# SCIENTIFIC DISCUSSION

**This module reflects the initial scientific discussion for the approval of Evista. This scientific discussion has been updated until 1 October 2003. For information on changes after this date please refer to module 8B.**

## 1.    Introduction

Osteoporosis is recognised as a major public health problem, which is estimated to affect one in three postmenopausal women and the majority of the elderly. It is a systemic skeletal disorder characterised by low bone mass and micro-architectural deterioration of bone tissue, with a consequent increase in bone fragility and susceptibility to fracture. The most common sites of fracture are the vertebrae, distal radius (Colles' fracture), and hip.

Two distinct phases of bone loss can be recognised: a slow, age-related phase that occurs in both sexes beginning at about age 35, and an accelerated phase that occurs during the first ten years after menopause in women. During this accelerated phase, women experience a drastic increase in bone turnover with bone resorption becoming predominant over bone formation. This is mainly due to the effects of estrogen deficiency on the bone remodelling system. Furthermore, a number of risk factors may also contribute to the pathogenesis of osteoporosis, including the ageing process itself, premature menopause, genetic factors, physical inactivity, nutritional factors (decrease in calcium intake, vitamin D deficiency), smoking and excessive alcohol consumption.

The diagnosis of postmenopausal osteoporosis is based upon epidemiological data on the relationship between fracture risk and bone mineral density (BMD). BMD measurements are expressed by using standard deviation scores expressed in relation to young adult BMD reference data (T score). Osteoporosis is defined as a BMD T score below –2.5. Osteopenia may be defined as a BMD T score between –1 and –2.5. The term severe or established osteoporosis denotes a T score below –2.5 in the presence of one or more fragility fractures.

**Prevention of osteoporosis**

Untreated postmenopausal women may lose 1 to 3% of bone mass per year. The most appropriate therapeutic approach to postmenopausal osteoporosis currently is the prevention of skeletal loss during the first five years of the menopause. Estrogen replacement therapy is the cornerstone of preventive therapy for osteoporosis. Estrogens effectively inhibit postmenopausal bone loss, but may be associated with an increase in the risks of deep venous thrombosis, endometrial and breast cancer with long-term therapy. Other antiresorptive medicinal products may be used, but they are only effective when bone turnover is high and they may have other untoward effects. In addition, pharmacological doses of calcium and/or vitamin D have been reported to slow down the decrease in BMD.

**Treatment of osteoporosis in postmenopausal women**

Vertebral fractures form an integral component of the osteoporotic syndrome. They often occur spontaneously or as a result of minimal trauma such as during coughing or lifting. Vertebral fractures are the most common osteoporotic fractures; 5% of women at 50 and 25% at 80 have had at least one vertebral fracture. At age 70, the general population incidence is approximately 1% per annum (Melton et al. 1989). Therapies used in the treatment of postmenopausal osteoporosis aim to reduce the incidence of new vertebral fractures.

Raloxifene hydrochloride is a new chemical entity characterised as a selective estrogen receptor modulator (SERM), based on its ability to bind to and activate estrogen receptors, inducing estrogen agonist effects in some tissues (bone, lipid metabolism) but not in the uterus or mammary gland. Its biological actions, like those of estrogens, are mediated through high-affinity binding to estrogen receptors and regulation of gene expression. The binding results in differential expression of multiple estrogen receptor-regulated genes in different tissues.

Raloxifene hydrochloride is intended for the treatment and prevention of osteoporosis in postmenopausal women. The proposed dose is 60 mg daily (equivalent to 56 mg raloxifene free base).

## 2.    Chemical, pharmaceutical and biological aspects

Raloxifene hydrochloride is an orally active synthetic benzothiophene derivative characterised as a SERM. It is presented as Evista white elliptical film coated tablets. Each film coated-tablet contains 60 mg raloxifene hydrochloride, equivalent to 56 mg raloxifene freebase. Different package sizes are: 14, 28 and 84 tablets in blisters, and 100 tablets in plastic bottles.

**Composition**

The film-coated tablets are made with standard core and film-coat excipients. The excipients are povidone, polysorbate 80, anhydrous lactose, lactose monohydrate, crospovidone, magnesium stearate, hypromellose, macrogol 400, carnauba wax, modified pharmaceutical glaze, and propylene glycol. The tablets are coated with a film coat containing titanium dioxide (E171) as a colorant and imprinted with edible blue ink containing indigo carmine (E132) as a colorant.

Many different formulations, dosage forms and strengths were used in the clinical trials. The commercial scale tablets have been shown to be bioequivalent to the representative clinical batches used in pivotal efficacy and safety trials.

Solubility and hydrophobicity of the active substance have been of particular concern when formulating the medicinal product to ensure that the drug substance dissolves in the gastrointestinal tract. Specifications were set for the particle size. An aqueous film coat has been applied to mask the taste of the tablet core and provide a smoother surface for ease of swallowing. A 1% overage in the formulation has been justified. The selection of excipients and their concentration ranges have all been justified. The development pharmaceutics have been adequately described.

**Method of preparation**

The manufacturing process has been adequately validated on 7 batches from the two finished product-manufacturing sites. The in-process controls and limits proposed are satisfactory.

**Control of starting materials**

The specifications for drug substance include tests for identity, assay, particle size, related substances, volatiles, residual solvents, residue on ignition and heavy metals. Most of the tests are based on the general methods of Ph. Eur., USP or JP. All the tests used have been adequately validated.

Raloxifene hydrochloride is manufactured in a multistep organic synthesis. The structure of the active substance has been confirmed by X-ray crystallography; NMR, UV, IR, and Raman spectroscopy; mass spectrometry; and elemental analysis. Raloxifene hydrochloride contains no asymmetric centre, and does not show optical isomerism.

Only two process impurities are present at a level greater than 0.1%. All other related substances are present at a level below 0.1%. Residual solvents are routinely controlled within acceptable limits. Heavy metals are also routinely controlled.

The active substance batch analytical data are satisfactory.

All the excipients, except the film coating mixture and the printing ink, comply with the requirements of the current version of the PhEur. Additional microbiological tests are performed for carnauba wax.

The colouring agents are on the list of permitted food colours and comply with the EEC requirements. The testing methods and certificates of analysis of the colour mixture and the ink are provided.

Bulk tablets are packaged in a primary and secondary low-density polyethylene liner. The marketed containers proposed are PVC/aluminium blisters, PVC/Aclar/aluminium blisters and natural high-density polyethylene (NHDPE) bottles. The bottles are packed with a cotton pharmaceutical coiler and sealed with plastic screw cap closures with heat seal liner. Packaging materials testing is satisfactory; certificates of analysis are provided.

**Control tests on the finished product**

The drug product specification includes standard tests for physical appearance, identity, assay, purity, water, dissolution, microbial contamination and dye identity. All tests have been adequately validated.

The identification test for chlorides is performed only on the active substance batches. Some of the test parameters (microbial purity, dye identity) are not routinely controlled, but in acceptable frequency.

The dissolution specification limits have been set in order to guarantee a dissolution profile similar to that of the clinical batches. The release and shelf life specifications for degradation products and total related substances are acceptable. Suitability criteria for the HPLC method guarantee acceptable resolution between raloxifene hydrochloride and the degradation products.

Batch analytical results provided for seven commercial batches from different manufacturing sites comply with the specifications.

**Stability**

**Active substance**

Three batches of the active substance manufactured at two different sites have been stored for up to 6-15 months and four production scale batches up to 3 months at different temperatures and relative humidity (30°C/60%RH, 40°C/75%RH). All data from these stability tests met the proposed specifications. The packaging materials were intact.

Long-term stability results of 24 months from the primary stability batches and 9 months from the production scale batches of active substance have been provided later. The updated results for the primary stability batches indicate no significant change in the drug substance assay and related substances.

**Finished product**

Seven production scale batches of finished products manufactured at the two different sites, using the commercial formulation and containers, have been stored for up to 12 months at different temperature and relative humidity (25°C/60%RH, 30°C/60%RH, 40°C/75%RH). The data showed that the finished products meet the proposed shelf life specifications during the 12 months storage at the long-term and mostly also at accelerated conditions. Thermal stress and light testing has shown, only at extremely high temperature (105°C), significant increase of two related substances. No degradation occurred under simulated daylight or at 60°C, which confirms the good stability of the product in solid state.

Further finished product stability data at the long-term storage conditions (25°C/60%RH) for up to 18-24 months showed no significant change in the amount of the active substance or related substances. All data comply with the specifications for assay and for total related substances. The results for tablets stored in the HDPE bottles and Aclar blisters supported the proposed 24 months shelf life. 2 years shelf life is therefore recommended for tablets in Aclar blisters, PVC blisters or HDPE bottles, stored at room temperature (15-25°C) in a dry place. These conditions are reflected in the SPC.


### 3. Toxico-pharmacological aspects

**Pharmacodynamics**

**Effects related to the proposed indication**

The applicant has performed several preclinical animal studies to investigate effects of raloxifene on bone. These studies, which have been conducted mainly in rats and cynomolgus monkeys, have used ovariectomised (OVX) or sexually immature animals as a model of estrogen deficiency. Several analytical methods have been applied to evaluate different aspects of the effects on bone including analysis of bone mineral density, biomechanical strength, histomorphometry, and biochemical markers of bone metabolism.

The doses used (0.001-30 mg/kg/day in rats and 1-5 mg/kg/day in monkeys) result in an exposure consistent with that in women receiving the proposed daily dose of 60 mg.

The duration of some studies (particularly the two chronic studies of 12 months in OVX rats and 2 years in OVX cynomolgus monkeys) is adequate to demonstrate the beneficial effects on bone turnover.

There is sufficient preclinical evidence that raloxifene has a tissue-selective estrogen-receptor (ER) agonist or antagonist profile. Concerning the mimetic actions, there is sufficient preclinical evidence supporting the anti-osteoporotic properties of raloxifene in conditions of estrogen deficiency.

Furthermore, the studies also demonstrated that raloxifene lowers serum cholesterol levels in OVX rats, rabbits and monkeys mimicking actions of estrogens (however raloxifene is less potent than estrogens in reducing cholesterol levels and does not prevent the development of atherosclerotic alterations).

On the other hand, raloxifene behaves in reproductive sites, such as mammary tissue and uterus, like an ER antagonist. Its lack of uterine stimulation distinguishes raloxifene from other antiestrogens, like tamoxifen, which have partial agonist activity on the endometrium.

**General pharmacodynamics**

A wide range of studies has been performed *in vitro* and *in vivo* (rabbit, mouse, guinea pig). At oral doses up to 600 mg/kg/day raloxifene showed no marked cardiovascular, renal, gastrointestinal or smooth muscle activity.

**Pharmacokinetics/Toxicokinetics**

The majority of the pharmacokinetic studies were performed in rats, mice and monkeys, with a few studies performed in dogs. Many studies relied on $^{14}$C-raloxifene; authentic raloxifene was also measured by HPLC.

The data have shown good oral absorption, extensive "first-pass" metabolism in the intestinal mucosa and liver to form glucuronide conjugates, a high level of plasma protein binding and faecal excretion of raloxifene and its metabolites via the bile.

A wide range of oral doses was used in pharmacology studies (1-5 mg/kg) with much higher doses in toxicology studies (up to 600-1700 mg/kg). In general, plasma concentrations of raloxifene increased with dose in mice, rats and monkeys, but increases were not always proportional, especially at high doses. A similar pattern was observed in postmenopausal women given doses up to 600 mg orally.

The results seen in the animal models are consistent with the higher exposure levels in animals compared to humans. Systemic exposure to raloxifene after 1 year or more of daily dosing was approximately 41, 505 and 13 times greater in mice, rats and monkeys, respectively, than in postmenopausal women given 60 mg/day for two years. It can be concluded that animals were appropriately exposed to the compound in these studies.

**Toxicology**

**Single dose toxicity** was evaluated in two rodent (mice and rats) and two non-rodent (Beagle dogs and rhesus monkeys) species, by oral and intraperitoneal (in rats) route. Acute toxicity was low. No mortality was observed with doses up to 5000 mg/kg orally to mice and rats. Few rats showed toxicity after i.p. injection of a 2000 mg/kg dose of raloxifene.

**Repeated dose toxicity** was investigated in mice (3 months), rats (up to 1 year), dogs (6 months) and cynomolgus monkeys (up to 1 year) following oral administration. In general, raloxifene was well tolerated and observations from these studies were considered to reflect the pharmacodynamic actions of raloxifene on reproductive tissues and estrous cycle due to the SERM-like activity. A no-effect level was not determined.

**Reproductive toxicity:** The applicant has performed adequate reproductive toxicity studies in rats and rabbits. The observed effects were all consistent with the known action of raloxifene on the estrogen receptor. 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 ($\geq$ 0.1 mg/kg) and hydrocephaly ($\geq$ 10 mg/kg) were seen. In rats, retardation of foetal development, wavy ribs and kidney cavitation occurred ($\geq$ 1 mg/kg).

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These studies are however of limited interest since the proposed indication is limited to postmenopausal women.

**Genotoxicity**: Results from the standard battery of *in vitro* and *in vivo* mutagenicity tests show that raloxifene is devoid of genotoxic potential.

**Carcinogenicity:** The oncogenic/carcinogenic potential of raloxifene has been investigated in mice (21 month study) and in rats (24 month), with appropriate exposure multiples over human doses. An increased incidence of ovarian neoplasias was observed in both species, as well as an increase of serum ALT levels. Treatment of female rodents with raloxifene throughout their lives produced specific hormonal imbalances. Such imbalances are known to result in ovarian tumours in rodents, which have not been observed in women who have received raloxifene.

**Environmental risk assessment:** Analysis was performed to determine potential environmental issues associated with production, use, and disposal of raloxifene. Factors considered were physical/chemical properties of the bulk drug substance, the proposed use pattern of raloxifene as a therapeutic agent, human metabolism and excretion, environmental fate, inert ingredients in the tablets and disposal of packaging. The calculation of a variety of safety factors revealed very large margins of safety for surface waters and soil. It can be concluded that the use of raloxifene will not present a hazard to the environment.

In summary, the preclinical documentation provided was overall of good quality. The data demonstrate the anti-osteoporotic and hypocholesterolemic effects of raloxifene in estrogen-deficient animal models of postmenopausal osteoporosis.

## 4.    Clinical aspects

Forty-nine clinical studies had been initiated when the first indication was approved; of these, 31 were clinical efficacy and safety studies, 15 were completed, 15 were ongoing and 1 was discontinued. The majority of the ongoing studies were still blinded.

The core clinical documentation for the prevention of osteoporosis in postmenopausal women indication consisted of three main Phase III studies (randomised, multicentre, double-blind, placebo-controlled parallel groups) and several Phase II studies. The study programme was conducted in compliance with GCP. All the subjects enrolled in these prevention studies received daily calcium supplement.  The core clinical documentation for the treatment of osteoporosis in postmenopausal women indication was based on 3-year data from a single, very large Phase III study (randomised, multicentre, double-blind, placebo-controlled parallel group) (Study GGGK) involving 7705 women with osteoporosis.  All the subjects enrolled in this treatment study received daily calcium and vitamin D supplementation.

**Pharmacodynamics**

**Prevention indication**

Raloxifene belongs to the class of selective estrogen receptor modulators (SERM). It acts through the induction of estrogen agonistic effects on bone and lipid metabolism but not in uterine or breast tissues. Its actions are mediated through high affinity binding to estrogen receptors and regulation of gene expression, resulting in differential expression of multiple-regulated genes in different tissues. Several randomised studies, open-label, or double blind, or uncontrolled have been carried-out in healthy postmenopausal women in order to elucidate the mechanism of action in humans.

The effect of raloxifene (60 mg/day) compared to estrogens (0.625 mg/day) plus medroxyprogesterone acetate (5 mg/day) on bone remodelling kinetics has been evaluated for up to 8 months (study GGGR). A shift from negative calcium balance to positive balance was statistically significant compared to placebo in both active treatment groups. Calcium resorption significantly decreased with both treatment groups. Both treatment groups suppressed bone remodelling by suppressing resorption; the effects were however clearer with the conjugated estrogens/medroxyprogesterone acetate group.

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Evaluation of histomorphometry (study GGGM) is based on data from bone biopsies (22 subjects) from postmenopausal women assigned to treatment with raloxifene (60 mg/day for 6 months) or conjugated estrogens (0.625 mg/day) for 6 months. Overall the effects of raloxifene on bone histomorphometry indices were similar to those of estrogens, but of smaller magnitude. Bone quality was normal in both groups. Moreover, the changes in biochemical markers of bone formation (bone-specific alkaline phosphatase, osteocalcin) and resorption (collagen crosslinks, hydroxyproline, deoxypyridinoline) were consistent with the histomorphometric and BMD data, and were as expected from drugs with estrogenic activity. At the higher raloxifene dose (150 mg/day, study GGHI), there was no evidence of compromised bone quality including no suggestion of woven bone, cellular toxicity, marrow fibrosis or mineralisation defect.

Studies on the effects of endocrine function showed that in women with normal menstrual cycles, raloxifene (100, 200 or 400 mg/day) was weakly antiestrogenic (study GGGJ). Raloxifene neither markedly affected the gonadotropin levels, nor blocked the actions of estrogen on endometrium.

In postmenopausal women, no clinical changes in the markers of function of the pituitary adrenal axis were seen (raloxifene 200 mg/day, study GGGE). Slightly increased serum cortisol was observed, an effect consistent with estrogenic action.

Typical estrogenic effects (increases in TBG, T3 and T4) were observed in postmenopausal women after 4 weeks of raloxifene (150 mg/day, study GGHE). The increases in T3 and T4 were approximately 20%. A slight increase (20%) was observed in TSH in this study, but not in GGGB with doses up to 600 mg/day.

**Treatment indication**

Population pharmacodynamic analyses of lumbar spine and femoral neck BMD, and serum osteocalcin were performed on the 36-month data from Study GGGK. These analyses confirmed that raloxifene-treated patients with the most severe osteoporosis (e.g. the lowest baseline lumbar spine BMD, the highesst baseline osetocalcin or total alkaline phosphatase) had the largest increases in lumbar spine and femoral neck BMD and the greatest decreases in serum osteocalcin. There were no differences in the effectiveness of raloxifene 60-mg vs raloxifene 120-mg.

**Pharmacokinetics**

**Prevention indication**

The pharmacokinetics of raloxifene has been studied in healthy volunteers, postmenopausal women, and patients with hepatic impairment (5 subjects with cirrhosis).

The mean oral bioavailability of raloxifene was low, approximately 2%. However, the median estimate of absorption of total drug-related substance is much higher and the absolute oral bioavailability is dependent on metabolic interconversion between raloxifene and its glucuronides. Most of the raloxifene in the systemic circulation appears to be derived from deconjugation of the glucuronides.

Raloxifene is a high clearance drug, with a clearance approximately equal to liver blood flow. It undergoes significant enterohepatic circulation.

Following single oral doses (study GGGI), the $T_{max}$ for raloxifene was approximately 6 hours (ranging from 1-24 hours), $t_{1/2}$ was 33 hours (23-92 hours). According to a study with $^{14}$C-raloxifene, peak concentrations of total raloxifene in hydrolysed plasma (TRHP) represented more than 99% of total radioactivity in plasma, indicating rapid glucuronidation. The terminal half-lives of raloxifene, TRHP and glucuronides were similar, ranging from 15.6 to 21.8 hours. After repeated oral doses, raloxifene kinetics (e.g. elimination rate constant, clearance and volume of distribution) was linear with respect to time. The raloxifene concentration-dose relationship was linear, but not dose-proportional.

Raloxifene and its glucuronides are highly bound to plasma proteins, including both albumin (>95%) and alpha-1-glycoprotein (89%). Neither raloxifene nor the glucuronides are distributed into the cellular component of blood.

The only metabolites detected in plasma and urine are glucuronide conjugates (raloxifene-4'-glucuronide, -6'-glucuronide and –6,4'-diglucuronide. No oxidative metabolites have been found.

Raloxifene and its metabolites are primarily excreted in the faeces, less than 6% is recovered in urine. The amount of unchanged raloxifene in urine is negligible.

The effect of food on the pharmacokinetic parameters of raloxifene is not significant.

Population pharmacokinetic analyses (NONMEM model) confirmed the results from individual pharmacokinetic studies. The pharmacokinetics of raloxifene and TRHP are characterised by large intra- and inter-subject variability. Pharmacokinetics was not affected by age, dose or ethnic factors. Self-reported alcohol consumption (>3 drinks per week) did not influence raloxifene pharmacokinetics. In smokers, raloxifene clearance was approximately 20% greater than in non-smokers, but this difference is less than the 30% within-subject variability.

A formal study in patients with renal impairment has not been performed, as renal excretion of raloxifene is a minor pathway. Dose adjustment does not appear necessary in subjects with mild renal impairment on the basis of population pharmacokinetic analysis. In the absence of data, raloxifene is contraindicated in severe renal impairment.

In subjects with hepatic cirrhosis and mild hepatic impairment (Child-Pugh Class A), the Cmax and AUC for plasma raloxifene, TRHP and raloxifene-glucuronide (single dose of raloxifene) were significantly higher than in healthy control subjects. A statistically significant association was observed between raloxifene-glucuronide, TRHP and raloxifene AUC versus serum total bilirubin. Raloxifene is contraindicated in hepatic impairment, including cholestasis.

A number of tablet formulations have been used in clinical trials. The different formulations and the market-image tablets have been shown to be bioequivalent.

**Treatment indication**

Population pharmacokinetic analyses from patients (postmenopausal women with osteoporosis) in Study GGGK demonstrated that the pharmacokinetics of raloxifene were not clinically significantly affected by age, body weight or BMI, cigarette smoking, chronic alcohol use or decreased renal function. However, in the absence of data, raloxifene is contraindicated in severe renal impairment.

**Interaction studies**

In *in vitro* studies, significant plasma protein binding interactions were not observed with warfarin, phenytoin, tamoxifen or testosterone.

In *in vivo* studies, an approximately 40% reduction in systemic raloxifene exposure was observed after cholestyramine, therefore cholestyramine should not be co-administered with raloxifene. Calcium carbonate and aluminium hydroxide/magnesium hydroxide antacid did not modify the absorption and exposure to raloxifene and metabolites. Oral ampicillin therapy resulted in lower raloxifene concentrations, but the interaction is probably not of significant consequence during short-term antibiotic treatment. Raloxifene reduces the efficacy of warfarin treatment. A significant decrease in the peak and AUC of the prothrombin time response to warfarin was observed after multiple doses of raloxifene; careful monitoring of prothrombin time is necessary over several weeks. Concomitant administration of raloxifene resulted in increase in $C_{max}$ of digoxin (by less than 5%), but did not affect overall exposure. These interactions are referred to in the SPC.

In the population pharmacokinetic analyses, histamine H1-receptor antagonists, laxatives and fibre were associated with slight decreases in observed average raloxifene concentrations.

For other frequently co-administered drugs such as paracetamol, non-steroidal anti-inflammatory drugs (e.g. acetylsalicylic acid, ibuprofen and naproxen), oral antibiotics, H1 antagonists, H2 antagonists and benzodiazepines, no clinically relevant effects of co-administration on raloxifene plasma concentrations were identified.

The Phase I study GGIP, which assessed the pharmacokinetic interaction of raloxifene after multiple administration of methilprednisolone in postmenopausal women with no concomitant hormone replacement therapy, showed that raloxifene has no effect on the pharmacokinetics of methylprednisolone given as a single dose.

**Efficacy**

**Dose-ranging studies**

The dose-ranging program was mainly based on two multicentre, double-blind, randomised, short-term studies (GGGB and GGGC) in a total of 491 healthy postmenopausal women. It documented, over 8 weeks, primarily the dose-response relationship of raloxifene as compared to placebo (GGGC) and/or conjugated estrogen (GGGB) on mineral homeostasis and bone metabolism, and serum lipid profile in healthy postmenopausal women.

Compared to placebo (GGGB), all active treatment groups (raloxifene 200 and 600 mg, estrogen 0.625 mg) had significant decreases in biochemical markers of bone metabolism; no significant difference between active treatment groups was observed. The two doses of raloxifene demonstrated comparable efficacy, but the higher dose (600 mg) resulted in a greater frequency of hot flushes.

Relative to placebo (GGGC), serum osteocalcin significantly decreased only in raloxifene 200 mg group, serum alkaline phosphatase decreased significantly at raloxifene 50 mg and 200 mg groups. On the other hand, biochemical markers were unaffected at 10 mg raloxifene, indicating that this is a no effect dose.

In addition, an early Phase II multicentre, 24-week Japanese study (201J) was conducted in postmenopausal patients with a decrease in BMD and osteoporosis (n=112, 104 received medication). Statistically significant increase in lumbar spine BMD was observed in both active treatment groups (raloxifene 30 and 90 mg) versus placebo. The difference between both treatment groups was not significant.

The minimum effective dose was not reliably established in these dose-ranging studies. However, raloxifene 600 mg/day was concluded to be an unacceptable dose and 10 mg/day did not appear to have any significant effects on bone. With respect to effect on lumbar spine BMD, 30 mg appeared to be as effective as 90 mg. On the other hand, significant changes were observed at 50 mg and 200 mg compared to placebo.

1. **Efficacy package in support of the Osteoporosis Prevention in postmenopausal women indication**

1.1. **Main Phase III Efficacy Studies: Prevention of Osteoporosis** (GGGF, GGGG and GGGH)

These main studies enrolled a total of 1754 postmenopausal women for long-term double-blind treatment with placebo or raloxifene (30, 60 or 150 mg/day). Study GGGH enrolled subjects who had undergone hysterectomies, and included an unopposed conjugated estrogen treatment arm (0.625 mg/day). Two-year interim reports with intention-to-treat and per protocol analyses have been provided.

The study population was women (mean age of 54 years) who were 2 to 8 years postmenopausal, except for the study GGGH in which women who were 0 to 15 years postmenopausal were included. The inclusion criteria comprised subjects with T-scores for lumbar spine BMD ranging from -2.5 to +2.0 inclusive. The osteopenic population, with T-scores from -2.5 to -1, is considered most relevant for the claimed indication; approximately 50% of the study population had osteopenia.

The primary efficacy criteria in these studies were change and percent change from baseline to endpoint in lumbar spine (L1-L4) and total hip BMD. Secondary efficacy criteria included markers of bone metabolism (serum osteocalcin, serum total and bone-specific alkaline phosphatase, urinary type I collagen fragment C-telopeptide), serum lipids, measures of coagulation and fibrinolytic activity and assessment of endometrial thickness.

**Effects on bone:**

- **GGGF** was a European study to establish the effects of long-term therapy with three doses of raloxifene compared to placebo on BMD of the lumbar spine and total hip. Randomised patients received placebo (n=150) or raloxifene 30 mg (n=152), 60 mg (n=152), or 150 mg (n=147) daily.

After 24 months of treatment, the mean percentage changes from baseline for lumbar spine BMD were –0.8% (placebo), +1.3% (30 mg), +1.6% (60 mg) and +2.2% (150 mg). At the level of the total hip,

the changes were –0.8% (placebo), +1.0% (30 mg), +1.6% (60 mg) and +1.5% (150 mg). Increases in BMD were statistically significant compared to placebo at all measurements sites (except the distal and ultradistal radius) for all doses of raloxifene. The results are clinically significant and relevant with respect to the proposed indication. The biochemical markers of bone metabolism decreased significantly in all raloxifene groups versus placebo, consistent with decreased bone turnover.

- **GGGG** was a US study to establish the effects of long-term therapy with three doses of raloxifene compared to placebo on BMD of the lumbar spine and total hip. Randomised patients received placebo (n=136) or raloxifene 30 mg (n=136), 60 mg (n=134), 150 mg (n=138) o.d.

Over 24 months of treatment, the mean percentage changes from baseline for lumbar spine BMD were –1.2% (placebo), +0.4% (30 mg), +0.8% (60 mg) and +0.8% (150 mg). At the level of the total hip, the changes were –0.8% (placebo), +1.0% (30 mg), +1.2% (60 mg) and +1.6% (150 mg). Although the effects of raloxifene on lumbar spine and total hip BMD (except for the radius and total body BMD) and bone markers (except for the specific alkaline phosphatase in the raloxifene 30 mg group) were clearly distinguishable from placebo, the effects on lumbar spine BMD were weaker compared to study GGGF. Nevertheless, the effect of raloxifene 60 mg/day was statistically significant compared to placebo. Raloxifene 30 mg appeared to be less effective than 60 mg and 150 mg.

- **GGGH** was a study to establish the effects of long-term therapy with two doses of raloxifene or unopposed conjugated estrogen compared to placebo on BMD of the lumbar spine and total hip. Randomised patients received placebo (n=152) or raloxifene 60 mg (n=152), 150 mg (n=157), or conjugated equine estrogen 0.625 mg (n=158) o.d.

After 24 months of treatment, the mean percentage changes from baseline for lumbar spine BMD were –1.6% (placebo), +0.2% (60 mg), +0.4% (150 mg) and +3.8% (estrogen). At the level of the total hip, the changes were –0.5% (placebo), +0.8% (60 mg), +0.5% (150 mg) and +2.4% (estrogen).

At both doses, raloxifene had a weak, but statistically significant effect compared to placebo on lumbar and total hip BMD. However, the magnitude of the effect of estrogen was significantly greater. The actual "mean benefit" from raloxifene and estrogen compared to placebo was 1.8% and 5.0% respectively. A slight downward slope in the lumbar spine and total hip BMD curves was noted during the second year of raloxifene, but not in the estrogen groups. This was only observed at the 150-mg/day doses, not at 30 mg/day, 60 mg/day or in other phase III studies. However, the mean BMD values remained at, or slightly above baseline for up to 24 months. Raloxifene and estrogen had similar effects on biochemical markers of bone metabolism, but the magnitude of the effect of estrogen was also clearly more pronounced than that of raloxifene.

Raloxifene has a well-documented effect compared with placebo on lumbar spine and total hip BMD. Although qualitatively the effects of raloxifene on BMD and biochemical markers of bone metabolism are similar to those of estrogen, their magnitude is less. Hence, evidence of fracture benefit in patients with osteoporosis was required, even for the proposed osteoporosis prevention claim.

A 2-year interim analysis of an ongoing double blind, placebo-controlled phase III study in osteoporotic postmenopausal women was provided. This study enrolled a total of 7705 patients randomly assigned to one of three treatment groups: raloxifene 60 mg, 120 mg or placebo. Both postmenopausal women with osteoporosis and established osteoporosis (prevalent vertebral fractures) were included. The diagnostic criteria and evaluation for incident fractures are appropriate.

Both raloxifene doses significantly reduced the proportion of patients having at least one incident vertebral fracture during 24 months of treatment compared to vitamin D and calcium supplemented placebo. The reduction in the risk of experiencing at least one incident fracture was in the range of 35% to 55% in patients with and without prevalent vertebral fracture at baseline, showing the same range of figures as those reported in observational studies evaluating the anti-fracture efficacy of estrogen (HRT). The 3-year analysis of this study was submitted in 1999 to support the extension of the indication to include treatment of postmenopausal osteoporosis. In contrast to estrogen, no data are currently available on the ability of raloxifene to prevent non-vertebral fractures.

Similar efficacy related subgroup analyses were carried out in studies GGGF and GGGG. Raloxifene was observed to improve BMD regardless of BMI (Body mass index). Population pharmacodynamic analyses for the main efficacy studies supported the proposed dose of raloxifene 60 mg/day.

**Effects on serum lipid profile**

Raloxifene has clear effects on serum lipid profile. At 60 mg/day, raloxifene decreases total cholesterol by approximately 3-6%, LDL cholesterol by 4-10%, HDL cholesterol by 1-4%, LDL/HDL ratio by 7% and total cholesterol/HDL ratio by 5% over 24 months. However, HDL cholesterol has decreased slightly more during placebo than raloxifene. Raloxifene does not affect serum triglyceride levels, which may increase during estrogen treatment. It also slightly decreased lipoprotein A and apolipoprotein B levels. Overall, the effects of raloxifene (60 mg/day) on serum lipids were similar to those of estrogen, but weaker. Raloxifene did not have adverse effects on lipid profile. In contrast to estrogen, no data are yet available to demonstrate the benefit of raloxifene on atherosclerotic cardiovascular disease. Similar efficacy related subgroup analyses carried out in studies GGGF and GGGG indicated that in smokers, the reduction in LDL cholesterol was less pronounced than in non-smokers.

## 1.2 Supportive studies: Treatment of osteoporosis

In addition, one Phase II, multicentre, randomised, double blind, placebo-controlled supportive study was submitted (GGGN). It evaluated the effect of raloxifene (60 or 120 mg/day) on incident vertebral and non-vertebral fractures. The analysis of incident fractures using the protocol-predefined cut-off of at least a 15% decrease in vertebral height did not suggest any benefit of raloxifene. *Post-hoc* analyses using more stringent criteria, however, suggested a trend of decreasing incidence of vertebral fractures in favour of raloxifene over placebo. Although it was argued that by using the 15% cut-off, the number of false positive findings might increase, the mean incident fracture rate was not numerically smaller in the raloxifene groups compared to placebo (daily calcium and vitamin D supplementation only). However, due to the rather small study population (130 osteoporosis patients completed the 12 months), the interpretation of these findings is limited.

Two additional multicentre, double-blind studies were ongoing: a Phase III comparison of raloxifene (60 mg and 120 mg) versus placebo in the treatment of postmenopausal osteoporosis in over 7000 patients (GGGK) and a Phase II comparison of raloxifene (60 mg and 150 mg) versus placebo in the treatment of postmenopausal osteopenia (GGGP).

## 2. Efficacy package in support of the treatment of osteoporosis in postmenopausal women indication

## 2.1 Main Phase III Osteoporosis Treatment Efficacy Study (GGGK)

GGGK was a Phase 3, multicentre, double-blind, placebo-controlled, randomised clinical study which compared raloxifene 60 mg/day, raloxifene 120 mg/day and placebo in the treatment of postmenopausal women with osteoporosis or established osteoporosis. It was designed as a completed 36-month core treatment phase and a 12-month extension phase. It randomly assigned 7705 eligible patients to one of the three treatment groups (placebo, N=2576; raloxifene 60mg, N-2557 and ralozifene 120mg, N=2572). All patients were supplemented with calcium and vitamin D. The study population was postmenopausal women (mean age 66.5 years) who had osteoporosis.

GGGK was designed as two separate substudies. Substudy I included patients with osteoporosis by BMD criteria (BMD T-score <-2,5 in either the femoral neck or lumbar spine). Substudy II included patients who were were osteoporotic by BMD and also had at least one moderate or 2 mild prevalent vertebral fractures or at least 2 moderate prevalent vertebral fractures regardless of BMD. Approximately twice as many patients were enrolled into Substudy I (n=5064) as into Substudy II (n=2641).

Primary efficacy objectives of this study and each substudy were to assess the effects of raloxifene 60mg and 120 mg compared with placebo on incidence of new vertebral fractures and change and percentage change in lumbar spine (L1-L4) and femoral neck BMD. Additional secondary efficacy objectives included the effects of raloxifene compared with placebo on nonvertebral fractures, on total body and radial BMD, on biochemical markers of bone turnover, and on serum lipids and other markers of cardiovascular risk.

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**Effects on bone**

Based on the three-year analysis of data from Study GGGK, each dose of raloxifene (60 mg and 120 mg per day) in each substudy statistically and clinically significantly decreased the proportion of women with at least one adjudicated new incident vertebral fracture vs placebo. In patients in Substudy I, raloxifene 60mg-day was associated with a 47% reduction (RR 0.53, 95% CI 0.35, 0.79) in the risk of new vertebral fractures and raloxifene 120mg/day was associated with a 38% risk reduction (RR 0.62, CI 0.44, 0.93). In patients in Substudy II, there was a 31% risk reduction (RR 0.69, CI 0.56, 0.86) with raloxifene 60mg and a 49% risk reduction (RR 0.51, CI 0.40, 0.65) with raloxifene 120mg. The proportion of women with at least one adjudicated incident vertebral fracture was statistically significantly lower in the 120-mg group than in the 60-mg group in Substudy II, but not in Substudy I. However, no statistically significant differences were observed between the raloxifene doses for the reduction of new clinical or multiple vertebral fractures in patients in Substudy Substudy II or I. Overall, raloxifene 60mg/day was associated with a 41% reduction and raloxifene 120mg/day was associated with a 52% reduction in the risk of new clinically apparent vertebral fractures. The CPMP has agreed that the overall risk/benefit assessment favours the 60-mg dose over the 120-mg dose for the treatment of postmenopausal osteoporosis regardless of baseline disease severity. No effect on hip fractures has been demonstrated and this is clearly stated in the SPC Section 4.1.

Each dose of raloxifene in each substudy statistically significantly increased BMD at the lumbar spine and femoral neck by 2-3% vs placebo at 36 months. Total body and ultradistal radius BMD increased 1-2% vs placebo at 24 months. The doses were equivalent in their effects on BMD in both patients with and without prevalent vertebral fractures. Raloxifene treated patients had 15 to 25% greater reductions in markers of bone turnover (osteocalcin, bone specific alkaline phosphatase and Urinary Type I Collagen Fragment/Cr) than placebo treated patients who had 10 to 20% reductions. Each dose of raloxifene in each study was effective in reducing skeletal turnover.

**Effects on serum lipids and markers of cardiovascular risk**

In the osteoporosis treatment population, raloxifene also has clear effects on serum lipids and other markers of cardiovascular risk. Compared with placebo, raloxifene treated patients had consistent decreases of 6 to 7%, 10 to 12%, 10 to 13% and 7 to 9% in total cholesterol, LDL-cholesterol, fibrinogen and Apolipoprotein B, respectively at 36 months. There were no effects of raloxifene on HDL-cholesterol or glycosylated hemoglobin. While median percentage reductions in triglycerides were observed in raloxifene treated patients, the reductions were greater for the placebo group. A 3% increase in Apolipoprotein A was observed with raloxifene treatment compared with placebo. However, no data are available to demonstrate benefit of raloxifene on cardiovascular disease.

**Safety**

As of the cut-off date for the osteoporosis prevention indication (16 October 1996), a total of 2605 subjects had received at least one dose of raloxifene. An additional 5548 subjects had received raloxifene in seven ongoing-blinded studies. The primary safety database consisted of 12 controlled, double blind or open-label studies, which were pooled to comprise the placebo-, estrogen- and hormone replacement therapy (HRT)-controlled databases. The secondary safety database included the remaining clinical studies. The 60-mg dose had the most patient years of exposure. In the placebo-controlled primary database, approximately 65% subjects had been exposed to raloxifene for at least 12 months.

As of the cut-off date for the osteoporosis treatment indication (1 January 1999) total patient exposure was 19,680 patient-years, of which 13,118 patient-years was exposure to raloxifene. There were no statistically significant treatment group differences in exposure to study drug (placebo, 6562 patient-years; raloxifene 60-mg, 6519 patient-years and raloxifene 120-mg, 6599 patient-years). The primary safety database for the specific events of death, venous thromboembolic events (VTE), breast cancer, endometrial cancer and ovarian cancer were considered to be those placebo-controlled trials which were of at least 6 months duration and were fully enrolled as of 13 October 1998.

**Deaths**

**Osteoporosis prevention indication**

A total of 64 deaths had been reported in both completed and ongoing studies as of 28 February 1997. An additional update was then requested, it reported 80 deaths overall as of 22 September 1997 across all raloxifene trials conducted in postmenopausal women. This comprises 7 deaths in breast cancer treatment studies, 4 pre-randomisation deaths in GGGK study and 69 deaths occurred during post-randomisation (46 raloxifene, 22 placebo and 1 HRT; 65 of which were reported during all placebo-controlled studies). The ratio of therapies was approximately raloxifene 2.2:1 placebo. Relatively few patients received HRT (n=568).

The majority of deaths occurred in the ongoing study GGGK (59 deaths; patients' mean age at randomisation =66.5 years). The relative risk of death in patients on combined raloxifene compared with placebo was estimated at 1.14 (95% Cl 0.66; 1.98). The relative risk of death in patients on raloxifene 60 mg versus placebo was 0.60 (95% CI 0.30; 1.22).

In all placebo-controlled studies, 6 deaths were categorised as accidental injuries, 16 were due to cancer, 4 were suicidal deaths, 39 were unknown/sudden or miscellaneous. High numbers of cancer deaths were reported in the raloxifene high dose category. In breast cancer treatment studies, 5 patients died of study disease (metastatic breast cancer), 3 after discontinuation of raloxifene and 1 was due to myocardial infarction. None of the deaths were considered causally related to study drug, but its relationship could not be ruled out with absolute certainty. The relative risk of death in patients on combined raloxifene versus placebo was 1.08 (95% Cl 0.64; 1.83). High mortality hazard ratio of raloxifene versus placebo was observed during the initial 6 months of treatment. However, further evaluation of the data suggests that in the majority of cases of early death, a causal relationship with raloxifene appears unlikely.

**Osteoporosis treatment indication**

As of 1 February 1999, a total of 95 deaths had been reported in patients participating in the 11 placebo-controlled raloxifene studies, which are included in the primary safety database. An additional 26 deaths were reported in raloxifene clinical studies including 10 GGGK patients who died following discontinuation from the study: 11 patients in non-placebo-controlled trials; 2 patients in Study GGGN who died after reassignment of study drug and following discontinuation from the study; and 3 patients in placebo-controlled studies who died after discontinuation from the studies. There was no increased risk for death in each raloxifene group or in pooled raloxifene groups compared with placebo. For each cause of death, each dose of raloxifene and pooled raloxifene groups were not different from placebo. There was no evidence that chronic raloxifene administration adversely affected mortality.

In Study GGGK alone, as of the 36-month visit, 64 deaths were reported (placebo, n-23; raloxifene 60-mg. n=13; raloxifene 120-mg. n=28; overall p=0.07). Neither raloxifene group was statistically significantly different from placebo. However, there were statistically fewer deaths in raloxifene 60-mg group compared with the 120-mg group. Consistent with this, there were statistically significantly fewer cardiovascular body system death events in the raloxifene 60-mg group compared with both placebo and raloxifene 120-mg groups.

**Discontinuation rates**

**Osteoporosis prevention indication**

The proportion of subjects who discontinued treatment due to adverse events was similar in the placebo, estrogen and raloxifene groups. Vasodilatation (2-3% of subjects) and weight gain (<1%) were the most frequent adverse events leading to discontinuation of raloxifene. However, vasodilatation and weight gain did not lead to discontinuation of raloxifene more often than to discontinuation of placebo.

**Osteoporosis treatment indication**

In the 7705-patient treatment study, 25.3% of patients in the placebo group discontinued from the study before the 36-month visit, compared with 22.9% in the raloxifene 60-mg group and 22.0% in the 120-mg group. Only two reasons for discontinuation had statistically significant treatment differences

in discontinuation rates: early completion due to rapid bone loss or > 2 new vertebral fractures (3.9% for the placebo group, 1.1% for the raloxifene 60-mg group, and 1.0% for the 120-mg group; p<0.001), and adverse event (8.8% for the placebo group, 10.9% for the raloxifene 60-mg group, and 9.6% for the 120-mg group; p-0.41).   Two adverse events, which most frequently led to discontinuation from study drug, were breast carcinoma (greater incidence with placebo) and vasodilatation (greater incidence with raloxifene).

**Serious adverse events**

**Osteoporosis prevention indication**

The frequency of accidental injuries (graded as mild to moderate fractures or ligament injuries in the extremities) was higher in raloxifene-treated subjects compared to placebo. It was unclear whether raloxifene impairs postural balance and predisposes to accidental injuries. The possible effects of raloxifene on central nervous system estrogen receptors had not been considered. Although the updated data showed that statistically significant linear dose-response was no longer observed, a high proportion of subjects treated with raloxifene dose 150 mg/day reported accidental injuries. At the proposed dose of 60 mg/day, the frequency was not higher than in the placebo group.

Other serious adverse events were not clearly more frequent during raloxifene treatment compared to placebo.

**Osteoporosis treatment indication**

The only serious adverse event reported more frequently with raloxifene, which is thought to be causally associated with raloxifene treatment, is deep thrombophlebitis.  In the GGGK osteoporosis treatment study, the relative risk was comparable between the raloxifene 60-mg and the 120-mg doses. Analysis of reports by visit interval indicates that the magnitude of the risk of deep thrombophlebitis was greatest during the first 4 months of therapy.

**Other treatment-emergent adverse events**

**Osteoporosis prevention indication**

The majority (over 80%) of subjects in all treatment arms reported at least one adverse event during the long-term studies. There was no statistically significant difference in the overall frequency of reports.

The following adverse events were more frequent during raloxifene treatment compared to placebo: vasodilatation, accidental injury, leg cramps, peripheral edema, increased appetite, herpes simplex, contact dermatitis, uterine fibroids enlarged, sinusitis. Vasodilatation (raloxifene 24.3%, placebo 18.2%) was most frequently reported during the first 6 months of treatment, thereafter the frequencies were not statistically significantly different between the groups. Accidental injuries, leg cramps (placebo 1.9%, raloxifene 5.5%) and peripheral edema (placebo 1.9%, raloxifene 3.1%) were more frequent after the initial 6 months. The mechanisms for raloxifene-associated leg cramps, peripheral edema and enlarged uterine fibroids are unknown. These were infrequent causes of discontinuation. The growth of rat fibroid cells and guinea pig leiomyomas were not stimulated by raloxifene in the preclinical studies.

The following adverse events were more common compared to estrogen: vasodilatation, infection, accidental injury, pharyngitis, arthritis, leg cramps, flatulence, sweating and sleep disorder. However, breast pain, breast enlargement and urinary incontinence were more common with estrogen, and the incidence of breast symptoms and uterine bleeding in raloxifene group was significantly lower than in either form of HRT groups.

Sleep disturbances may be associated with vasodilatation and increased sweating, but the mechanisms are not clear. No dose-dependent trend was observed for terms of infections (e.g. sinusitis, herpes simplex). The increased incidence of sinusitis in raloxifene-treated subjects is probably a chance finding. No cognitive function related adverse effects were observed after 6 and 12 months of raloxifene or placebo treatment. Treatment-emergent affect- and anxiety-related adverse event analysis did not suggest adverse effects on mood and affective symptoms.

**Osteoporosis treatment indication**

From Study GGGK, five treatment-emergent adverse events were common (>1% incidence) and reported statistically significantly more frequently with raloxifene treatment vs placebo; flu syndrome, vasodilatation, leg cramps, peripheral edema, "uterine disorder" (a classification term more often associated with fluid in the endometrial cavity), and diabetes mellitus. Vasodilatation and leg cramps were minor adverse events associated with raloxifene. The increased reporting of diabetes mellitus as a treatment-emergent adverse event is likely a spurious finding due to imbalances in the treatment groups at baseline. There is no evidence that raloxifene has any deleterious effect on glucose metabolism. The increased reporting of flu syndrome and "uterine disorder" with raloxifene therapy is not considered clinically important. Peripheral edema was associated only with the raloxifene 120-mg dose.

**Vital signs and laboratory abnormalities**

No statistically significant differences between raloxifene and placebo in mean change from baseline to endpoint were observed for blood pressure, pulse, weight and height. Slight decreases in serum inorganic phosphorus, calcium, albumin, total protein, alkaline phosphatase and bilirubin were observed during raloxifene (as well as for estrogen) treatment. Consistent decrease (6-10%) in platelet count was observed, but this was similarly decreased during estrogen treatment. There were no clinically significant shifts from baseline in the other mean hematology variables. Clinically significant changes in serum parathyroid hormone, 25-OH or 1,25-dihydroxy vitamin D levels, and in mean fasting blood glucose, BUN, creatinine and CK have not been reported. However, several cases of moderate increases in serum AST and/or ALT have been reported where a causal relationship with raloxifene can not be excluded. A similar frequency of increases was noted among placebo patients.

In Study GGGK similar decreases in serum calcium, inorganic phosphorus, albumin, total protein, platelet count, and alkaline phosphatase were observed. The change in fasting glucose over the 36 month study period was not different for placebo vs raloxifene 60-mg or raloxifene 120-mg. The proportion of patients who had increases in fasting glucose >20%, >40% and >60% were not different for raloxifene vs placebo. No effect of raloxifene was observed on serum AST. Significant decreases in ALT, GGT and bilirubin were demonstrated with raloxifene treatment. Despite its extensive hepatic metabolism, raloxifene does not appear to be associated with hepatic abnormalities.

In the osteoporosis treatment population, no clinically significant changes in blood pressure, pulse or height were observed. A small weight gain in raloxifene groups was observed for those in the lowest weight tertile at baseline.

**Treatment-emergent cardiovascular adverse events**

In the prevention studies, a total of 2 subjects experienced acute myocardial infarction and 7 subjectsexperienced a stroke (3 received raloxifene). The incidence is not higher than expected. In the osteoporosis treatment study there was no increased risk of myocardial infarction or stroke. Fifty one patients experienced a myocardial infarction (placebo, 16 [0.6%]; raloxifene 60-mg. 20[0.8%]; raloxifene 120-mg 15[0.6%]}. Sixty patients experienced a stroke (placebo, 26 [1.0%]; raloxifene 60-mg, 16 [0.6%]; raloxifene 120-mg 18 [0.7%]).

Venous thromboembolic events (VTE) were defined as any acute venous thrombosis involving a deep peripheral vein, acute pulmonary embolism, or other acute serious vein thrombosis (including mesenteric, intracerebral and retinal veins). Idiopathic cases were identified by excluding cases associated with either major (established) or minor predisposing factors (e.g. hypertension, varicose veins, bilateral oophorectomy, obesity, current smoking).

As of 1 January 1999, a total of 84 cases of VTE (idiopathic and non-idiopathic) were reported in patients across all raloxifene clinical studies. Seventy-five (75) of these were ported in patients participating in the 11 raloxifene placebo-controlled clinical studies. Nine additional cases were also reported (5 patients in non-placebo-controlled trials; and 4 patients who experienced VTE after reassignment of study drug). The majority of cases (68) were reported in the osteoporosis treatment study (GGGK), which included older subjects than the prevention studies. The estimates of relative risk in all raloxifene treated subjects compared with placebo varied from 2.13 to 3.43, with Category 1 (defined as all VTE) and Category 2 (defined as all VTE except RVT) significantly greater than 1.0. There was not a statistically significant difference between all raloxifene treated patients and

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placebo in Category 3 (defined as PE with or without DVT), although the magnitude of the risk was similar to Category 1 and Category 2. There was no difference in risk between the raloxifene doses in any category. Altogether 22 cases of pulmonary embolism were reported during raloxifene treatment.

No controlled, randomised, prospective head-to-head studies are available for comparison of the risk of VTE in HRT versus raloxifene users. There has been an attempt to compare the risk of idiopathic VTE between raloxifene and HRT in women below the median age of 72 years. The raloxifene-attributable annual risk estimate was 45 per 100,000 compared to HRT-attributable risk of 16-32 per 100,000. However, the risk associated with HRT may be underestimated in uncontrolled observational studies. The incidence of VTE during raloxifene treatment was highest during the first year and did not appear to increase thereafter.

Raloxifene treatment confers a risk of venous thromboembolic complications independently of other risk factors. The relative risk of these complications with estrogen (HRT) is approximately 2 to 4. Across all placebo-controlled clinical trials, VTE including deep-vein thrombosis, pulmonary embolism and retinal vein thrombosis occurred in a frequency of 0.7%. A relative risk of 2.13 (CI 1.21,3.75) was observed in raloxifene treated patients compared to placebo. The relative risk of all VTE for raloxifene-treated versus estrogen and HRT patients was 1.0 (CI 0.3, 6.2). According to analysis of updated data, the risk of all VTEs during raloxifene treatment is similar to that during estrogen/HRT.

Raloxifene may have slightly different effects on coagulation and fibrinolysis than estrogen, but the clinical significance of these differences is doubtful. In study GGGH, both raloxifene and estrogen slightly increased prothrombin fragment (F1+2) and slightly reduced plasmin-alpha-2-antiplasmin complex. Active or past histories of venous thromboembolic events are contraindications of raloxifene.

### Breast related adverse events

In clinical trials with EVISTA involving over 12,000 patients, most of whom have been exposed to at least 42 months therapy, the relative risk of newly diagnosed breast cancer was significantly lower, 64 % reduction (RR 0.36, CI 0.20, 0.65) in EVISTA treated than in placebo treated postmenopausal women in a combined analysis of several studies. Overall the risk of an invasive estrogen receptor (ER) positive breast cancer was reduced by 80 % (RR 0.20, CI 0.09, 0.41). EVISTA has no effect on the risk of ER negative breast cancers. These observations support the conclusion that raloxifene has no intrinsic estrogen agonist activity in breast tissue. The long-term effect of EVISTA on breast cancer is unknown.

### Endometrial and uterine surveillance

Cases of endometrial carcinoma have been reported and were reviewed by an independent board. In all cases, pre-existing disease was suggested. Updated endometrial data do not suggest that the incidence of endometrial cancinoma is higher during raloxifene than placebo treatment. Due to the short treatment time (study GGGB) and the high raloxifene dose used, which is higher than the intended recommended dose (study GGGB and GGGZ), a conclusion could not be drawn that raloxifene protects from endometrial cancer.

Uterine surveillance algorithm was introduced late in to the clinical trials. This monitoring programme investigated subjects who experienced episodes of vaginal bleeding and/or development of a thickened endometrium (> 5 mm) by means of transvaginal ultrasound. Overall, the analysis suggests that in postmenopausal women, raloxifene does not have clinically meaningful estrogenic effect on the uterus, but does have antiestrogenic effect on the uterus at doses exceeding that intended for osteoporosis prevention. There are no sufficient data based on paired biopsies (histomorphology, estrogenicity grades) that would allow a conclusion that raloxifene has a clinically meaningfulantiestrogenic effect on the uterus at 60 mg/day. The mean change from baseline to endpoint (24 months) in endometrial thickness (studies GGGN, GGGF and GGGG) did not reveal statistically significant differences within raloxifene (30 mg, 60 mg, 150 mg) or between raloxifene and placebo groups. However, statistically significant increases in endometrial thickness were observed in estrogen treated subjects.

Based on the three-year analysis of data from the study GGGK, the CPMP considered the argument

presented by the applicant that benign endometrial polyps are a frequent finding in postmenopausal women with bleeding. In postmenopausal women who received raloxifene treatment for 3 years, benign endometrial polyps were reported in 0.7% compared to 0.2% in women who received placebo treatment. The frequency of endometrial polyps was higher in raloxifene groups vs. placebo only in the subgroup of patients who underwent blind endometrial sampling due to bleeding but had normal endometrial thickness. This difference was not statistically significantly different and the finding was not reproduced in other analyses.

No increase in the risk of endometrial carcinoma has been observed so far in postmenopausal women who have been treated with raloxifene. Although routine endometrial screening in asymptomatic patients was not consider necessary by the CPMP, any uterine bleeding must be evaluated by a specialist and the current warning in Section 4.4 was strengthened.

Compared to placebo, raloxifene was not associated with spotting or vaginal bleeding. Vaginal dryness, vaginitis or dyspareunia were not reported more frequently than during placebo treatment.

In September 1999, the section 4.8 of the SPC and the Package Leaflet were updated following first Periodic Safety Update Report, including information on cases of rash very rarely reported and gastrointestinal symptoms such as nausea, vomiting, abdominal pain and dyspepsia very rarely (<1/10,000) reported in postmarketing experience.

**Overall benefit/risk assessment**

The clinical pharmacology of raloxifene has been adequately studied. The minimum effective dose was not reliably established by the short-term dose ranging studies.

In 3 well conducted, double blind clinical trials, the primary and secondary criteria of efficacy are relevant. Raloxifene was statistically significantly superior to placebo (calcium supplementation only) with respect to the primary efficacy criteria. Although the three-raloxifene doses examined (30, 60 and 150 mg) were not statistically different and the dose response relationship was weak, the population pharmacodynamic analyses support the proposed raloxifene dose of 60 mg/day. Qualitatively the effects of raloxifene on bone mineral density and resorption are similar to those of estrogen, but of lesser magnitude. Moreover, a reduction in the risk of incident vertebral fractures has been demonstrated in women with osteoporosis compared to placebo.

In studies involving over 2000 women with a treatment duration ranging from 2-24 months, the majority of undesirable effects did not usually require cessation of therapy. Discontinuation of therapy due to any clinical adverse experience occurred in 10.7% of 581 raloxifene-treated patients and 11.1% of 584 placebo-treated patients. The treatment-emergent events associated with the use of raloxifene that occurred with a significant difference between raloxifene and placebo treatment were: venous thromboembolic events (occurred in a frequency of 0.8%), superficial vein thrombophlebitis, modest increase of vasodilatation (hot flushes), leg cramps and peripheral oedema.

When comparing raloxifene patients (n=317) with continuous combined HRT (n=110) or cyclic HRT (n=205) 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. Raloxifene does not have adverse effects on the lipid profile. No clinically significant changes in vital signs and safety laboratory tests have been seen.

The Phase III study GGGK showed that at 36 months raloxifene 60mg/day and 120mg/day statistically and clinically significantly decreased the proportion of women with at least one adjudicated new incident vertebral fracture vs placebo regardless of baseline disease severity. Both raloxifene 60mg and 120mg effectively increased lumbar spine, femoral neck and total body BMD and decreased markers of bone turnover. Raloxifene significantly decreased LDL cholesterol and other intermediate markers of cardiovascular disease (fibrinogen) without a concomitant rise in serum triglycerides.

Raloxifene, in the osteoporosis treatment population, did not induce endometrial proliferation or vaginal bleeding and was not associated with an increased risk of uterine or endometrial malignancy. Raloxifene did not cause breast pain and was associated with a reduction in the risk of breast cancer (median duration 40 months). Vasodilatation and leg cramps were side effects also observed in this

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population. The only serious risk was that of VTE and the risk continues to be similar to that reported for estrogen use. Current or past history of VTE is a contraindication to raloxifene therapy.

The CPMP agreed that the benefit/risk was positive for the proposed indications. It was also concluded that the overall risk/benefit assessment favours the 60mg dose over the 120mg dose. Therefore the CPMP considered that the data presented were sufficient to recommend that the indications prevention and treatment of postmenopausal osteoporosis should be granted.

In March 2003, the sections 4.4 and 5.1 of the SPC were updated on the basis of the cumulative four years results on new clinical safety and efficacy data of the MORE (Comparison of Raloxifene Hydrochloride and Placebo in the Treatment of Postmenopausal Women With Osteoporosis) study. The study confirmed that treatment with raloxifene for 4 years decreased the rate of new vertebral fractures by 46% in osteoporotic patients. In addition, in the 4th year alone, EVISTA reduced the new vertebral fracture risk by 39% (during the 4th year, patients were permitted the concomitant use of bisphosphonates, calcitonin and fluorides). There was no significant difference in the number of non-vertebral fractures. A cumulative analysis also showed a reduction of clinical vertebral fractures.

No indicators for an increased risk of malignant endometrial tumours were shown. The overall rate of breast cancer was reduced in the raloxifene groups as compared to the placebo group. EVISTA treatment compared to placebo reduced the risk of total breast cancer by 62%, the risk of invasive breast cancer by 71% and the risk of invasive estrogen receptor (ER) positive breast cancer by 79%. The decrease was explained by the decrease of ER-positive (invasive) tumours. A significant increase in the number of venous thromboembolic events was seen in the raloxifene groups, especially in the early phase of the treatment. However, this risk is already acknowledged in the SPC. No significant differences between the groups were seen in the ECG and in the reporting of clinical cardiac and cerebrovascular events. There were favourable changes in the lipid profile, except for a small increase in serum triglycerides.

Hormone replacement therapy aggravates certain complications of pelvic floor relaxation, but safety information following 3 years of raloxifene treatment supported that raloxifene treatment did not increase pelvic floor relaxation and pelvic floor surgery.


5.      Conclusions

The quality of raloxifene hydrochloride 60-mg film coated tablets, as demonstrated in the chemical and pharmaceutical documentation is acceptable.

The pharmacological activity of raloxifene has been demonstrated in ovariectomised and sexually immature animal models and postmenopausal women. Raloxifene exhibits estrogen agonistic effects on bone and lipid metabolism but not in uterine or breast tissues.

The clinical data provided showed that the effect of raloxifene on bone mineral density and resorption is qualitatively similar to that of estrogen although of lesser magnitude, and clearly superior to placebo (calcium supplementation only). Raloxifene 60 mg/day prevents bone loss in postmenopausal women, who are at increased risk of developing osteoporosis and decreases the risk of incident vertebral fractures.

Based on the three-year analysis of data from study GGGK, raloxifene (60 mg per day) statistically and clinically significantly decreased the proportion of women with at least one new adjudicated incident vertebral fracture vs placebo both in postmenopausal women with and without prevalent vertebral fractures. It is concluded that raloxifene 60 mg treats osteoporosis in postmenopausal women. No effect on hip fractures has been demonstrated

Raloxifene does not appear to have estrogenic effects on the breast or on the uterus, but the frequency of postmenopausal symptoms may be increased. The relative risk of venous thromboembolic events observed during raloxifene treatment was 2.13 (CI 1.21, 3.75) when compared to placebo, and was 1.0 (CI 0.3, 6.2) when compared to estrogen or hormonal replacement therapy. With respect to the incidence of reported uterine bleeding, there were no differences between the raloxifene and placebo groups. After 3 years, raloxifene did not increase the risk of endometrial cancer. With regard to the

occurrence of breast cancer, although the relative risk of newly diagnosed breast cancer is found to be lower during relatively short-term raloxifene treatment (median 40 months), the longer-term effect of raloxifene on the risk of breast cancer is unknown.

The overall safety issues have been addressed and appropriate warnings and precautions have been included in the relevant sections of the SPC. When determining the choice of raloxifene or estrogen (hormonal replacement therapy) for an individual postmenopausal woman, consideration should be given to menopausal symptoms, effects on breast tissue, and cardiovascular risks and benefits.

Based on these data, the CPMP considered the benefit to risk assessment positive and the granting of a Marketing Authorisation was recommended for this medicinal product. At the time of the 5-year renewal, the CPMP considered that the benefit/risk profile of EVISTA continued to be favourable and recommended the renewal of the Community Marketing Authorisation on 22 May 2003.