ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Raloxifene Teva 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.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.

White to off-white, film coated, oval shaped tablets, embossed with the number “60” on one side and “N” on the other side of the tablet.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Raloxifene 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.

When determining the choice of raloxifene 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

Posology
The recommended dose is one tablet daily.Due to the nature of this disease process, raloxifene 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.

Patients with renal impairment:
Raloxifene should not be used in patients with severe renal impairment (see section 4.3). In patients with moderate and mild renal impairment, raloxifene should be used with caution.

Patients with hepatic impairment:
Raloxifene should not be used in patients with hepatic impairment (see section 4.3 and 4.4).

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

Method of administration
Oral administration.
The tablet can be taken at any time of the day without regard to meals.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Must not be used in women with child bearing potential.

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.

Raloxifene 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. Raloxifene 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 bleeding during raloxifene 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 to 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) 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 raloxifene 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.

Limited clinical data suggest that in patients with a history of oral oestrogen-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 raloxifene in patients with breast cancer has not been adequately studied. No data are available on the concomitant use of raloxifene and agents used in the treatment of early or advanced breast cancer. Therefore, raloxifene 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 oestrogens, is limited, such use is not recommended.

Raloxifene is not effective in reducing vasodilatation (hot flushes), or other symptoms of the menopause associated with oestrogen deficiency.

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 raloxifene treatment is started in patients who are already on coumarin anticoagulant therapy.

Raloxifene has no effect on the pharmacokinetics of methylprednisolone given as a single 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 oestrogen preparations was allowed in the clinical trial programme, if necessary to treat atrophic vaginal symptoms. Compared to placebo there was no increased use in raloxifene 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.

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.

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 total hormone concentrations. These changes do not affect concentrations of free hormones.

4.6 Fertility, pregnancy and lactation

Pregnancy
Raloxifene is only for use in postmenopausal women.

Raloxifene 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).

Breast-feeding
It is not known whether raloxifene is excreted in human milk. Its clinical use, therefore, cannot be recommended in breast-feeding women. Raloxifene may affect the development of the baby.

4.7 Effects on ability to drive and use machines

Raloxifene has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

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

b. Tabulated summary of adverse reactions
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 arising from postmarketing reports. The duration of the treatment in these studies ranged from 6 to 60 months. The majority of adverse reactions have not usually required cessation of therapy.

The frequencies for postmarketing reports were 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 adverse reaction occurred in 10.7 % of 581 raloxifene treated patients and 11.1 % of 584 placebo-treated patients. In the treatment population discontinuations of therapy due to any clinical adverse event occurred in 12.8 % of 2,557 raloxifene treated patients and 11.1 % of 2,576 placebo treated patients.

The following convention has been used for the classification of the adverse reactions: very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 1/1,000) very rare (< 1/10,000), not known (cannot be estimated from the available data).

Blood and lymphatic system disorders *Uncommon:* Thrombocytopenia[a]
Nervous system disorders *Common:* Headache, including migraine[a] *Uncommon:* Fatal strokes
Vascular disorders *Very common:* Vasodilation (hot flushes) *Uncommon:* Venous thromboembolic events, including deep vein thrombosis, pulmonary embolism, retinal vein thrombosis, superficial vein thrombophlebitis, Arterial thromboembolic reactions[a]
Gastrointestinal disorders *Very common:* Gastrointestinal symptoms[a] such as nausea, vomiting, abdominal pain, dyspepsia
Skin and subcutaneous tissue disorders *Common*: Rash[a]
Musculoskeletal and connective tissue disorders

Common: Leg cramps
Reproductive system and breast disorders *Common:* Mild breast symptoms[a] such as pain, enlargement and tenderness
General disorders and administration site conditions *Very common:* Flu syndrome *Common:* Peripheral oedema
Investigations *Very common:* Increased blood pressure[a]

[a]Term(s) included based on postmarketing experience.

c. Description of selected adverse reactions

Compared with placebo-treated patients the occurrence of vasodilatation (hot flushes) was modestly increased in raloxifene patients (clinical trials for the prevention of osteoporosis, 2 to 8 years postmenopausal, 24.3 % raloxifene and 18.2 % placebo; clinical trials for the treatment of osteoporosis, mean age 66, 10.6 % for raloxifene and 7.1 % placebo). This adverse 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 1,000 patient years. A relative risk of 1.60 (CI 0.95, 2.71) was observed in raloxifene 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 adverse reaction observed was leg cramps (5.5 % for raloxifene, 1.9 % for placebo in the prevention population and 9.2 % for raloxifene, 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 raloxifene 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 raloxifene and 1.9 % for placebo; and in the treatment population occurred at an incidence of 7.1 % for raloxifene 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 can not 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 %).

Raloxifene (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.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

In some clinical trials, daily doses were given up to 600 mg for 8 weeks and 120 mg, for 3 years. No cases of raloxifene overdose were reported during clinical trials.

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 oestrogen receptor modulator. ATC code: G03XC01

Mechanism of action and Pharmacodynamic effect

As a selective oestrogen receptor modulator (SERM), raloxifene has selective agonist or antagonist activities on tissues responsive to oestrogen. 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 oestrogen, are mediated through high affinity binding to oestrogen receptors and regulation of gene expression. This binding results in differential expression of multiple oestrogen-regulated genes in different tissues. Recent data suggests that the oestrogen 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 oestrogen 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, raloxifene reduces the incidence of vertebral fractures, preserves bone mass and increases bone mineral density (BMD).

Based on these risk factors, prevention of osteoporosis with raloxifene 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, raloxifene 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 7,705 postmenopausal women with a mean age of 66 years and with osteoporosis or osteoporosis with an existing fracture, raloxifene 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 raloxifene for 3 years to prevent one or more vertebral fractures. Raloxifene 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 4^{th} year alone, raloxifene reduced the new vertebral fracture risk by 39 % (RR 0.61, CI 0.43, 0.88). An effect on non-vertebral fractures has not been demonstrated. From the 4^{th} to the 8^{th} year, patients were permitted the concomitant use of bisphosphonates, calcitonin and fluorides and all patients in this study received calcium and vitamin D supplementation.

In the RUTH study overall clinical fractures were collected as a secondary endpoint. Raloxifene 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.

ii) Bone Mineral Density (BMD): The efficacy of raloxifene 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 1,764 postmenopausal women who were treated with raloxifene and calcium or calcium supplemented placebo. In one of these trials the women had previously undergone hysterectomy. Raloxifene 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 raloxifene 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.

iii) Calcium kinetics. Raloxifene and oestrogen affect bone remodelling and calcium metabolism similarly. Raloxifene 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.

iv) Histomorphometry (bone quality). In a study comparing raloxifene with oestrogen, 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 bone 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 raloxifene 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 raloxifene decreased fibrinogen (6.71 %). In the osteoporosis treatment study, significantly fewer raloxifene-treated patients required initiation of hypolipidaemic therapy compared to placebo.

Raloxifene 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 to oestrogen 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, raloxifene did not stimulate the postmenopausal uterine endometrium. Compared to placebo, raloxifene was not associated with spotting or bleeding or endometrial hyperplasia. Nearly 3,000 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 to 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 raloxifene 60 mg daily demonstrated non-proliferative endometrium in all patients. In addition, in a study with 2.5 x the recommended daily dose of raloxifene 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 (1,644 patients) for 4 years. Endometrial thickness measurements in raloxifene treated women were not different from baseline after 4 years of therapy. There was no difference between raloxifene and placebo treated women in the incidences of vaginal bleeding (spotting) or vaginal discharge. Fewer raloxifene 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 to 0.3 % in women who received placebo treatment.

d) Effects on breast tissue

Raloxifene does not stimulate breast tissue. Across all placebo-controlled trials, raloxifene 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), raloxifene 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 oestrogen receptor (ER) positive breast cancer by 79 % (RR 0.21, CI 0.07, 0.50). Raloxifene has no effect on the risk of ER negative breast cancers. These observations support the conclusion that raloxifene has no intrinsic oestrogen agonist activity in breast tissue.

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 exten
sive. 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 %).

Biotransformation
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).

Elimination

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 to 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 antioestrogen in the rat uterus and prevented growth of oestrogen-dependent mammary tumours in rats and mice.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:
Pregelatinized starch (maize)
Magnesium stearate
Povidone (K30)
Colloidal anhydrous silica
Microcrystalline cellulose, silicified

Tablet coating:
Polydextrose (E1200)
Titanium dioxide (E171)
Hypromellose (E464)
Macrogol 4000

6.2 Incompatibilities

Not applicable

6.3 Shelf life

2 years

6.4 Special precautions for storage

Do not store above 25°C. Store in the original package to protect from moisture.

6.5 Nature and contents of container

Transparent PVC/PVdC - Aluminium blisters. Pack sizes of 14, 28 and 84 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Teva B.V.
Swensweg 5
2031GA Haarlem
The Netherlands

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/10/627/001-003

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 29 April 2010
Date of first renewal: 06 February 2015

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu

ANNEX II

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer(s) responsible for batch release

TEVA Pharmaceutical Works Private Limited Company
Pallagi ùt 13, 4042 Debrecen
Hungary

Pharmachemie B.V.
Swensweg 5, 2031 GA, Haarlem
The Netherlands

Merckle GmbH
Ludwig-Merckle-Straße 3
89143 Blaubeuren
Germany

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to medical prescription

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic Safety Update Reports**

The PSUR submission schedule for Raloxifene Teva should follow PSUR submission schedule for the reference medicinal product.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk Management Plan (RMP)**

Not applicable

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

Raloxifene Teva 60 mg film-coated tablets
raloxifene hydrochloride

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 60 mg raloxifene hydrochloride, equivalent to 56 mg raloxifene free base.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablet

14 film-coated tablets
28 film-coated tablets
84 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Swallow tablets whole.
Read the package leaflet before use.
Oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 25°C. Store in the original package to protect from moisture.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Teva B.V.
Swensweg 5
2031GA Haarlem
The Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/10/627/001 14 film coated tablets
EU/1/10/627/002 28 film coated tablets
EU/1/10/627/003 84 film coated tablets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Raloxifene Teva 60 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC:
SN:
NN:

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

1. NAME OF THE MEDICINAL PRODUCT

Raloxifene Teva 60 mg film-coated tablets
raloxifene hydrochloride

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Teva B.V.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the user

Raloxifene Teva 60 mg film-coated tablets
raloxifene hydrochloride

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet:

1. What Raloxifene Teva is and what it is used for

Raloxifene Teva is used to treat and prevent osteoporosis in postmenopausal women. Raloxifene Teva reduces the risk of vertebral fractures in women with postmenopausal osteoporosis. A reduction in the risk of hip fractures has not been shown.

How Raloxifene Teva works

Raloxifene Teva belongs to a group of non-hormonal medicines called selective oestrogen receptor modulators (SERMs). When a woman reaches the menopause, the level of the female sex hormone oestrogen goes down. Raloxifene Teva mimics some of the helpful effects of oestrogen after the menopause.

Osteoporosis is a disease that causes your bones to become thin and fragile - this disease is especially common in women after the menopause. Although it may have no symptoms at first, osteoporosis makes you more likely to break bones, especially in your spine, hips and wrists and may cause back pain, loss of height and a curved back.

2. What you need to know before you take Raloxifene Teva

Do not take Raloxifene Teva
- If you are allergic to raloxifene or any of the other ingredients of this medicine (listed in section 6).
- If there is still a possibility that you can get pregnant, Raloxifene Teva could harm your unborn child.
- If you are being treated or have been treated for blood clots (deep vein thrombosis, pulmonary embolism or retinal vein thrombosis).
- If you have liver disease (examples of liver disease include cirrhosis, mild hepatic impairment or cholestatic jaundice).
- If you have any unexplained vaginal bleeding. This must be investigated by your doctor.

- If you have active uterine cancer, as there is insufficient experience of Raloxifene Teva use in women with this disease.
- If you have severe kidney problems.

Warnings and precautions

Talk to your doctor or pharmacist before taking Raloxifene Teva:

- If you are immobilised for some time such as being wheel-chair bound, needing to be admitted to a hospital or having to stay in bed while recovering from an operation or an unexpected illness.
- If you are receiving oral oestrogen therapy.
- If you are suffering from breast cancer, as there is insufficient experience of Raloxifene Teva use in women with this disease.
- If you have had a cerebrovascular accident (e.g. stroke), or if your doctor has told you that you are at high risk of having one.
- If you have liver problems, as there is insufficient experience in people with liver problems. If you do have liver problems and your doctor still recommends treatment, then you may need some blood tests during treatment.

It is unlikely that Raloxifene Teva will cause vaginal bleeding. So any vaginal bleeding while you take Raloxifene Teva is unexpected. You should have this investigated by your doctor.

Raloxifene Teva does not treat postmenopausal symptoms, such as hot flushes.

Raloxifene Teva lowers total cholesterol and LDL ("bad") cholesterol. In general, it does not change triglycerides or HDL ("good") cholesterol. However, if you have taken oestrogen in the past and had extreme elevations in triglycerides, you should talk to your doctor before taking Raloxifene Teva.

Other medicines and Raloxifene Teva

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.

If you are taking digitalis medicines for your heart or anticoagulants like warfarin to thin your blood, your doctor may need to adjust your dose of these medicines.

Tell your doctor if you are taking cholestyramine which is mainly used as lipid-lowering medicine.

Pregnancy and breast-feeding
Raloxifene Teva is for use only by postmenopausal women and must not be taken by women who could still have a baby. Raloxifene Teva could harm your unborn child.

Do not take Raloxifene Teva if you are breast-feeding as it might be excreted in mother's milk.

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicines.

Driving and using machines
Raloxifene Teva has no or negligible effects on driving or using machines.

3. How to take Raloxifene Teva

Always take this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure.

The recommended dose is one tablet a day. It does not matter at what time of the day you take your tablet but taking the tablet at the same time each day will help you remember to take it. You may take it with or without food.

The tablets are for oral use.
Swallow the tablet whole. If you wish you may take a glass of water with it.

Your doctor will tell you how long you should continue to take Raloxifene Teva. The doctor may also advise you to take calcium and vitamin D supplements.

If you take more Raloxifene Teva than you should
Tell your doctor or pharmacist. If you take more Raloxifene Teva than you should you could have leg cramps and dizziness.

If you forget to take Raloxifene Teva
Take a tablet as soon as you remember and then continue as before.
Do not take a double dose to make up for a forgotten dose.

If you stop taking Raloxifene Teva
You should talk to your doctor first.
It is important that you continue taking Raloxifene Teva for as long as your doctor prescribes the medicine.
Raloxifene Teva can treat or prevent your osteoporosis only if you continue to take the tablets.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them. The majority of side effects seen with Raloxifene Teva have been mild.

Very common (may affect more than 1 in 10 people)
- Hot flushes (vasodilatation).
- Flu syndrome.
- Gastrointestinal symptoms such as nausea, vomiting, abdominal pain and stomach upset
- Increased blood pressure

Common (may affect up to 1 in 10 people)
- Headache including migraine
- Leg cramps.
- Swelling of hands, feet and legs (peripheral oedema).
- Gallstones.
- Rash
- Mild breast symptoms such as pain, enlargement and tenderness

Uncommon (may affect up to 1 in 100 people)
- Increased risk of blood clots in the legs (deep vein thrombosis).
- Increased risk of blood clots in the lungs (pulmonary embolism).
- Increased risk of blood clots in the eyes (retinal vein thrombosis).
- Skin around the vein is red and painful (superficial vein thrombophlebitis).
- Blood clot in an artery (for example stroke, including an increased risk of dying from stroke)
- Decrease in the number of the platelets in the blood

In rare cases, blood levels of liver enzymes may increase during treatment with Raloxifene Teva.

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Raloxifene Teva

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the outer carton or foil after EXP. The expiry date refers to the last day of that month.

Do not store above 25°C. Store in the original package to protect from moisture.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help to protect the environment.

6. Contents of the pack and other information

What Raloxifene Teva contains

- The active substance is raloxifene hydrochloride. Each film-coated tablet contains 60 mg raloxifene hydrochloride, equivalent to 56 mg raloxifene.
- The other ingredients are:
  Tablet core: pregelatinized starch (maize), magnesium stearate, povidone (K30), colloidal anhydrous silica and microcrystalline cellulose, silicified.
  Tablet coating: polydextrose (E1200), titanium dioxide (E171), hypromellose (E464) and macrogol 4000.

What Raloxifene Teva looks like and contents of the pack

The film-coated tablets are white to off-white, oval shaped and embossed with the number “60” on one side and “N” on the other side.

Raloxifene Teva 60 mg is available in pack sizes of 14, 28 and 84 film-coated tablets.

Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer

Marketing Authorisation Holder:
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The Netherlands

Manufacturers:
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Pharmachemie B.V.

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Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu/