Public Assessment Report

Decentralised Procedure

RALOXIFENE STADA 60 MG FILM-COATED TABLETS

UK/H/2834-5/001/DC
UK Licence No: PL 11204/0235-6

STADA ARZNEIMITTEL AG
LAY SUMMARY

On 26th September 2011, the UK granted STADA Arzneimittel AG Marketing Authorisations (licences) for Raloxifene Stada 60 mg film-coated tablets.

Raloxifene Stada 60 mg film-coated tablets contain the active ingredient, raloxifene hydrochloride. Raloxifene hydrochloride belongs to a group of medicines called Selective Oestrogen (Estrogen) Receptor Modulators (SERMs).

When a woman reaches the menopause, the level of the female sex hormone oestrogen goes down. Raloxifene Stada 60 mg film-coated tablets mimic some of the helpful effects of oestrogen after the menopause.

Raloxifene Stada 60 mg film-coated tablets are used to treat and prevent osteoporosis in postmenopausal women. Raloxifene Stada 60 mg film-coated tablets reduce the risk of vertebral fractures in women with postmenopausal osteoporosis. A reduction in the risk of hip fractures has not been shown.

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.

No new or unexpected safety concerns arose from this application and it was, therefore, judged that the benefits of taking Raloxifene Stada 60 mg film-coated tablets outweigh the risks and Marketing Authorisations were granted.
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3 Non-clinical aspects
4 Clinical aspects
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Module 6: Steps taken after initial procedure  Not applicable
### Module 1

<table>
<thead>
<tr>
<th><strong>Product Name</strong></th>
<th>Raloxifene STADA 60 mg film-coated tablets</th>
</tr>
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<tbody>
<tr>
<td><strong>Type of Application</strong></td>
<td>Generic application, Article 10.1</td>
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<tr>
<td><strong>Active Substance</strong></td>
<td>Raloxifene hydrochloride</td>
</tr>
<tr>
<td><strong>Form</strong></td>
<td>Film-coated tablets</td>
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<tr>
<td><strong>Strength</strong></td>
<td>60 mg</td>
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</table>
| **MA Holder** | STADA Arzneimittel AG  
Stadastr. 2 – 18,  
D-61118 Bad Vilbel  
Germany |
| **Reference Member State (RMS)** | UK |
| **Concerned Member States (CMS)** | UK/H/2834/001/DC: Austria (AT), Belgium (BE), Germany (DE), Spain (ES), France (FR), Luxembourg (LU), Portugal (PT), Sweden (SE)  
UK/H/2835/001/DC: Germany (DE) |
| **Procedure Number** | UK/H/2834-5/001/DC |
| **End of Procedure** | Day 210: 8th August 2011 |
Module 2
Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT
Raloxifene STADA 60 mg film-coated tablets.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each film coated tablet contains 60 mg raloxifene hydrochloride, equivalent to 56mg raloxifene free base.
Excipient: each tablet contains lactose monohydrate (1.5 mg).
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Film coated tablet.
Elliptically shaped, white tablets

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
Raloxifene STADA 60 mg film-coated tablets 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 STADA 60 mg film-coated tablets 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. No dose adjustment is necessary for the elderly. Due to the nature of this disease process, Raloxifene STADA 60 mg film-coated tablets is intended for long-term use.

Generally, calcium and vitamin D supplements are advised in women with a low dietary intake.

Use in renal impairment:
Raloxifene STADA 60 mg film-coated tablets should not be used in patients with severe renal impairment (see section 4.3). In patients with moderate and mild renal impairment, Raloxifene STADA 60 mg film-coated tablets should be used with caution.

Use in hepatic impairment:
Raloxifene STADA 60 mg film-coated tablets should not be used in patients with hepatic impairment (see section 4.3).

4.3 Contraindications
- Hypersensitivity to the active substance or to any of the excipients.
- Must not be used in women with childbearing 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 STADA 60 mg film-coated tablets 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
STADA 60 mg film-coated tablets 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, hospitalised 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 1,000 women per year for placebo versus 2.2 per 1,000 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 ischaemic attack or atrial fibrillation.

There is no evidence of endometrial proliferation. Any uterine bleeding during Raloxifene STADA 60 mg film-coated tablets 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 STADA 60 mg film-coated tablets 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 hypertriglyceridaemia (>5.6mmol/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 STADA 60 mg film-coated tablets 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 STADA 60 mg film-coated tablets is not effective in reducing vasodilatation (hot flushes), or other symptoms of the menopause associated with oestrogen deficiency.

Raloxifene STADA 60 mg film-coated tablets 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 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\text{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.

\textit{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 \textbf{Fertility, pregnancy and lactation}

Raloxifene STADA 60 mg film-coated tablets is only for use in postmenopausal women.

Raloxifene STADA 60 mg film-coated tablets must not be taken by women of childbearing 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 is excreted in human milk. Its clinical use, therefore, cannot be recommended in lactating women. Raloxifene STADA 60 mg film-coated tablets may affect the development of the baby.

4.7 \textbf{Effects on ability to drive and use machines}

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

4.8 \textbf{Undesirable effects}

In osteoporosis treatment and prevention studies involving over 13,000 postmenopausal women, all undesirable reactions were recorded. 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.

In the prevention population, discontinuations of therapy due to any undesirable 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 experience occurred in 12.8% of 2,557 raloxifene-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 summarised 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 (≥1/1,000 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).

\begin{tabular}{|l|}
\hline
\textbf{Vascular disorders} \\
\textit{Very common}: Vasodilatation (hot flushes). \\
\textit{Uncommon}: Venous thromboembolic events, including deep vein thrombosis, pulmonary embolism, retinal vein thrombosis. Superficial vein thrombophlebitis. \\
\hline
\end{tabular}
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 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 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 thromboembolitis 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 1,000 patient-years in the raloxifene group and 1.4% or 2.70 cases per 1,000 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 thromboembolitis occurred at a frequency of 1% in the raloxifene group and 0.6% in the placebo group.

Another undesirable 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 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%).

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.

The events reported in post-marketing experience are presented in the table below.
<table>
<thead>
<tr>
<th>Blood and lymphatic system disorders</th>
<th>Very rare: Thrombocytopenia.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrointestinal disorders</td>
<td>Very rare: Gastrointestinal symptoms, such as nausea, vomiting, abdominal pain, dyspepsia.</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td>Rare: Peripheral oedema.</td>
</tr>
<tr>
<td>Investigations</td>
<td>Very rare: Increased blood pressure.</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>Very rare: Headache, including migraine.</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>Very rare: Rash.</td>
</tr>
<tr>
<td>Reproductive system and breast disorders</td>
<td>Very rare: Mild breast symptoms, such as pain, enlargement, and tenderness.</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td>Rare: Venous thromboembolic reaction. Very rare: Arterial thromboembolic reaction.</td>
</tr>
</tbody>
</table>

### 4.9 Overdose

In clinical trials, daily doses were given up to 600mg for 8 weeks and 120mg, 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 120mg as a single ingestion.

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

Pharmacotherapeutic group: Selective Oestrogen Receptor Modulator, ATC code: G03XC01.

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 4th 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 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.

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 non-vertebral 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 estrogen affect bone remodelling and calcium metabolism similarly. Raloxifene was associated with reduced bone resorption and a mean positive shift in calcium balance of 60mg per day, due primarily to decreased urinary calcium losses.

iv) Histomorphometry (bone quality). In a study comparing Raloxifene 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 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 60mg 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, hospitalised 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 5mm increase in endometrial thickness, assessed with transvaginal ultrasound, was observed in 1.9% of the 211 women treated with raloxifene 60mg/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 60mg 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 7,705 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 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 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 tumours of granulosa/theca cell origin was observed in high-dose females (279mg/kg/day). Systemic exposure (AUC) of raloxifene in this group was approximately 400-times that in postmenopausal women administered a 60mg 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 210mg/kg, and prostatic leiomyoblastoma in males given 210mg/kg. In female mice, an increased incidence of ovarian tumours in animals given 9 to 242mg/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 10mg/kg/day in female rats, raloxifene disrupted oestrus 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 (≥0.1mg/kg) and hydrocephaly (≥10mg/kg) were seen. In rats, retardation of foetal development, wavy ribs, and kidney cavitation occurred (≥1mg/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:
- Sodium starch glycolate
- Citric acid monohydrate
- Microcrystalline Cellulose
- Calcium hydrogen phosphate
- Poloxamer
- Magnesium stearate

Tablet coating:
- Hypromellose
- Lactose monohydrate
- Titanium dioxide (E171)
- Macrogol

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
3 years.

6.4 Special precautions for storage
Keep the blister in the outer carton in order to protect from light and moisture.

6.5 Nature and contents of container
Raloxifene STADA 60 mg film-coated tablets are packed in a transparent PVC/PE/PVDC blister with Aluminum foil.

PL 11204/0235: Blister boxes contain 10, 14, 28, 30, 84, 90, 98, 100 or 126 tablets.
PL 11204/0236: Blister boxes contain 14, 28 or 84 tablets.

Not all pack sizes may be marketed in all countries.

6.6 Special precautions for disposal
No special requirements.

7 MARKETING AUTHORISATION HOLDER
STADA Arzneimittel AG
Stadastr. 2 – 18,
D-61118 Bad Vilbel
Germany

8 MARKETING AUTHORISATION NUMBER(S)
PL 11204/0235-6

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
26/09/2011

10 DATE OF REVISION OF THE TEXT
26/09/2011
Module 3

Patient Information Leaflet

Please note that there are no mock-ups available. The marketing authorisation holder has stated that it does not intend to market the products and, thus, no UK-specific documents have been submitted. The marketing authorisation holder has committed to submit the UK PILs for review to the regulatory authority before marketing the products.

PACKAGE LEAFLET: INFORMATION FOR THE USER

Raloxifene 60 mg film-coated tablets
(raloxifene hydrochloride)

Please read this information carefully before you start to take your medicine.

- Keep this leaflet until you have finished this pack as you may want to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:
1. What Raloxifene 60 mg film-coated tablets is and what it is used for
2. Before you take Raloxifene 60 mg film-coated tablets
3. How to take Raloxifene 60 mg film-coated tablets
4. Possible side effects
5. How to store Raloxifene 60 mg film-coated tablets
6. Further information

1. WHAT RALOXIFENE 60 MG FILM-COATED TABLETS IS AND WHAT IT IS USED FOR

Raloxifene 60 mg film-coated tablets 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 estrogen goes down. Raloxifene 60 mg film-coated tablets mimics some of the helpful effects of estrogen after the menopause.

Raloxifene 60 mg film-coated tablets is used to treat and prevent osteoporosis in postmenopausal women. Raloxifene 60 mg film-coated tablets reduces the risk of vertebral fractures in women with postmenopausal osteoporosis. A reduction in the risk of hip fractures has not been shown.

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. BEFORE YOU TAKE RALOXIFENE 60 MG FILM-COATED TABLETS

Do not take Raloxifene 60 mg film-coated tablets:

- If you are allergic (hypersensitive) to raloxifene or any of the ingredients of Raloxifene 60 mg film-coated tablets.
- If there is a possibility that you can get pregnant. Raloxifene 60 mg film-coated tablets could harm your unborn baby.
- 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 60 mg film-coated tablets use in women with this disease.
- If you have severe kidney problems.

Take special care with Raloxifene 60 mg film-coated tablets:
The following are reasons why this product may not be suitable for you. If any of them apply to you, talk to your doctor before you take the medicine.

- 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 60 mg film-coated tablets 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.

It is unlikely that Raloxifene 60 mg film-coated tablets will cause vaginal bleeding. So any vaginal bleeding while you take Raloxifene 60 mg film-coated tablets is unexpected. You should have this investigated by your doctor.

Raloxifene 60 mg film-coated tablets does not treat postmenopausal symptoms, such as hot flushes.

Raloxifene 60 mg film-coated tablets lowers total cholesterol and LDL ("bad") cholesterol. In general, it does not change triglycerides or HDL ("good") cholesterol. However, if you have taken estrogen in the past and had extreme elevations in triglycerides, you should talk to your doctor before taking Raloxifene 60 mg film-coated tablets.

**Taking other medicines**

Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

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 60 mg film-coated tablets is for use only by postmenopausal women and must not be taken by women who could still have a baby. Raloxifene 60 mg film-coated tablets could harm your unborn child.

Do not take raloxifene 60 mg film-coated tablets if you are breast-feeding as it might be excreted in mother's milk.

**Driving and using machines**

Raloxifene 60 mg film-coated tablets has no known effects on driving or using machines.

**Important information about some ingredients of Raloxifene 60 mg film-coated tablets:**

If you have been told by your doctor that you have an intolerance to lactose, a type of sugar, contact your doctor before taking this medicinal product.

3. **HOW TO TAKE RALOXIFENE 60 MG FILM-COATED TABLETS**

Always take this product exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.
The dose is one tablet a day. It does not matter what time of 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 60 mg film-coated tablets. The doctor may also advise you to take calcium and vitamin D supplements.

If you stop taking Raloxifene 60 mg film-coated tablets
You should talk to your doctor first

If you have the impression that the effect of this product is too strong or too weak, talk to your doctor or pharmacist

If you forget to take Raloxifene 60 mg film-coated tablets
Take a tablet as soon as you remember and then continue as before.

If you take more Raloxifene 60 mg film-coated tablets than you should
Tell your doctor or pharmacist.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Raloxifene 60 mg film-coated tablets can cause side effects although not everybody gets them. The majority of side effects seen with raloxifene have been mild.

The most common side effects (affects more than 1 user in 10) are:
• Hot flushes (vasodilation)
• Flu syndrome

Common side effects (affects 1 to 10 users in 100) are:
• Leg cramps
• Swelling of hands, feet and legs (peripheral oedema)
• Gallstones

Uncommon side effects (affects 1 to 10 users in 1000) are:
• 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)

Very rare side effects (affects less than 1 user in 10,000) are:
• Rash
• Gastrointestinal symptoms such as nausea, vomiting, abdominal pain and stomach upset
• Increased blood pressure
• Decrease in the number of the platelets in the blood
• Blood clot in an artery (for example stroke)
• Headache including migraine
• Mild breast symptoms such as pain, enlargement and tenderness

In rare cases, blood levels of liver enzymes may increase during treatment with raloxifene 60 mg film-coated tablets.
If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. HOW TO STORE RALOXIFENE 60 MG FILM-COATED TABLETS

Keep out of the reach and sight of children.

Do not use after the expiry date which is stated on the pack.

Keep the blister in the outer carton in order to protect from light and moisture. Do not freeze.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What Raloxifene 60 mg film-coated tablets contains

- The active substance is raloxifene hydrochloride. Each tablet contains 60 mg of raloxifene hydrochloride, which is equivalent to 56 mg raloxifene.
- The other ingredients of Raloxifene 60 mg film-coated tablets are:
  Tablet core: Sodium starch glycolate, citric acid monohydrate, microcrystalline cellulose, calcium hydrogen phosphate, poloxamer, magnesium stearate
  Tablet coating: Hypromellose, lactose monohydrate, titanium dioxide (E171) and macrogol

What Raloxifene 60 mg film-coated tablets looks like and contents of the pack

Raloxifene 60 mg film-coated tablets are white elliptical, film coated tablets. They are packed in blisters. The blister boxes contain 10, 14, 28, 50, 84, 90, 100 or 126 tablets. Not all pack sizes may be marketed.

Marketing Authorisation Holder

STADA Arzneimittel AG
Stadastr. 2 – 18,
D-61118 Bad Vilbel
Germany
Phone: +49 6101 603-0
Fax: +49 6101 603-259
e-mail: info@stada.de

Manufacturer(s)

ALIUD Pharma GmbH, Gottlieb-Daimler-Strasse 19, 89150 Laichingen, Germany
Eurogenerics N.V., Eigenlostraat 5-9100 Sint-Niklaas, Belgium
STADA Arzneimittel AG, Stadastrasse 2 – 18, 61118 Bad Vilbel, Germany
STADA Arzneimittel GmbH, Muthgasse 36/2, A-1190 Wien, Austria
Pharmathen S.A., 6, Dervenakion Str., 153 51 Pallini, Attikis, Greece

This medicinal product is authorised in the Member States of the EEA under the following names:

AT Raloxifen STADA 60 mg Filmtabletten
BE Raloxifene EG 60 mg filmomhulde tabletten
DE Raloxifen STADA 60 mg Filmtabletten
ES Raloxifeno STADA 60 mg comprimido recubierto con película
FR RALOXIFENE EG 60 mg comprimé pelliculé
LU Raloxifene EG 60 mg comprimés pelliculés
PT  Raloxifeno Ciclum
SE  Raloxifen STADA 60 mg Filmdragerade tabletter
UK  Raloxifene STADA 60 mg film-coated tablets

This leaflet was last approved in: {08/2011}
Module 4
Labelling

Please note that there are no mock-ups available. The marketing authorisation holder has stated that it does not intend to market the products and, thus, no UK-specific documents have been submitted. The marketing authorisation holder has committed to submit the UK labelling for review to the regulatory authority before marketing the products.

| PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND THE IMMEDIATE PACKAGING |
| Box |

| 1. NAME OF THE MEDICINAL PRODUCT |
| Raloxifene 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 |

| 3. LIST OF EXCIPIENTS |
| Contains lactose monohydrate |
| See leaflet for further information |

| 4. PHARMACEUTICAL FORM AND CONTENTS |
| 10 film coated tablets |
| 14 film coated tablets |
| 28 film coated tablets |
| 30 film coated tablets |
| 84 film coated tablets |
| 90 film coated tablets |
| 98 film coated tablets |
| 100 film coated tablets |
| 120 film coated tablets |

| 5. METHOD AND ROUTE(S) OF ADMINISTRATION |
| For oral use |

| 6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN |
| Keep out of the reach and sight of children. |

| 7. OTHER SPECIAL WARNING(S), IF NECESSARY |

| 8. EXPIRY DATE |
| EXP {MM/YYYY} |
9. SPECIAL STORAGE CONDITIONS

Keep the blister in the outer carton in order to protect from light and 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

STADA Arzneimittel AG
Stadastr. 2 – 18,
D-61118 Bad Vilbel
Germany
Phone: +49 6101 603-0
Fax: +49 6101 603-259
e-mail: info@stada.de

12. MARKETING AUTHORISATION NUMBER(S)

PL 11204/0235

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

To be completed nationally
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<th>1. NAME OF THE MEDICINAL PRODUCT</th>
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**PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND THE IMMEDIATE PACKAGING**

**Box**

1. **NAME OF THE MEDICINAL PRODUCT**

Raloxifene 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

3. **LIST OF EXCIPIENTS**

Contains lactose monohydrate

See leaflet for further information

4. **PHARMACEUTICAL FORM AND CONTENTS**

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

5. **METHOD AND ROUTE(S) OF ADMINISTRATION**

For oral use

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

Keep out of the reach and sight of children.

7. **OTHER SPECIAL WARNING(S), IF NECESSARY**

8. **EXPIRY DATE**

EXP {MM/YYYY}

9. **SPECIAL STORAGE CONDITIONS**

Keep the blister in the outer carton in order to protect from light and 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**

   STADA Arzneimittel AG  
   Stadastr. 2 – 18,  
   D-61118 Bad Vilbel  
   Germany  
   Phone: +49 6101 603-0  
   Fax: +49 6101 603-259  
   e-mail: info@stada.de

12. **MARKETING AUTHORISATION NUMBER(S)**

   PL 11204/0236

13. **BATCH NUMBER**

   Lot

14. **GENERAL CLASSIFICATION FOR SUPPLY**

   Medicinal product subject to medical prescription.

15. **INSTRUCTIONS ON USE**

16. **INFORMATION IN BRAILLE**

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Module 5
Scientific discussion during initial procedure

I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, Austria, Belgium, Germany, Spain, France, Luxembourg, Portugal, Sweden and the UK considered that the application for Raloxifene Stada 60 mg film-coated tablets could be approved. This prescription only medicine (POM) 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.

This application for Raloxifene Stada 60 mg film-coated tablets was submitted according to Article 10.1 of Directive 2001/83/EC, as amended, claiming to be a generic medicinal product of Evista 60 mg film-coated tablets, first authorised in the EEA in 1998 to Eli Lilly Nederland B.V. This is a centrally authorised product and is licensed in all EEA member states.

Raloxifene is a selective oestrogen receptor modulator, with selective agonist or antagonist activities on tissues responsive to oestrogen. It has oestrogenic actions on the bone and partially on cholesterol metabolism. Raloxifene has no oestrogenic effects on the uterus and breast.

No new non-clinical studies were conducted, which is acceptable given that the product contains a widely-used, well-known active substance. No clinical studies, with the exception of the bioequivalence study, have been performed and none are required for this application as the pharmacology of raloxifene is well-established.

For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

For manufacturing sites outside the community, the RMS has accepted copies of current GMP Certificates or satisfactory inspection summary reports, ‘close-out letters’ or ‘exchange of information’ issued by the inspection services of the competent authorities (or those countries with which the EEA has a Mutual Recognition Agreement for their own territories) as certification that acceptable standards of GMP are in place at those non-Community sites.

The RMS considers that the pharmacovigilance system as described by the applicant fulfils the requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

Satisfactory justification has been provided for the absence of a Risk Management Plan.
II. ABOUT THE PRODUCT

| Name of the product in the Reference Member State | Raloxifene STADA 60 mg film-coated tablets |
| Name(s) of the active substance(s) (INN)          | Raloxifene hydrochloride                   |
| Pharmacotherapeutic classification (ATC code)    | Selective Oestrogen Receptor Modulator (G03XC01) |
| Pharmaceutical form and strength(s)              | 60 mg film-coated tablets                  |
| Reference numbers for the Decentralised Procedure | UK/H/2834/001/DC                              |
|                                                  | UK/H/2835/001/DC                              |
| Reference Member State                           | United Kingdom                               |
| Member States concerned                          | UK/H/2834/001/DC: Austria (AT), Belgium (BE), Germany (DE), Spain (ES), France (FR), Luxembourg (LU), Portugal (PT) and Sweden (SE) |
|                                                  | UK/H/2835/001/DC: Germany (DE)               |
| Marketing Authorisation Number(s)                | PL 11204/0235                                 |
|                                                  | PL 11204/0236                                 |
| Name and address of the authorisation holder      | STADA Arzneimittel AG                        |
|                                                  | Stadastr. 2 – 18,                            |
|                                                  | D-61118 Bad Vilbel                           |
|                                                  | Germany                                     |
III SCIENTIFIC OVERVIEW AND DISCUSSION
III.1 QUALITY ASPECTS
S. Active substance
INN name: Raloxifene hydrochloride
Chemical name: 6-hydroxy-2-(p-hydroxyphenyl)benzo[b]thien-3-yl)-p-(2-piperidinoethoxy)phenyl ketone hydrochloride

Structural formula:

![Structural Formula](image)

Molecular formula: $\text{C}_{28}\text{H}_{27}\text{NO}_4\text{S.HCl}$

Appearance: An almost white to pale yellow powder.

Molecular weight: 510.05 g/mol
Solubility: Slightly soluble in dimethylformamide and methanol; very slightly soluble in ethanol, practically insoluble in acetone, ethyl acetate, methylene chloride, pentane, cyclohexane, water, chloroform and toluene.

Raloxifene hydrochloride complies with in-house specifications.

Synthesis of the active substance from the designated starting materials has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specification tests are in place for all starting materials and reagents and these are supported by relevant Certificates of Analysis.

An appropriate specification is provided for the active substance. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications.

Appropriate proof-of-structure data have been supplied for the active substance. All potential known impurities have been identified and characterised. Satisfactory Certificates of Analysis have been provided for all working standards. Batch analysis data are provided and comply with the proposed specification.

Suitable specifications have been provided for all packaging used. The primary packaging has been shown to comply with current guidelines with regards to food contact.

Appropriate stability data have been generated to support a suitable retest period when stored in the proposed packaging.
P. Medicinal Product
Other Ingredients
Other ingredients in the tablet core consist of the pharmaceutical excipients, sodium starch glycolate, citric acid monohydrate, microcrystalline cellulose, calcium hydrogen phosphate, poloxamer and magnesium stearate.

Ingredients in the tablet film-coating are hypromellose, lactose monohydrate, titanium dioxide (E171) and macrogol.

All excipients comply with their respective European Pharmacopoeia monographs.

None of the excipients contain material of human origin. The suppliers of the excipients have provided declarations that neither the excipients nor any material used in the production of the excipients pose a TSE risk. The supplier of magnesium stearate has confirmed that it is of vegetable origin. The applicant has provided a declaration that the milk used in the production of anhydrous lactose is sourced from healthy animals under the same conditions as those intended for human consumption.

No genetically modified organisms (GMO) have been used in the preparation of this product.

Pharmaceutical Development
The objective of the development programme was to produce a safe, efficacious product containing raloxifene hydrochloride that could be considered a generic medicinal product of Evista 60 mg film-coated tablets.

The applicant has provided suitable product development information. Justification for the use and amounts of each excipient has been provided and is valid.

Comparative in vitro impurity, assay and dissolution profiles have been provided for the proposed and reference product.

The reference product used in the bioequivalence study is Evista 60 mg film-coated tablets, licensed in Greece. As this is a centrally authorised product, it is identical in all member states.

Manufacturing Process
A satisfactory batch formula has been provided for the manufacture of the product, along with an appropriate account of the manufacturing process. The manufacturing process has been validated and has shown satisfactory results. Satisfactory process validation data on pilot-scale batches have been provided. The applicant has committed to perform process validation on future commercial-scale batches.

Finished Product Specification
The finished product specification is acceptable. Test methods have been described and adequately validated, as appropriate. Batch data have been provided and comply with the release specifications. Certificates of Analysis have been provided for any working standards used.
Container-Closure System
This product is packaged in blister packs made of polyvinyl chloride (PVC), polyethylene (PE) and polyvinylidene chloride (PVDC) with aluminium foil.

The product comes in the following pack sizes:
PL 11204/0235: 10, 14, 28, 30, 84, 90, 98, 100 or 126 film-coated tablets.
PL 11204/0236: 14, 28 or 84 film-coated tablets.

Satisfactory specifications and Certificates of Analysis have been provided for all packaging components. All primary product packaging complies with relevant EU legislation.

Stability of the product
Stability studies were performed on batches of the finished product in the packaging proposed for marketing and in accordance with current guidelines. These data support a shelf-life of 3 years with the storage instructions, ‘Keep the blister in the outer carton in order to protect from light and moisture’.

Summary of Product Characteristics (SmPCs), Patient Information Leaflet (PIL) and Labels
The SmPCs, PIL and labelling are pharmaceutically acceptable. A representative sample of the UK PIL and label texts are included in modules 3 and 4 of this report.

User testing results have been submitted for the PIL. The results indicate that the PIL is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that it contains.

MAA forms
The MAA forms are pharmaceutically satisfactory.

Expert report
The pharmaceutical expert report has been written by an appropriately qualified person and is a suitable summary of the pharmaceutical dossier.

Conclusion
It is recommended that Marketing Authorisations are granted for these applications from a quality point of view.
III.2 NON-CLINICAL ASPECTS

The pharmacodynamics, pharmacokinetics and toxicological properties of raloxifene hydrochloride are well-known. As raloxifene hydrochloride is a widely used, well-known active substance, the applicant has not provided any new non-clinical data and none are required. An overview based on literature review is appropriate.

The non-clinical expert report has been written by an appropriately qualified person and is a suitable summary of the non-clinical aspects of the dossier.

Satisfactory justification has been provided for the absence of an Environmental Risk Assessment.

It is recommended that Marketing Authorisations are granted for these applications from a non-clinical point of view.
III.3 CLINICAL ASPECTS  
CLINICAL PHARMACOLOGY

With the exception of the following bioequivalence study, no new pharmacokinetic or pharmacodynamic data were submitted with this application and none were required.

Pharmacokinetics

A randomised, open-label, randomised, single dose, four-way crossover replicate study to compare the pharmacokinetics of the test product Raloxifene Stada 60 mg film-coated tablets versus the reference product Evista (raloxifene hydrochloride) 60 mg Tablets (Eli Lilly Nederland B.V., Greece) in healthy subjects under fasted conditions.

Blood samples were taken pre- and up to 144 hours post-dose. There was a washout period of at least 21 days between each treatment period. Pharmacokinetic parameters were measured from the plasma and analysed statistically. Raloxifene hydrochloride and its glucuronide conjugates, raloxifene-4’-glucuronide, and raloxifene-6’-glucuronide were measured.

Results for raloxifene hydrochloride, raloxifene-4’-glucuronide, and raloxifene-6’-glucuronide are presented below as log-transformed values:

Raloxifene hydrochloride

<table>
<thead>
<tr>
<th>Treatment</th>
<th>AUC₀→ₜ</th>
<th>AUC₀→∞</th>
<th>Cₘₐₓ</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(pg.h/mL)</td>
<td>(pg.h/mL)</td>
<td>(pg/ml)</td>
</tr>
<tr>
<td>Test (T)</td>
<td>14074.60</td>
<td>15346.34</td>
<td>419.99</td>
</tr>
<tr>
<td></td>
<td>14216.18</td>
<td>15405.61</td>
<td>467.39</td>
</tr>
<tr>
<td>Reference (R)</td>
<td>13945.96</td>
<td>15128.89</td>
<td>437.08</td>
</tr>
<tr>
<td></td>
<td>14001.45</td>
<td>15175.59</td>
<td>478.78</td>
</tr>
<tr>
<td>T/R Ratio</td>
<td>100.41</td>
<td>100.28</td>
<td>96.94</td>
</tr>
<tr>
<td>(90% CI)</td>
<td>94.76 – 106.40</td>
<td>94.60 – 106.29</td>
<td>88.25 – 106.49</td>
</tr>
</tbody>
</table>

AUC₀→ₜ  area under the plasma concentration-time curve from time zero to infinity  
AUC₀→∞  area under the plasma concentration-time curve from time zero to t hours  
Cₘₐₓ  maximum plasma concentration

Raloxifene-4’-glucuronide

<table>
<thead>
<tr>
<th>Treatment</th>
<th>AUC₀→ₜ</th>
<th>AUC₀→∞</th>
<th>Cₘₐₓ</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(ng.h/mL)</td>
<td>(ng.h/mL)</td>
<td>(ng/ml)</td>
</tr>
<tr>
<td>Test (T)</td>
<td>2957.23</td>
<td>3071.77</td>
<td>153.67</td>
</tr>
<tr>
<td></td>
<td>2968.50</td>
<td>3131.86</td>
<td>161.04</td>
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<tr>
<td>Reference (R)</td>
<td>2859.65</td>
<td>2975.83</td>
<td>168.26</td>
</tr>
<tr>
<td></td>
<td>2885.14</td>
<td>2971.91</td>
<td>165.00</td>
</tr>
<tr>
<td>T/R Ratio</td>
<td>101.56</td>
<td>101.95</td>
<td>94.31</td>
</tr>
<tr>
<td>(90% CI)</td>
<td>95.79 – 107.67</td>
<td>95.91 – 108.36</td>
<td>90.20 – 98.61</td>
</tr>
</tbody>
</table>
Raloxifene-6'-glucuronide

<table>
<thead>
<tr>
<th>Treatment</th>
<th>AUC₀⁻ᵗ (ng.h/mL)</th>
<th>AUC₀⁻∞ (ng.h/mL)</th>
<th>C_max (ng/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test (T)</td>
<td>713.74</td>
<td>748.09</td>
<td>28.24</td>
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<td>708.08</td>
<td>757.35</td>
<td>30.45</td>
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<tr>
<td>Reference (R)</td>
<td>655.75</td>
<td>715.91</td>
<td>28.44</td>
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<td>683.70</td>
<td>715.27</td>
<td>29.79</td>
</tr>
<tr>
<td>T/R Ratio (90% CI)</td>
<td>102.43</td>
<td>102.38</td>
<td>100.20</td>
</tr>
<tr>
<td></td>
<td>96.05 – 109.23</td>
<td>95.57 – 109.67</td>
<td>94.09 – 106.70</td>
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</table>

The results for the primary variables indicated that the 90% confidence intervals test/reference ratio of geometric means for AUC₀⁻ᵗ, AUC₀⁻∞ and C_max for raloxifene hydrochloride, raloxifene-4’-glucuronide and raloxifene-6’-glucuronide lie within acceptable limits. Bioequivalence has therefore been shown between the test and reference products in this study.

**Efficacy**

No new efficacy data were submitted with this application and none were required.

**Safety**

With the exception of the data submitted during the bioequivalence study, no new safety data were submitted with this application and none were required. No new or unexpected safety concerns were raised during the bioequivalence study.

**Summary of Product Characteristics (SmPCs), Patient Information Leaflet (PIL) and Labelling**

The SmPCs, PIL and labelling are medically satisfactory and consistent with those for the reference product, where appropriate.

**Clinical Expert Report**

The clinical expert report has been written by an appropriately qualified physician and is a suitable summary of the clinical aspects of the dossier.

**MAA Forms**

The MAA forms are clinically satisfactory.

**Conclusions**

It is recommended that Marketing Authorisations are granted for these applications from a clinical point of view.
IV OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT
QUALITY
The important quality characteristics of Raloxifene Stada 60 mg film-coated tablets are well defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit-risk balance.

NON-CLINICAL
No new non-clinical data were submitted and none are required for applications of this type.

EFFICACY
Bioequivalence has been demonstrated between the applicant’s Raloxifene Stada 60 mg film-coated tablets and the reference product Evista 60 mg film-coated tablets.

No new or unexpected safety concerns arose from these applications.

The SmPCs, PIL and labelling are satisfactory and consistent with those for the reference product.

BENEFIT-RISK ASSESSMENT
The quality of the product is acceptable and no new non-clinical or clinical safety concerns have been identified. Extensive clinical experience with raloxifene hydrochloride is considered to have demonstrated the therapeutic value of the compound. The benefit-risk ratio is therefore considered to be positive.
Module 6

STEPS TAKEN AFTER INITIAL PROCEDURE - SUMMARY

<table>
<thead>
<tr>
<th>Date submitted</th>
<th>Application type</th>
<th>Scope</th>
<th>Outcome</th>
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