally for the treatment of menopausal symptoms and other conditions arising from oestrogen deficiency. It has also been used as the oestrogen component of combined oral contraceptive preparations.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Qui-Lea.
Multi-ingredient: ***Arg.:*** Soluna.

Raloxifene Hydrochloride

(BANM, USAN, rINNM) ⊗

Hidrocloruro de keoxifeno; Hidrocloruro de raloxifeno; Keoxifene Hydrochloride; LY-156758; LY-139481 (raloxifene); Raloksifen Hidroklorür; Raloxifène, chlorhydrate de; Raloxifeni hydrochloridum. 6-Hydroxy-2-(*p*-hydroxyphenyl)benzo[*b*]thien-3-yl-*p*-(2-piperidinoethoxy)phenyl ketone hydrochloride.

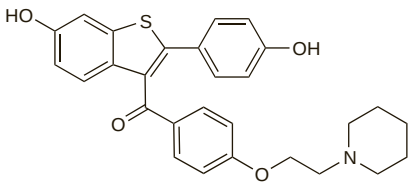
Ралоксифена Гидрохлорид

$C_{28}H_{27}NO_4S,HCl$ = 510.0.

CAS — 84449-90-1 (raloxifene); 82640-04-8 (raloxifene hydrochloride).

ATC — G03XC01.

ATC Vet — QG03XC01.



(raloxifene)

Pharmacopoeias. In *US.*

USP 31 (Raloxifene Hydrochloride). An almost white to pale yellow powder. Very slightly soluble in water, in isopropyl alcohol, and in octanol; slightly soluble in alcohol; sparingly soluble in methyl alcohol; freely soluble in dimethyl sulfoxide; practically insoluble in ether and in ethyl acetate.

Adverse Effects

The most common adverse effects of raloxifene are hot flushes, leg cramps, and a flu-like syndrome. Raloxifene is associated with an increased risk of venous thromboembolic events, particularly during the first 4 months of treatment. Peripheral oedema has also been reported. Rashes, gastrointestinal disturbances, thrombocytopenia, increased blood pressure, headache including migraine, and mild breast symptoms such as pain, enlargement, and tenderness have occurred very rarely.

Incidence of adverse effects. An observational cohort study[1] examined postmarketing adverse events that occurred during raloxifene use in primary care in England. The cohort of 13 987 patients consisted largely of women aged about 62 years, who were receiving raloxifene for the prevention or treatment of osteoporosis. Of the 461 events reported, the most common included flushing, headache or migraine, malaise or lassitude, cramp, oedema, sweating, depression, weight gain, and gastrointestinal disturbances such as nausea, vomiting, dyspepsia, and diarrhoea. Other less common effects included mastalgia and other breast symptoms, vaginal bleeding, thrombophlebitis, and visual disturbances. Rare events included cerebrovascular attack, transient ischaemic attack, pulmonary embolus, deep-vein thrombosis, bullous eruption, leucopenia, thrombocytopenia, upper gastrointestinal haemorrhage, and perforated duodenal ulcer.

The incidence of *cardiovascular* effects associated with raloxifene treatment was examined in the 4-year Multiple Outcomes of Raloxifene Evaluation (MORE), which studied its effects in postmenopausal women with osteoporosis, and in a subsequent 4-year follow-up (Continuing Outcomes Relevant to Evista; CORE).[2] There were 7705 women in the MORE study, of whom 4011 were enrolled in CORE. Overall no significant differences were seen between active treatment and placebo for any cardiovascular event over the 8 years; the calculated incidence was 72 per 10 000 woman-years in those taking raloxifene and 62 per 10 000 in the placebo group. Another large placebo-controlled study[3] (Raloxifene Use for The Heart: RUTH) investigated the cardiovascular effects of raloxifene in postmenopausal women with, or at increased risk of, ischaemic heart disease. After treatment for about 5 years there was no significant difference between the groups for overall cardiovascular events and related deaths. However, in those given raloxifene there was an increased risk of fatal stroke (absolute risk increase, 0.7 per 1000 women-years) and venous thromboembolism (1.2 per 1000 women-years).

1. Layton D, *et al.* Safety profile of raloxifene as used in general practice in England: results of a prescription-event monitoring study. *Osteoporosis Int* 2005; **16:** 490–500.
2. Ensrud K, *et al.* Effect of raloxifene on cardiovascular adverse events in postmenopausal women with osteoporosis. *Am J Cardiol* 2006; **97:** 520–7.
3. Barrett-Connor E, *et al.* Effects of raloxifene on cardiovascular events and breast cancer in postmenopausal women. *N Engl J Med* 2006; **355:** 125–37.

Effects on the liver. Hepatitis, probably associated with the drug, occurred in a woman a month after starting raloxifene.[1] Non-alcoholic steatohepatitis was associated with raloxifene in a woman with minor liver dysfunction, a fatty liver, and a family history of cryptogenic liver cirrhosis.[2] Her liver function worsened during the 3 months after starting the drug, and had returned to baseline 3 months after stopping.

1. Vilches AR, *et al.* Raloxifene-associated hepatitis. *Lancet* 1998; **352:** 1524–5.
2. Takamura T, *et al.* Selective estrogen receptor modulator raloxifene-associated aggravation of nonalcoholic steatohepatitis. *Intern Med* 2007; **46:** 579–81.

Precautions

Raloxifene should be avoided in women with active venous thromboembolism, or a history of thromboembolic disorders. It should be stopped at least 72 hours before periods of prolonged immobilisation, such as post-surgical recovery. Raloxifene should be used with caution in women with risk factors for venous thromboembolism including congestive heart failure or active malignancy, or risk factors for stroke such as transient ischaemic attack or atrial fibrillation. It should be avoided in hepatic and severe renal impairment, and used with caution in moderate renal impairment (but see also Administration in Renal Impairment, below).

Raloxifene had adverse effects in *animal* teratogenicity studies and should not be used in women who are or may become pregnant. It should not be given to women with undiagnosed uterine bleeding. An increase in triglycerides has been reported in some women with a history of hypertriglyceridaemia caused by oestrogen therapy.

Interactions

Colestyramine reduces the absorption and enterohepatic recycling of raloxifene, and they should not be given together. Raloxifene may decrease the efficacy of warfarin.

Fibrates. Cholestasis developed when *fenofibrate* was given to a woman who had been on raloxifene therapy for about 3 years.[1] The authors reviewed other rare reports of liver reactions to either raloxifene or fibrates and suggested that the reaction was likely to be due to an interaction, although the mechanism was not clear.

1. Lucena MI, *et al.* Prolonged cholestasis after raloxifene and fenofibrate interaction: a case report. *World J Gastroenterol* 2006; **12:** 5244–6.

Pharmacokinetics

Raloxifene is absorbed from the gastrointestinal tract and undergoes extensive first-pass hepatic metabolism to the glucuronide conjugates. It is highly bound to plasma proteins, principally albumin and α_1-acid glycoprotein. Raloxifene undergoes enterohepatic recycling, and has a half-life of about 27 hours. It is excreted almost entirely in the faeces.

Renal impairment. The pharmacokinetics of raloxifene are not expected to be affected by renal impairment because the renally excreted fraction is only about 6% in healthy subjects. However, a study[1] in male subjects found the clearance of a single oral dose of 120 mg to be significantly reduced in 10 men with renal impairment (creatinine clearance 24 to 51 mL/minute) compared with a group of 10 with normal renal function. It was calculated that steady-state concentrations could be about 2.3 times higher in patients with renal impairment. The authors suggested that this unexpected observation might be caused by reduced metabolic clearance in the renal tubules or by impairment of biliary excretion of raloxifene glucuronides by uraemic toxins.

1. Czock D, *et al.* Raloxifene pharmacokinetics in males with normal and impaired renal function. *Br J Clin Pharmacol* 2005; **59:** 479–82.

Uses and Administration

Raloxifene hydrochloride is a selective oestrogen receptor modulator; it is a benzothiophene that appears to have oestrogen agonist effects on bone and antagonist effects in uterine and breast tissue. It is used, in oral doses of 60 mg daily, for the prevention and treatment of postmenopausal osteoporosis (below). The same dose is also used to reduce the risk of invasive breast cancer in postmenopausal women who have osteoporosis or are at high risk of invasive breast cancer (below).

◊ Reviews.

1. Khovidhunkit W, Shoback DM. Clinical effects of raloxifene hydrochloride in women. *Ann Intern Med* 1999; **130:** 431–9.
2. Snyder KR, *et al.* Raloxifene hydrochloride. *Am J Health-Syst Pharm* 2000; **57:** 1669–75.
3. Barrett-Connor E. Raloxifene: risks and benefits. *Ann N Y Acad Sci* 2001; **949:** 295–303.
4. Heringa M. Review on raloxifene: profile of a selective estrogen receptor modulator. *Int J Clin Pharmacol Ther* 2003; **41:** 331–45.
5. Trémollières F, Ribot C. Indications du raloxifène chez la femme ménopausée. *Gynecol Obstet Fertil* 2006; **34:** 147–53.

Administration in renal impairment. Although unexpected, renal impairment reduced raloxifene clearance in a pharmacokinetic study (see above). Licensed product information in the UK contra-indicates the use of raloxifene in severe renal impairment, and in the USA it advises caution in moderate and severe impairment. Nevertheless, raloxifene has been studied in postmenopausal women with renal impairment and severe osteopenia or osteoporosis. An oral dose of 60 mg daily for 1 year was given to 25 women on haemodialysis and found to improve bone mineral density of the lumbar spine, compared with 25 women given placebo; there were no reported adverse effects.[1]

1. Hernández E, *et al.* Effects of raloxifene on bone metabolism and serum lipids in postmenopausal women on chronic hemodialysis. *Kidney Int* 2003; **63:** 2269–74.

Hyperparathyroidism. The effects of raloxifene have been reported in postmenopausal women with mild primary hyperparathyroidism (p.1087). Reductions in markers of bone turnover and plasma concentrations of calcium have been described in an observational report[1] and a small, short-term, placebo-controlled study.[2] An increase in bone mineral density was also detected after 12 months of treatment with raloxifene.[1]

1. Zanchetta JR, Bogado CE. Raloxifene reverses bone loss in postmenopausal women with mild asymptomatic primary hyperparathyroidism. *J Bone Miner Res* 2001; **16:** 189–90.
2. Rubin MR, *et al.* Raloxifene lowers serum calcium and markers of bone turnover in postmenopausal women with primary hyperparathyroidism. *J Clin Endocrinol Metab* 2003; **88:** 1174–8.

Malignant neoplasms of the breast. Studies have found raloxifene to be effective for the prophylaxis of breast cancer (p.662). In a placebo-controlled study[1] of postmenopausal women with osteoporosis and no history of breast cancer (MORE), the use of raloxifene for about 3 years reduced the risk of developing breast cancer. This was seen as a reduction in the risk of invasive oestrogen-receptor positive breast cancer, as there was no effect on the risk of oestrogen-receptor negative disease. The reduction in risk was maintained in an extension[2] of this study (CORE) to a total of 8 years of treatment. Similar results were reported in a large placebo-controlled study (RUTH)[3] of postmenopausal women who were treated for about 5 years. Both MORE/CORE[4] and RUTH[3] reported risk reduction in women at either high or low risk, but the MORE study[4] found the effect to be greater in women with a family history of breast cancer.

In a study[5] of postmenopausal women with a predicted increased risk of breast cancer (STAR), prophylactic raloxifene for up to 5 years was found to be as effective as tamoxifen in reducing the risk of invasive breast cancer.

1. Cummings SR, *et al.* The effect of raloxifene on risk of breast cancer in postmenopausal women: results from the MORE randomized trial. *JAMA* 1999; **281:** 2189–97. Correction. *ibid.*; **282:** 2124.
2. Martino S, *et al.* Continuing outcomes relevant to Evista: breast cancer incidence in postmenopausal osteoporotic women in a randomized trial of raloxifene. *J Natl Cancer Inst* 2004; **96:** 1751–61.