EVISTA®
60mg film coated tablets
raloxifene hydrochloride

1. NAME OF THE MEDICINAL PRODUCT
EVISTA 60 mg film coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Each film coated tablet contains 60 mg raloxifene hydrochloride, equivalent to 56 mg raloxifene free base.

Excipients with known effect:
Each tablet contains lactose (149.40 mg).

For excipients, see Section 6.1.

3. PHARMACEUTICAL FORM
Film coated tablets for oral use. Elliptically shaped, white tablets imprinted with the code 4165.

4. CLINICAL PARTICULARS
4.1. Therapeutic indications
EVISTA is indicated for the treatment and prevention of osteoporosis in postmenopausal women. A significant reduction in the incidence of vertebral, but not hip fractures has been demonstrated. For those postmenopausal women taking EVISTA for osteoporosis treatment, EVISTA has been to shown to reduce the risk of invasive breast cancer.

When determining the choice of EVISTA or other therapies, including oestrogens, for an individual postmenopausal woman, consideration should be given to menopausal symptoms, effects on uterine and breast tissues, and cardiovascular risks and benefits (see Section 5.1).

4.2. Posology and method of administration
The recommended posology is one tablet daily by oral administration, which may be taken at any time of the day without regard to meals. Due to the nature of this disease process, EVISTA is intended for long term use.
Generally calcium and vitamin D supplements are advised in women with a low dietary intake.

Elderly
No dose adjustment is necessary for the elderly.

Renal impairment
EVISTA should not be used in patients with severe renal impairment (see section 4.3). In patients with moderate and mild renal impairment, EVISTA should be used with caution.

Hepatic impairment
EVISTA should not be used in patients with hepatic impairment (see section 4.3 and 4.4).

Paediatric population

EVISTA should not be used in children of any age. There is no relevant use of EVISTA in the paediatric population.

4.3. Contraindications

Hypersensitivity to the active substance or to any of the excipients.
Must not be used in women with child bearing potential. EVISTA therapy during pregnancy may be associated with an increased risk of congenital defects in the fetus.
Active or past history of venous thromboembolic events (VTE), including deep vein thrombosis, pulmonary embolism and retinal vein thrombosis.
Hepatic impairment including cholestasis.
Severe renal impairment.
Unexplained uterine bleeding.
EVISTA should not be used in patients with signs or symptoms of endometrial cancer as safety in this patient group has not been adequately studied.

4.4. Special warnings and precautions for use

Raloxifene is associated with an increased risk for venous thromboembolic events that is similar to the reported risk associated with current use of hormone replacement therapy. The risk-benefit balance should be considered in patients at risk of venous thromboembolic events of any aetiology. EVISTA should be discontinued in the event of an illness or a condition leading to a prolonged period of immobilisation. Discontinuation should happen as soon as possible in case of the illness, or from 3 days before the immobilisation occurs. Therapy should not be restarted until the initiating condition has resolved and the patient is fully mobile. In a study of postmenopausal women with documented coronary heart disease or at increased risk for coronary events, raloxifene did not affect the incidence of myocardial infarction, hospitalized acute coronary syndrome, overall mortality, including overall cardiovascular mortality, or stroke, compared to placebo. However, there was an increase in death due to stroke in women assigned to raloxifene. The incidence of stroke mortality was 1.5 per 1000 women per year for placebo versus 2.2 per 1000 women per year for raloxifene. This finding should be considered when prescribing raloxifene for postmenopausal women with a history of stroke or other significant stroke risk factors, such as transient ischemic attack or atrial fibrillation. There is no evidence of endometrial proliferation. Any uterine/genital bleeding during EVISTA therapy is unexpected and should be fully investigated by a specialist.
The two most frequent diagnoses associated with uterine bleeding during raloxifene treatment were endometrial atrophy and benign endometrial polyps. In postmenopausal women who received raloxifene treatment for 4 years, benign endometrial polyps were reported in 0.9% compared with 0.3% in women who received placebo treatment.
Raloxifene is metabolised primarily in the liver. Single doses of raloxifene given to patients with cirrhosis and mild hepatic impairment (Child-Pugh class A) with total serum bilirubin ranging from 0.6 to 2.0 mg/dL, produced plasma concentrations of raloxifene which were approximately 2.5 times the controls. The increase correlated with total bilirubin concentrations. Until safety and efficacy have been evaluated further in patients with hepatic insufficiency, the use of EVISTA is not recommended in this patient population. Serum total bilirubin, gamma-glutamyl transferase, alkaline phosphatase, ALT and AST should be closely monitored during treatment if elevated values are observed.
Premenopausal Use: There is no indication for premenopausal use of raloxifene (see section 4.3).
Limited clinical data suggest that in patients with a history of oral estrogen-induced hypertriglyceridemia (>5.6 mmol/l), raloxifene may be associated with a marked increase in serum triglycerides. Patients with this medical history should have serum triglycerides monitored when taking raloxifene.

The safety of EVISTA in patients with breast cancer has not been adequately studied. No data are available on the concomitant use of EVISTA and agents used in the treatment of early or advanced breast cancer. Therefore, EVISTA should be used for osteoporosis treatment and prevention only after the treatment of breast cancer, including adjuvant therapy, has been completed.
As safety information regarding co-administration of raloxifene with systemic hormone therapy (estrogens with or without progestin) is limited, such use is not recommended.
EVISTA is not effective in reducing vasodilatation (hot flushes), or other symptoms of the menopause associated with estrogen deficiency.
EVISTA contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5. Interaction with other medicinal products and other forms of interaction
Concurrent administration of either calcium carbonate or aluminium and magnesium-hydroxide containing antacids do not affect the systemic exposure of raloxifene.
Co-administration of raloxifene and warfarin does not alter the pharmacokinetics of either compound. However, modest decreases in the prothrombin time have been observed, and if raloxifene is given concurrently with warfarin or other coumarin derivatives, the prothrombin time should be monitored. Effects on prothrombin time may develop over several weeks if EVISTA treatment is started in patients who are already on coumarin anticoagulant therapy.
The chronic administration of raloxifene has no effect on the pharmacokinetics of methylprednisolone given as a single oral dose.
Raloxifene does not affect the steady-state AUC of digoxin. The C_{max} of digoxin increased by less than 5%.
The influence of concomitant medication on raloxifene plasma concentrations was evaluated in the prevention and treatment trials. Frequently co-administered medicinal products included: paracetamol, non-steroidal anti-inflammatory drugs (such as acetylsalicylic acid, ibuprofen, and naproxen), oral antibiotics, H1 antagonists, H2 antagonists, and benzodiazepines. No clinically relevant effects of the co-administration of the agents on raloxifene plasma concentrations were identified. Concomitant use of vaginal estrogen preparations was allowed in the clinical trial programme, if necessary to treat atrophic vaginal symptoms. Compared to placebo there was no increased use in EVISTA-treated patients.
In vitro, raloxifene did not interact with the binding of warfarin, phenytoin, or tamoxifen.
Raloxifene should not be co-administered with cholestyramine (or other anion exchange resins), which significantly reduces the absorption and enterohepatic cycling of raloxifene. Although not specifically studied, it is anticipated that other anion exchange resins would have a similar effect.

Peak concentrations of raloxifene are reduced with co-administration with ampicillin. However, since the overall extent of absorption and the elimination rate of raloxifene are not affected, raloxifene can be concurrently administered with ampicillin.

The following changes in analyte concentrations are commonly observed in raloxifene therapy: increased serum HDL-2 cholesterol subfraction and apolipoprotein A_1; and reduced serum total cholesterol, LDL cholesterol, fibrinogen, apolipoprotein B, and lipoprotein. Raloxifene modestly increases hormone-binding globulin concentrations, including sex steroid binding globulins (SHBG), thyroxine binding globulin (TBG), and corticosteroid binding globulin (CBG), with corresponding increases in measured total hormone concentrations. There is no evidence that these changes affect concentrations of free hormones.

Carcinogenesis, Mutagenesis, Impairment of Fertility

In a 2-year carcinogenicity study in rats, an increased incidence in ovarian tumors of granulosa/theca cell origin was observed in females given 279 mg/kg. Systemic exposure (AUC) of raloxifene in this group was approximately 400 times that in postmenopausal women administered a 60-mg dose. In a 21-month carcinogenicity study in mice, there was in increased incidence of testicular interstitial cell tumors and prostatic adenomas and adenocarcinomas in males given 41 or 210 mg/kg, and prostatic leiomyoblastoma in males given 210 mg/kg. In female mice, an increased incidence or ovarian tumors in animals given 9 to 242 mg/kg (0.3 to 32 times the AUC in humans) including benign and malignant tumors of granulosa/theca cell origin and benign tumors of epithelial cell origin. The female rodents in these studies were treated during their reproductive lives when their ovaries were functional and highly responsive to hormonal stimulation. In contrast to the highly responsive ovaries in this rodent model, the human ovary after menopause is relatively unresponsive to reproductive hormonal stimulation.

Raloxifene was not genotoxic in any of the conventional *in vivo* or *in vitro* routine test systems.

No pregnancies occurred when raloxifene (≥ 5 mg/kg) was administered to male and female rats prior to and during mating. In female rats, raloxifene disrupted estrous cycles during treatment, but fertile matings were not delayed after treatment termination, although marginally reduced litter size, increased gestation length, and altered timing of neonatal development occurred.

Treatment of mated female rats during the preimplantation period delayed and/or disrupted embryo implantation, resulting in reduced litter size. These effects on reproduction are consistent with the estrogen receptor activity of raloxifene (see section 4.3).

4.6. Pregnancy and lactation

EVISTA is only for use in postmenopausal women.

EVISTA must not be taken by women of child bearing potential. Raloxifene may cause foetal harm when administered to a pregnant woman. If this medicinal product is used mistakenly during pregnancy or the patient becomes pregnant while taking it, the patient should be informed of the potential hazard to the foetus (see Section 5.3). It is not known whether raloxifene/ raloxifene metabolites are excreted in human milk. A risk to the newborns/infants cannot be excluded. Its clinical use, therefore, cannot be recommended in lactating women. EVISTA may affect the development of the baby.

4.7. Effects on ability to drive and use machines

Raloxifene has no known effect on driving or the ability to use machinery.

4.8. Undesirable effects

a. <u>Summary of the safety profile</u>

The clinically most important adverse reactions reported in postmenopausal women treated with EVISTA were venous thromboembolic events (see section 4.4), which occurred less than 1% of treated patients.

b. <u>Tabulated summary of adverse reactions</u>

The table below gives the adverse reactions and frequencies observed in treatment and prevention studies involving over 13,000 postmenopausal women, along with adverse reactions rising from postmarketing reports.
The duration of treatment in these studies ranged from 6 to 60 months. The majority of undesirable reactions have not usually required cessation of therapy.

The frequencies of adverse reactions were based on postmarketing experience or calculated from placebo-controlled clinical trials (comprising a total of 15,234 patients, 7,601 on raloxifene 60 mg and 7,633 on placebo) in postmenopausal women with osteoporosis, or established coronary heart disease (CHD) or increased risk for CHD, without comparison to the frequencies of adverse events in the placebo assignment groups.

In the prevention population discontinuations of therapy due to any undesirable reaction occurred in 10.7% of 581 EVISTA-treated patients and 11.1% of 584 placebo-treated patients. In the treatment population discontinuations of therapy due to any clinical adverse experience occurred in 12.8% of 2,557 EVISTA-treated patients and 11.1% of 2,576 placebo-treated patients.
The undesirable reactions associated with the use of raloxifene in osteoporosis clinical trials are summarized in the table below. The following convention has been used for the classification of the adverse reactions: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1000 to <1/100), rare (≥1/10,000 to <1/1000), very rare (<1/10,000), not known (cannot be estimated from the available data).

Vascular disorders	
Very common:	Vasodilation (hot flushes)
Uncommon:	Venous thromboembolic events, including deep vein thrombosis, pulmonary embolism, retinal vein thrombosis. Superficial vein thrombophlebitis.
Nervous system disorders	
Uncommon:	Fatal strokes
Musculoskeletal and Connective Tissue Disorders	
Common:	Leg cramps
General Disorders and Administration Site Conditions	
Very common:	Flu syndrome
Common:	Peripheral oedema

Compared with placebo-treated patients the occurrence of vasodilatation (hot flushes) was modestly increased in EVISTA patients (clinical trials for the prevention of osteoporosis, 2 to 8 years postmenopausal, 24.3% EVISTA and 18.2% placebo; clinical trials for the treatment of osteoporosis, mean age 66, 10.6% for EVISTA and 7.1% placebo). This undesirable reaction was most common in the first 6 months of treatment, and seldom occurred de novo after that time.
In a study of 10,101 postmenopausal women with documented coronary heart disease or at increased risk for coronary events (RUTH), the occurrence of vasodilatation (hot flushes) was 7.8% in the raloxifene-treated patients and 4.7% in the placebo-treated patients.

Across all placebo-controlled clinical trials of raloxifene in osteoporosis,venous thromboembolic events, including deep vein thrombosis, pulmonary embolism, and retinal vein thrombosis occurred at a frequency of approximately 0.8% or 3.22 cases per 1000 patient-years. A relative risk of 1.60 (CI 0.95, 2.71) was observed in EVISTA-treated patients compared to placebo. The risk of a thromboembolic event was greatest in the first four months of therapy. Superficial vein thrombophlebitis occurred in a frequency of less than 1%.

In the RUTH study, venous thromboembolic events occurred at a frequency of approximately 2.0% or 3.88 cases per 1000 patient-years in the raloxifene group and 1.4% or 2.70 cases per 1000 patient years in the placebo group. The hazard ratio for all VTE events in the RUTH study was HR = 1.44, (1.06 – 1.95). Superficial vein thrombophlebitis occurred in a frequency of 1% in the raloxifene group and 0.6% in the placebo group.

In the RUTH study, raloxifene did not affect the incidence of stroke, compared to placebo. However, there was an increase in death due to stroke in women assigned to raloxifene. The incidence of stroke mortality was 2.2 per 1,000 women per year for raloxifene versus 1.5 per 1,000 women per year for placebo (see section 4.4). During an average follow-up of 5.6 years, 59 (1.2%) raloxifene-treated women died due to a stroke compared to 39 (0.8%) placebo-treated women.

Another undesirable reaction observed was leg cramps (5.5% for EVISTA, 1.9% for placebo in the prevention population and 9.2% for EVISTA, 6.0% for placebo in the treatment population). In the RUTH study, leg cramps were observed in 12.1% of raloxifene-treated patients and 8.3% of placebo-treated patients. Flu syndrome was reported by 16.2% of EVISTA-treated patients and 14.0% of placebo-treated patients.

One further change was seen which was not statistically significant ($p>0.05$), but which did show a significant dose trend. This was peripheral oedema which occurred in the prevention population at an incidence of 3.1% for EVISTA and 1.9% for placebo; and in the treatment population occurred at an incidence of 7.1% for EVISTA and 6.1% for placebo.

In the RUTH study, peripheral oedema occurred in 14.1% of the raloxifene-treated patients and 11.7% of the placebo-treated patients, which was statistically significant. Slightly decreased (6-10%) platelet counts have been reported during raloxifene treatment in placebo-controlled clinical trials of raloxifene in osteoporosis.

Rare cases of moderate increases in AST and/or ALT have been reported where a causal relationship to raloxifene cannot be excluded. A similar frequency of increases was noted among placebo patients.

In a study (RUTH) of postmenopausal women with documented coronary heart disease or at increased risk for coronary events, an additional adverse reaction of cholelithiasis occurred in 3.3% of patients treated with raloxifene and 2.6% of patients treated with placebo. Cholecystectomy rates for raloxifene (2.3%) were not statistically significantly different from placebo (2.0%).

EVISTA (n=317) was compared with continuous combined (n=110) hormone replacement therapy (HRT) or cyclic (n=205) HRT patients in some clinical trials. The incidence of breast symptoms and uterine bleeding in raloxifene-treated women was significantly lower than in women treated with either form of HRT.

The events reported in post-marketing experience are presented in the table below. The following convention has been used for the classification of the adverse reactions: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1000 to <1/100), rare (≥1/10,000 to <1/1000), very rare (<1/10,000), not known (cannot be estimated from the available data).

Blood and Lymphatic System Disorders	
Uncommon:	Thrombocytopenia

Gastrointestinal Disorders	
Very common:	Gastrointestinal symptoms such as nausea, vomiting, abdominal pain, dyspepsia
Investigations	
Very common:	Increased blood pressure
Nervous System Disorders	
Common:	Headache, including migraine
Skin and Subcutaneous Tissue Disorders	
Common:	Rash
Reproductive System and Breast Disorders	
Common:	*Mild breast symptoms such as pain, enlargement and tenderness*
Vascular Disorders	
Uncommon:	Arterial thromboembolic reaction

4.9. Overdose

In clinical trials, daily doses of 600 mg for 8 weeks and 120 mg for 3 years were well tolerated.

In post marketing spontaneous reports, overdose has been reported very rarely (less than 1 out of 10,000 [<0.01%] patients treated).

In adults, symptoms of leg cramps and dizziness have been reported in patients who took more than 120 mg as a single ingestion.

In accidental overdose in children younger than 2 years of age, the maximum reported dose has been 180 mg. In children, symptoms of accidental overdose included ataxia, dizziness, vomiting, rash, diarrhea, tremor, and flushing, and elevation in alkaline phosphatase.

The highest overdose has been approximately 1.5 grams. No fatalities associated with overdose have been reported.

There is no specific antidote for raloxifene hydrochloride.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmaco-therapeutic group: Selective Estrogen Receptor Modulator (SERM).

ATC code: G03XC01

As a selective estrogen receptor modulator (SERM), raloxifene has selective agonist or antagonist activities on tissues responsive to estrogen. It acts as an agonist on bone and partially on cholesterol metabolism (decrease in total and LDL-cholesterol), but not in the hypothalamus or in the uterine or breast tissues. Raloxifene's biological actions, like those of estrogen, are mediated through high affinity binding to estrogen receptors and regulation of gene expression. This binding results in differential expression of multiple estrogen-regulated genes in different tissues. Recent data suggests that the estrogen receptor can regulate gene expression by at least two distinct pathways which are ligand-, tissue-, and/or gene-specific.

a) Skeletal Effects

The decrease in estrogen availability which occurs at menopause leads to marked increases in bone resorption, bone loss and risk of fracture. Bone loss is particularly rapid for the first 10 years after menopause when the compensatory increase in bone formation is inadequate to keep up with

resorptive losses. Other risk factors which may lead to the development of osteoporosis include early menopause; osteopenia (at least 1 SD below peak bone mass); thin body build; Caucasian or Asian ethnic origin; and a family history of osteoporosis. Replacement therapies generally reverse the excessive resorption of bone. In postmenopausal women with osteoporosis, EVISTA reduces the incidence of vertebral fractures, preserves bone mass and increases bone mineral density (BMD).

Based on these risk factors, prevention of osteoporosis with EVISTA is indicated for women within ten years of menopause, with BMD of the spine between 1.0 and 2.5 SD below the mean value of a normal young population, taking into account their high lifetime risk for osteoporotic fractures. Likewise, EVISTA is indicated for the treatment of osteoporosis or established osteoporosis in women with BMD of the spine 2.5 SD below the mean value of a normal young population and/or with vertebral fractures, irrespective of BMD.

i) Incidence of fractures. In a study of 7705 postmenopausal women with a mean age of 66 years and with osteoporosis or osteoporosis with an existing fracture, EVISTA treatment for 3 years reduced the incidence of vertebral fractures by 47% (RR 0.53, CI 0.35, 0.79; $p<0.001$) and 31% (RR 0.69, CI 0.56, 0.86; $p<0.001$) respectively. Forty-five women with osteoporosis or 15 women with osteoporosis with an existing fracture would need to be treated with EVISTA for 3 years to prevent one or more vertebral fractures. EVISTA treatment for 4 years reduced the incidence of vertebral fractures by 46% (RR 0.54, CI 0.38, 0.75) and 32% (RR 0.68,CI 0.56, 0.83) in patients with osteoporosis or osteoporosis with an existing fracture respectively. In the 4th year alone, EVISTA reduced the new vertebral fracture risk by 39% (RR 0.61, CI 0.43, 0.88). An effect on nonvertebral fractures has not been demonstrated. From the 4th to the 8th year, patients were permitted the concomitant use of bisphosphonates, calcitonin, and fluorides, and all patients in this study received calcium and vitamin D supplementation.

ii) In the RUTH study, overall clinical fractures were collected as a secondary endpoint. EVISTA reduced the incidence of clinical vertebral fractures by 35% compared with placebo (HR 0.65, CI 0.47, 0.89). These results may have been confounded by baseline differences in BMD and vertebral fractures. There was no difference between treatment groups in the incidence of new nonvertebral fractures. During the whole length of the study, concomitant use of other bone-active medications was permitted.

iii) Bone Mineral Density (BMD): The efficacy of EVISTA once daily in postmenopausal women aged up to 60 years and with or without a uterus was established over a two-year treatment period. The women were 2 to 8 years postmenopausal. Three trials included 1764 postmenopausal women who were treated with EVISTA and calcium or calcium-supplemented placebo. In one of these trials the women had previously undergone hysterectomy. EVISTA produced significant increases in bone density of hip and spine as well as total body mineral mass compared to placebo. This increase was generally a 2% increase in BMD compared to placebo.A similar increase in BMD was seen in the treatment population who received EVISTA for up to 7 years. In the prevention trials, the percentage of subjects experiencing an increase or decrease in BMD during raloxifene therapy was: for the spine 37% decreased and 63% increased; and for the total hip 29% decreased and 71% increased.

iv) Calcium kinetics. EVISTA and estrogen affect bone remodelling and calcium metabolism similarly. EVISTA was associated with reduced bone resorption and a mean positive shift in calcium balance of 60 mg per day, due primarily to decreased urinary calcium losses.

v) Histomorphometry (bone quality). In a study comparing EVISTA with estrogen,bone from patients treated with either medicinal product was histologically normal, with no evidence of mineralisation defects, woven bone or marrow fibrosis. Raloxifene decreases resorption of bone; this effect on bone is manifested as reductions in the serum and urine levels of one turnover markers, decreases in bone resorption based on radiocalcium kinetics studies, increases in BMD and decreases in the incidence of fractures.

b) Effects on lipid metabolism and cardiovascular risk

Clinical trials showed that a 60 mg daily dose of EVISTA significantly decreased total cholesterol (3 to 6%), and LDL cholesterol (4 to 10%). Women with the highest baseline cholesterol levels had the greatest decreases. HDL cholesterol and triglyceride concentrations did not change significantly. After 3 years therapy EVISTA decreased fibrinogen (6.71%). In the osteoporosis treatment study, significantly fewer EVISTA-treated patients required initiation of hypolipidaemic therapy compared to placebo.

EVISTA therapy for 8 years did not significantly affect the risk of cardiovascular events in patients enrolled in the osteoporosis treatment study. Similarly, in the RUTH study, raloxifene did not affect the incidence of myocardial infarction, hospitalized acute coronary syndrome, stroke or overall mortality, including overall cardiovascular mortality, compared to placebo (for the increase in risk of fatal stroke see Section 4.4).

The relative risk of venous thromboembolic events observed during raloxifene treatment was 1.60 (CI 0.95, 2.71) when compared to placebo, and was 1.0 (CI 0.3,6.2) when compared with estrogen or hormonal replacement therapy. The risk of a thromboembolic event was greatest in the first four months of therapy.

c) Effects on the endometrium and on the pelvic floor

In clinical trials, EVISTA did not stimulate the postmenopausal uterine endometrium. Compared to placebo, raloxifene was not associated with spotting or bleeding or endometrial hyperplasia. Nearly 3000 transvaginal ultrasound (TVUs) examinations were evaluated from 831 women in all dose groups. Raloxifene-treated women consistently had an endometrial thickness which was indistinguishable from placebo. After 3 years of treatment, at least a 5 mm increase in endometrial thickness, assessed with transvaginal ultrasound, was observed in 1.9% of the 211 women treated with raloxifene 60 mg/day compared with 1.8% of the 219 women who received placebo. There were no differences between the raloxifene and placebo groups with respect to the incidence of reported uterine bleeding.

Endometrial biopsies taken after six months therapy with EVISTA 60 mg daily demonstrated non-proliferative endometrium in all patients. In addition, in a study with 2.5 times the recommended daily dose of EVISTA there was no evidence of endometrial proliferation and no increase in uterine volume.

In the osteoporosis treatment trial, endometrial thickness was evaluated annually in a subset of the study population (1644 patients) for 4 years. Endometrial thickness measurements in EVISTA-treated women were not different from baseline after4 years of therapy. There was no difference between EVISTA- and placebo-treated women in the incidences of vaginal bleeding (spotting) or vaginal discharge. Fewer EVISTA-treated women than placebo-treated women required surgical intervention for uterine prolapse. Safety information following 3 years of raloxifene treatment suggests that raloxifene treatment does not increase pelvic floor relaxation and pelvic floor surgery.

After 4 years, raloxifene did not increase the risk of endometrial or ovarian cancer. In postmenopausal women who received raloxifene treatment for 4 years, benign endometrial polyps were reported in 0.9% compared with 0.3% in women who received placebo treatment.

d) Effects on breast tissue

EVISTA does not stimulate breast tissue. Across all placebo-controlled trials, EVISTA was indistinguishable from placebo with regard to frequency and severity of breast symptoms (no swelling, tenderness and breast pain). Over the 4 years of the osteoporosis treatment trial (involving 7705 patients), EVISTA treatment compared to placebo reduced the risk of total breast cancer by 62% (RR 0.38, CI 0.21, 0.69), the risk of invasive breast cancer by 71% (RR 0.29, CI 0.13, 0.58) and the risk of invasive estrogen receptor (ER) positive breast cancer by 79% (RR 0.21, CI 0.07, 0.50). EVISTA has no effect on the risk of ER negative breast cancers. These observations support the conclusion that raloxifene has no intrinsic estrogen agonist activity in breast tissue.

The risk reduction is not applicable to estrogen receptor negative (ER-) cancers and cancers of unknown estrogen receptor status. In the study, the effect was due primarily to the reduction in ER+ breast cancer.

e) Effects on cognitive function

No adverse effects on cognitive function have been seen.

5.2. Pharmacokinetic properties

Absorption

Raloxifene is absorbed rapidly after oral administration. Approximately 60% of an oral dose is absorbed. Presystemic glucuronidation is extensive. Absolute bioavailability of raloxifene is 2%. The time to reach average maximum plasma concentration and bioavailability are functions of systemic interconversion and enterohepatic cycling of raloxifene and its glucuronide metabolites.

Distribution

Raloxifene is distributed extensively in the body. The volume of distribution is not dose dependent. Raloxifene is strongly bound to plasma proteins (98-99%).

Metabolism

Raloxifene undergoes extensive first pass metabolism to the glucuronide conjugates: raloxifene-4´-glucuronide, raloxifene-6-glucuronide, and raloxifene-6,4´-diglucuronide. No other metabolites have been detected. Raloxifene comprises less than 1% of the combined concentrations of raloxifene and the glucuronide metabolites. Raloxifene levels are maintained by enterohepatic recycling, giving a plasma half-life of 27.7 hours.

Results from single oral doses of raloxifene predict multiple dose pharmacokinetics. Increasing doses of raloxifene result in slightly less than proportional increase in the area under the plasma time concentration curve (AUC).

Excretion

The majority of a dose of raloxifene and glucuronide metabolites are excreted within 5 days and are found primarily in the faeces, with less than 6% excreted in urine.

Special populations

Renal insufficiency — Less than 6% of the total dose is eliminated in urine. In a population pharmacokinetic study, a 47% decrease in lean body mass adjusted creatinine clearance resulted in a 17% decrease in raloxifene clearance and a 15% decrease in the clearance of raloxifene conjugates.

Hepatic insufficiency — The pharmacokinetics of a single dose of raloxifene in patients with cirrhosis and mild hepatic impairment (Child-Pugh class A) have been compared with that in healthy individuals. Plasma raloxifene concentrations were approximately 2.5-fold higher than in controls and correlated with bilirubin concentrations.

5.3. Preclinical safety data

In a 2-year carcinogenicity study in rats, an increase in ovarian tumors of granulosa/theca cell origin was observed in high-dose females (279 mg/kg/day). Systemic exposure (AUC) of raloxifene in this group was approximately 400 times that in postmenopausal women administered a 60 mg dose. In a 21-month carcinogenicity study in mice, there was an increased incidence of testicular interstitial cell tumours and prostatic adenomas and adenocarcinomas in males given 41 or 210 mg/kg, and prostatic leiomyoblastoma in males given 210 mg/kg. In female mice, an increased incidence of ovarian tumours in animals given 9 to 242 mg/kg (0.3 to 32 times the AUC in humans) included benign and malignant tumours of granulosa/theca cell origin and benign tumours of epithelial cell origin. The female rodents in these studies were treated during their reproductive lives, when their ovaries were functional and highly responsive to hormonal stimulation. In contrast to the highly responsive ovaries in this rodent model, the human ovary after menopause is relatively unresponsive to reproductive hormonal stimulation.

Raloxifene was not genotoxic in any of the extensive battery of test systems applied.

The reproductive and developmental effects observed in animals are consistent with the known pharmacological profile of raloxifene. At doses of 0.1 to 10 mg/kg/day in female rats, raloxifene disrupted estrous cycles of female rats during treatment, but did not delay fertile matings after treatment termination and only marginally reduced litter size, increased gestation length, and altered the timing of events in neonatal development. When given during the preimplantation period, raloxifene delayed and disrupted embryo implantation resulting in prolonged gestation and reduced litter size but development of offspring to weaning was not affected. Teratology studies were conducted in rabbits and rats. In rabbits, abortion and a low rate of ventricular septal defects (≥0.1 mg/kg) and hydrocephaly (≥10 mg/kg) were seen. In rats retardation of foetal development, wavy ribs and kidney cavitation occurred (≥1 mg/kg). Raloxifene is a potent antiestrogen in the rat uterus and prevented growth of estrogen-dependent mammary tumours in rats and mice.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Tablet Core: Povidone, polysorbate 80, anhydrous lactose, lactose monohydrate, crospovidone, magnesium stearate.

Tablet Coating: Titanium dioxide (E 171), polysorbate 80, hypromellose, macrogol 400, carnauba wax.

Ink: Shellac, propylene glycol, indigo carmine (E 132).

6.2. Incompatibilities

Not applicable

6.3. Shelf-life

2 years

6.4. Special precautions for storage

Do not store above 30°C. Store in the original package. Do not freeze.

6.5. Nature and content of container

EVISTA tablets are packed either in PVC blisters, Aclar blisters or in high density polyethylene bottles. Blister boxes contain 14, 28, or 84 tablets. Bottles contain 100 tablets. Not all pack sizes may be marketed in all countries.

6.6. Instructions for use and handling
No special requirements.

Manufactured by:
Lilly, S.A.
Avda. de la Industria, 30
28108 Alcobendas (Madrid), Spain
For:
Takeda Pharmaceutical Company Limited, Osaka 540-8645, Japan

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