improve within three menstrual cycles, but can be used for as long as the patient finds it to be beneficial.[3] *Etamsylate* has been used for menorrhagia, but it is less effective than NSAIDs and tranexamic acid, and is no longer recommended.[1,3]

In women who require contraception, a *combined oral contraceptive* appears to be effective,[1,3] although good evidence of this is actually lacking.[6] It has been suggested that extended-cycle regimens should be considered for women with menorrhagia, as there are fewer bleeding episodes per year of treatment.[2] Traditional therapy with *progestogens* such as norethisterone or medroxyprogesterone given during the luteal phase appears to be ineffective in women with normal ovulatory cycles,[1,3,7] although cyclical therapy may be of benefit in anovulatory patients as it imposes a cycle.[2] Progestogen therapy for 21 days of the cycle results in a significant reduction in menstrual blood loss,[1,3,7] but is associated with adverse effects that may limit its acceptability. Long-acting injectable progestogens, such as medroxyprogesterone acetate, reduce menstrual blood loss or induce amenorrhoea when they are used as contraceptives. They have therefore been used for menorrhagia, although specific studies for this indication are lacking.[1,3]

More recently, a contraceptive *levonorgestrel-containing IUD* has been shown to be very effective in reducing menstrual blood loss in menorrhagia.[1,2] UK guidelines[3] suggest that it should be considered first when either hormonal or non-hormonal treatment is acceptable and long-term use is anticipated, although comparative data are scanty.[8] There is also some evidence that it may be an effective alternative to surgery, but data from long-term follow-up are needed.[9] As there can be changes in bleeding pattern associated with this device, particularly in the first few cycles, use for at least 6 months is advised to enable full assessment of benefit.[3]

Danazol is also effective,[10] producing about a 50% reduction in menstrual blood loss,[1] but has significant adverse effects and treatment is usually limited to 3 to 6 months. *Gonadorelin analogues* are effective for menorrhagia associated with fibroids (p.2107).[1] When used pre-operatively for endometrial thinning, they produce more consistent results than danazol.[11] Gonadorelin analogues may therefore be considered before surgery or when other options for fibroids are contra-indicated, but 'add-back' hormone replacement is recommended for the management of adverse effects from oestrogen deficiency or if they are used for more than 6 months.[3]

In patients who fail to respond to drug treatment, or in whom such therapy is inappropriate, various *surgical options* exist. Conservative surgical techniques, where the endometrium is ablated or resected, are increasingly being used, and are an effective alternative to hysterectomy.[3,12] Hysterectomy is the ultimate therapy, but is associated with significant morbidity.

1. Roy SN, Bhattacharya S. Benefits and risks of pharmacological agents used for the treatment of menorrhagia. *Drug Safety* 2004; **27:** 75–90.
2. Nelson AL, Teal SB. Medical therapies for chronic menorrhagia. *Obstet Gynecol Surv* 2007; **62:** 272–81.
3. National Collaborating Centre for Women's and Children's Health/NICE. Heavy menstrual bleeding (issued January 2007). Available at: http://www.nice.org.uk/nicemedia/pdf/CG44FullGuideline.pdf (accessed 27/06/08)
4. Lethaby A, *et al*. Nonsteroidal anti-inflammatory drugs for heavy menstrual bleeding. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2007 (accessed 27/06/08).
5. Lethaby A, *et al*. Antifibrinolytics for heavy menstrual bleeding. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2000 (accessed 27/06/08).
6. Iyer V, *et al*. Oral contraceptive pills for heavy menstrual bleeding. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 1997 (accessed 27/06/08).
7. Lethaby A, *et al*. Cyclical progestogens for heavy menstrual bleeding. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2008 (accessed 27/06/08).
8. Lethaby AE, *et al*. Progesterone or progestogen-releasing intrauterine systems for heavy menstrual bleeding. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2005 (accessed 27/06/08).
9. Marjoribanks J, *et al*. Surgery versus medical therapy for heavy menstrual bleeding. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2006 (accessed 27/06/08).
10. Beaumont H, *et al*. Danazol for heavy menstrual bleeding. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2007 (accessed 27/06/08).
11. Sowter MC, *et al*. Pre-operative endometrial thinning agents before endometrial destruction for heavy menstrual bleeding. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2002 (accessed 27/06/08).
12. Lethaby A, *et al*. Endometrial resection and ablation versus hysterectomy for heavy menstrual bleeding. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 1999 (accessed 27/06/08).

Miscarriage. Threatened miscarriage is a common complication of pregnancy that presents before 20 weeks of gestation as vaginal bleeding, with or without abdominal pain, while the cervix is closed and the fetus is viable. Endogenous progesterone is normally produced by the corpus luteum to maintain pregnancy, and low concentrations have been associated with pregnancy loss. Progestogen therapy has therefore been widely used in the treatment of threatened miscarriage,[1] but there is a paucity of clinical study data to support routine use.[2] Similarly, progestogens have been used prophylactically to prevent miscarriage, but studies have suffered from various limitations.[3] A systematic review[4] found no evidence to support routine use, but there was limited evidence to suggest that women with a history of recurrent miscarriage (3 or more consecutive miscarriages) might gain some benefit. The *BNF* advises that progestogen prophylaxis in women with a history of recurrent miscarriage is not recommended. (See also Pregnancy, above, for reports of hypospadias in the offspring of women given hormonal support therapy.)

1. Sotiriadis A, *et al*. Threatened miscarriage: evaluation and management. *BMJ* 2004; **329:** 152–5.
2. Wahabi HA, *et al*. Progestogen for treating threatened miscarriage. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2007 (accessed 27/06/08).
3. Walch KT, Huber JC. Progesterone for recurrent miscarriage: truth and deceptions. *Best Pract Res Clin Obstet Gynaecol* 2008; **22:** 375–89.
4. Haas DM, Ramsey PS. Progestogen for preventing miscarriage. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2008 (accessed 27/06/08).

Premature labour. Recommendations have been made regarding progesterone therapy for the prevention of premature birth in women at risk of preterm delivery (see under Hydroxyprogesterone Caproate, p.2110).

Premenstrual syndrome. Progestogen therapy was once popular for premenstrual syndrome, but beneficial responses have not been universally achieved and the theory that progesterone was necessary to correct a hormone imbalance is now losing ground (see p.2099). Progesterone has been given orally, vaginally, and rectally, in continuous and luteal phase regimens. However, systematic reviews[1,2] have found no convincing evidence to support its use.

1. Wyatt K, *et al*. Efficacy of progesterone and progestogens in management of premenstrual syndrome: systematic review. *BMJ* 2001; **323:** 776–80.
2. Ford O, *et al*. Progesterone for premenstrual syndrome. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2006 (accessed 27/06/08).

Preparations

BP 2008: Progesterone Injection;
USP 31: Progesterone Injectable Suspension; Progesterone Injection; Progesterone Intrauterine Contraceptive System; Progesterone Vaginal Suppositories.

Proprietary Preparations (details are given in Part 3)
Arg.: Crinone; Faselut†; Gester; Mafel; Progest; Proluton; Utrogestan; ***Austral.:*** Crinone; Proluton; ***Austria:*** Utrogestan; ***Belg.:*** Crinone; Progestogel; Utrogestan; ***Braz.:*** Crinone; Evocanil; Utrogestan; ***Canad.:*** Crinone; Prometrium; ***Chile:*** Crinone†; Hormoral; Progendo; Progering; ***Cz.:*** Agolutin; Crinone; Utrogestan; ***Denm.:*** Crinone; ***Fin.:*** Crinone; Lugesteron; ***Fr.:*** Estima; Evapause†; Progestogel; Utrogestan; ***Ger.:*** Crinone; Progestogel; Utrogest; ***Gr.:*** Crinone; Promenorea; Utrogestan; ***Hong Kong:*** Crinone; Cyclogest; Endometrin; Progestogel; Utrogestan; ***Hung.:*** Utrogestan; ***India:*** Crinone; Dubagest; Naturogest; Profine†; Progest†; Remens; Uterone; ***Indon.:*** Crinone; ***Irl.:*** Crinone; Utrogestan; ***Israel:*** Crinone; Endometrin; Gestone; Utrogestan; ***Ital.:*** Crinone; Esolut; Lutogin†; Progeffik; Progestogel†; Progestol†; Prometrium; Prontogest; ***Malaysia:*** Crinone; Cyclogest; Utrogestan†; ***Mex.:*** Crinone; Cuerpo Amarillo Fuerte; Gepromi; Geslutin; Gestageno; Premastan; Prosphere; Utrogestan; ***Neth.:*** Progestan; ***Norw.:*** Crinone; ***NZ:*** Crinone; Gestone; ***Philipp.:*** Crinone; ***Pol.:*** Luteina; ***Port.:*** Crinone; Progenar†; Progestogel; Utrogestan; ***Rus.:*** Crinone (Крайнон); Progestogel (Прожестожель); Utrogestan (Утрожестан); ***S.Afr.:*** Crinone; Cyclogest; Utrogestan; ***Singapore:*** Crinone; Cyclogest; Utrogestan†; ***Spain:*** Crinone; Darstin; Progeffik; Progestogel†; Progestosol; Utrogestan; ***Swed.:*** Crinone; ***Switz.:*** Crinone; Progestogel; Utrogestan; ***Thai.:*** Crinone; Cyclogest; Gestone†; Progestogel; Utrogestan; ***Turk.:*** Crinone; Cyclogest; Progestan; ***UK:*** Crinone; Cyclogest; Gestone; Utrogestan; ***USA:*** Crinone; Endometrin; Prochieve; Progestasert†; Prometrium; ***Venez.:*** Crinone; Progendo; Progestogel; Utrogestan.

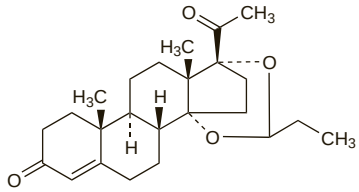
Multi-ingredient: ***Arg.:*** Cristerona; Fempack; Hosterona; Lubriderm; Menstrogen; Tropivag Plus; ***Braz.:*** Ginecoside†; Normomensil†; ***Fr.:*** Florgynal; Synergon; Trophigil; ***Ger.:*** Jephagynon†; ***Ital.:*** Biormon†; Menovis; ***Malaysia:*** Duogynon; ***Mex.:*** Damax; Genofort; Lutoginestryl F; Metrigen Fuerte; Ominol†; Primoson-F; Progediol†; Proger-F; ***Port.:*** Emmenovis†; ***Thai.:*** Duoton; Phenokinon-F; ***Turk.:*** Di-Pro; Synergon; ***Venez.:*** Cyclogesterin†; Ginecosid.

Proligestone *(BAN, rINN)*

Proligeston; Proligestona; Proligestoni; Proligestonum. 14a,17α-Propylidene dioxypregn-4-ene-3,20-dione.

Пролигестон

$C_{24}H_{34}O_4$ = 386.5.
CAS — 23873-85-0.
ATC Vet — QG03DA90.



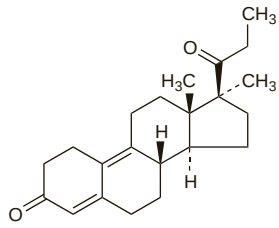
Profile
Proligestone is a progestogen used in veterinary medicine.

Promegestone *(rINN)*

Promegestona; Promégestone; Promegestonum; R-5020. 17α-Methyl-17-propionylestra-4,9-dien-3-one.

Промегестон

$C_{22}H_{30}O_2$ = 326.5.
CAS — 34184-77-5.
ATC — G03DB07.
ATC Vet — QG03DB07.



Profile
Promegestone is a progestogen structurally related to progesterone (p.2125). It has been given orally on a cyclical basis, in doses of 125 to 500 micrograms daily, in the treatment of menstrual disorders and mastalgia, and as the progestogen component of menopausal HRT.

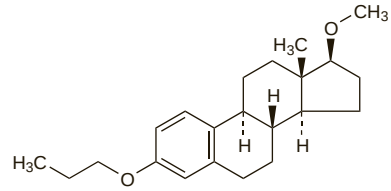
Preparations
Proprietary Preparations (details are given in Part 3)
Fr.: Surgestone; ***Port.:*** Surgestone.

Promestriene *(rINN)*

Promestrien; Promestrième; Promestrieno; Promestrienum. 17β-Methoxy-3-propoxyestra-1,3,5(10)-triene.

Проместриен

$C_{22}H_{32}O_2$ = 328.5.
CAS — 39219-28-8.
ATC — G03CA09.
ATC Vet — QG03CA09.



Profile
Promestriene is a derivative of estradiol (p.2097) that has been used topically in menopausal atrophic vaginitis, and in seborrhoea and acne.

Preparations
Proprietary Preparations (details are given in Part 3)
Arg.: Colpotrophine; ***Braz.:*** Colpotrofine; ***Cz.:*** Colpotrophine†; ***Hong Kong:*** Colpotrophine; ***Ital.:*** Colpotrophine; ***Mex.:*** Colpotrophine; ***Port.:*** Colpotrophine; ***Singapore:*** Colpotrophine; ***Spain:*** Colpotrofin; Delipoderm; ***Switz.:*** Colpotrophine; ***Turk.:*** Colpotrophine; ***Venez.:*** Colpotrofina†.

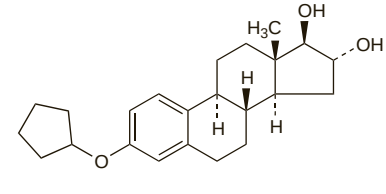
Multi-ingredient: ***Cz.:*** Colposeptine†; ***Hong Kong:*** Colposeptine; ***Port.:*** Trophoseptine; ***Turk.:*** Colposeptine.

Quinestradol *(BAN, rINN)*

Oestriol 3-Cyclopentyl Ether; Quinestradiol; Quinestradolum. 3-Cyclopentyloxyestra-1,3,5(10)-triene-16α,17β-diol.

Хинэстрадол

$C_{23}H_{32}O_3$ = 356.5.
CAS — 1169-79-5.



Profile
Quinestradol is a synthetic oestrogen that has been given orally for the treatment of menopausal vaginal symptoms.

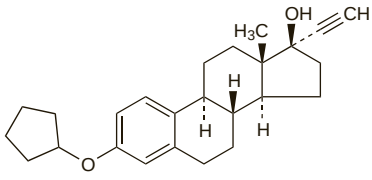
Quinestrol *(BAN, USAN, rINN)*

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.

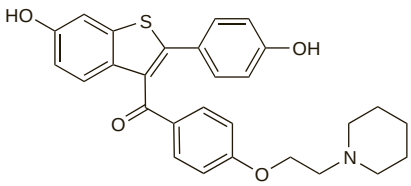
Ралоксифена Гидрохлорид

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