資料3－5　ラソフォキシフェン酒石酸塩（lasofoxifene tartrate）

ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

FABLYN 500 microgram film-coated tablets.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains lasofoxifene tartrate, equivalent to 500 micrograms lasofoxifene.

Excipient: Each film-coated tablet contains 71.34 mg lactose.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.

Triangular, peach-coloured, film-coated tablets debossed with "Pfizer" on one side and "OPR 05" on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

FABLYN is indicated for the treatment of osteoporosis in postmenopausal women at increased risk of fracture. A significant reduction in the incidence of vertebral and non-vertebral fractures but not hip fractures has been demonstrated (see section 5.1).

When determining the choice of FABLYN or other therapies, including estrogens, for a 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

Adult (postmenopausal women):

The recommended dose is one 500 microgram tablet daily.

The tablet may be taken any time of day without regard to food and beverage intake.

Supplemental calcium and/or vitamin D should be added to the diet if daily intake is inadequate. Postmenopausal women require an average of 1,500 mg/day of elemental calcium. The recommended intake of vitamin D is 400-800 IU daily.

Children and adolescents below 18 years of age:

There is no indication for FABLYN in children and adolescents below 18 years of age since the medicinal product is for use in postmenopausal women only. Therefore safety and efficacy have not been studied (see section 5.2).

Elderly women (65 years and older):

No dose adjustment is necessary in elderly female patients (see section 5.2).

Hepatic insufficiency:

No dose adjustment is required in patients with mild to moderate hepatic insufficiency (see section 5.2). Safety and efficacy of lasofoxifene have not been evaluated in patients with hepatic insufficiency with liver function test > 1.5 ULN; therefore, FABLYN should be used with caution in these patients.

Renal insufficiency:

No dose adjustment is necessary in patients with mild or moderate renal insufficiency (see section 5.2). Safety and efficacy of lasofoxifene have not been evaluated in patients with severe renal insufficiency; therefore, FABLYN should be used with caution in these patients.

Due to the chronic nature of the disease process, FABLYN is intended for long-term use (see section 5.1).

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients.

Active or past history of venous thromboembolic events, including deep vein thrombosis, pulmonary embolism and retinal vein thrombosis.

Unexplained uterine bleeding.

Pregnancy and lactation: FABLYN is only for use in postmenopausal women. It must not be taken by women of child-bearing potential, pregnant women and lactating women (see section 4.6).

4.4 Special warnings and precautions for use

In clinical trials, FABLYN-treated women had an increased risk of venous thromboembolic events (deep vein thrombosis and pulmonary embolism) compared to placebo. Other venous thromboembolic events could also occur. A less serious event, superficial thrombophlebitis, also has been reported more frequently with FABLYN compared to placebo. The risk-benefit balance should be considered in patients at risk of venous thromboembolic events of any aetiology (see sections 4.3 and 4.8). Because immobilization increases the risk for venous thromboembolic events independent of therapy, FABLYN should be discontinued at least 3 weeks prior to and during prolonged immobilization (e.g., post-surgical recovery, prolonged bed rest), and therapy should be resumed only after the patient is fully ambulatory. In addition, women taking FABLYN should be advised to move about periodically during prolonged travel.

Any unexplained vaginal bleeding should be investigated as clinically indicated. FABLYN-treated and placebo-treated groups had similar incidences of endometrial hyperplasia and endometrial cancer (see section 5.1).

Lasofoxifene has been associated with benign endometrial effects. These included, in some subjects, a small excess in the incidence of vaginal bleeding as well as endometrial cystic change viewed on ultrasound and histological benign cystic atrophy (a variant of atrophic endometrium). These cystic findings contributed to an approximate 1.5 mm increase in mean endometrial thickness. As a consequence of these benign effects, more FABLYN-treated patients had a diagnostic uterine procedure compared to placebo-treated patients in the PEARL trial (see section 5.1). However, in clinical practice, these benign findings do not warrant further evaluation in women with no vaginal bleeding (in accordance with guidelines for postmenopausal women), as the risks of diagnostic uterine procedures in asymptomatic women outweigh any benefits. Pathologists should be made aware of a history of lasofoxifene use when assessing endometrial histology, to ensure an accurate diagnosis of benign cystic atrophy when present.

The concurrent use of FABLYN and systemic estrogen or hormone therapy has not been studied and therefore concomitant use of FABLYN with systemic estrogens is not recommended.

FABLYN has not been studied in women with a prior history of breast cancer. No data are available on its concomitant use with agents used in the treatment of early or advanced breast cancer. Therefore, FABLYN should be used for the treatment of osteoporosis only after the treatment of breast cancer, including adjuvant therapy, has been completed.

Any unexplained breast abnormality occurring during FABLYN therapy should be investigated. FABLYN does not eliminate the risk of breast cancer (see section 5.1).

FABLYN may increase the incidence of hot flushes and is not effective in reducing hot flushes associated with estrogen deficiency. In some asymptomatic patients, hot flushes may occur upon beginning therapy.

Limited clinical data suggest that in patients with a history of oral oestrogen-induced hypertriglyceridemia (> 5.6 mmol/l), lasofoxifene may be associated with a marked increase in serum triglycerides. Patients with this medical history should have serum triglycerides monitored when taking lasofoxifene.

Lasofoxifene is highly protein bound, predominantly cleared by metabolism and is likely to undergo enterohepatic circulation (see section 5.2). Safety and efficacy of FABLYN have not been evaluated in patients with liver function test > 1.5 ULN; therefore, FABLYN should be used with caution in these patients.

Safety and efficacy of FABLYN have not been evaluated in patients with severe renal insufficiency; therefore, FABLYN should be used with caution in these patients (see section 4.2 and section 5.2).

FABLYN contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

4.5 Interaction with other medicinal products and other forms of interaction

Based on the absence of clinically relevant effects of cholestyramine (anion exchange resin), fluconazole (CYP2C9 inhibitor), ketoconazole (CYP3A4/5 inhibitor) and paroxetine (CYP2D6 inhibitor) on lasofoxifene pharmacokinetics, other anion exchange resins and other inhibitors of these CYP isoforms are unlikely to produce clinically meaningful alterations in FABLYN exposure and no dose adjustments are required.

Lasofoxifene clearance may be increased in patients chronically treated with inducers of CYP3A4 and UGTs (eg, phenytoin, carbamazepine, barbiturates and St John's Wort) resulting in reduced steady-state concentrations and may result in reduced efficacy.

Ketoconazole - The strong CYP3A4/5 inhibitor ketoconazole increased the systemic exposure of lasofoxifene by 20% which is not considered to be clinically meaningful.

Paroxetine - The strong CYP2D6 inhibitor paroxetine increased the systemic exposure of lasofoxifene by 35% which is not considered to be clinically meaningful.

Proton pump inhibitors – Data on the effect of concomitant administration of proton pump inhibitors (PPIs) with lasofoxifene is not available; thus, use of these agents with lasofoxifene should be considered with caution.

In clinical studies, lasofoxifene did not alter the metabolism of dextromethorphan (CYP2D6 substrate) and chlorzoxazone (CYP2E1 substrate) or the pharmacokinetics of warfarin (CYP2C9 substrate), methylprednisolone (CYP3A4 substrate) or digoxin (MDR1 P-glycoprotein substrate). Therefore FABLYN is unlikely to alter the pharmacokinetics of medicinal products that are cleared by metabolism via these CYP isoforms, or are transported by MDR1 P-glycoprotein.

Warfarin - Lasofoxifene had no effect on the pharmacokinetics of R- and S- warfarin. Mean international normalized ratio (INR) AUC and maximum value of INR after single-dose warfarin administration with lasofoxifene were approximately 8% and 16% lower, respectively, than after warfarin alone. These changes are not considered to be clinically meaningful.

4.6 Pregnancy and lactation

Pregnancy

FABLYN is only for use in postmenopausal women. FABLYN must not be taken by women of child-bearing potential (see section 4.3). There are no adequate data from the use of lasofoxifene in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). The potential risk for humans is unknown.

Lactation

FABLYN is only for use in postmenopausal women. FABLYN must not be taken during lactation (see section 4.3). It is not known whether lasofoxifene is excreted in human milk. Animal studies have shown excretion of lasofoxifene in milk.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed.

FABLYN has no known influence on the ability to drive and use machines.

4.8 Undesirable effects

The safety of FABLYN in the treatment of osteoporosis was assessed in a large (8,556 patients) double-blind, randomized, placebo-controlled multinational Phase 3 fracture trial (the PEARL study). The duration of treatment in postmenopausal women was 60 months, 2,852 were randomized to FABLYN and 2,852 were randomized to placebo.

Within this study, 12.9% of FABLYN-treated women and 12.3% of placebo-treated women discontinued therapy due to adverse events.

Venous Thromboembolic Events: The most serious adverse reaction related to FABLYN was VTE (deep venous thrombosis, pulmonary embolism, and retinal vein thrombosis). Through 5 years of follow-up, 37 FABLYN-treated women (1.3%, or 2.90 per 1,000 patients years) had a VTE compared to 18 placebo-treated women (0.6%, or 1.41 per 1,000 patients years) and the hazard ratio was 2.06 (95% CI: 1.17, 3.61).

As observed with other Selective Estrogen Receptor Modulators (SERMs), slightly decreased (approximately 4%) platelet counts were observed in lasofoxifene-treated patients in PEARL.

Common adverse reactions considered to be related to FABLYN therapy were muscle spasms, hot flush and vaginal discharge. Muscle spasms occurred in about one in 9 patients . Hot flush occurred in about one in 11 patients and was most commonly reported during the first 6 months of treatment. Vaginal discharge occurred in about one in 26 patients.

The safety of FABLYN in the treatment of osteoporosis was also assessed in a Phase 2 placebo-controlled trial in Japanese, Korean and Taiwanese women. The duration of treatment in postmenopausal women was 12 months, 124 were exposed to FABLYN and 125 were exposed to placebo. Within this study, 3.2% of FABLYN-treated women and 8.0% of placebo-treated women discontinued therapy due to adverse events.

Table 1 lists adverse reactions occurring in the two osteoporosis treatment clinical trials that occurred at an incidence greater than placebo.

Most of the adverse reactions occurring during the studies were mild and generally did not require discontinuation of therapy.

Adverse reactions are listed by system organ class and frequency (very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100) and rare (≥1/10,000 to <1/1,000)). In each system organ class and frequency, adverse reactions are not presented in order of decreasing seriousness but in alphabetical order.

Table 1: Adverse reactions observed in placebo-controlled osteoporosis treatment clinical trials in more FABLYN-treated women than in placebo-treated women

Infections and infestations	
Uncommon:	Urinary tract infection, vaginal candidiasis, vaginal infection, vulvovaginitis
Rare:	Arthritis infective, bronchitis, cellulitis, cervicitis, diverticulitis, fungal infection, furuncle, genital candidiasis, herpes simplex ophthalmic, impetigo, labyrinthitis, pyelonephritis, pyometra
Neoplasms benign, malignant and unspecified (including cysts and polyps)	
Uncommon:	Fibroma, uterine leiomyoma
Rare:	Benign breast neoplasm, breast fibroma, chronic lymphocytic leukaemia, endometrial neoplasm, female reproductive neoplasm, haemangioma, hepatic neoplasm malignant, leiomyoma, melanocytic naevus, multiple myeloma, neoplasm, parathyroid tumour benign
Blood and lymphatic system disorders	
Uncommon:	Anaemia, macrocytosis, thrombocytopenia
Rare:	Anaemia megaloblastic, hypochromasia
Immune system disorders	
Rare:	Seasonal allergy
Endocrine disorders	
Rare:	Hyperparathyroidism

Metabolism and nutrition disorders	
Uncommon:	Diabetes mellitus
Rare:	Anorexia, decreased appetite, hypertriglyceridaemia, hypoalbuminaemia, hypophosphataemia, increased appetite, tetany, type 2 diabetes mellitus
Psychiatric disorders	
Rare:	Abnormal dreams, cyclothymic disorder
Nervous system disorders	
Uncommon:	Burning sensation, cerebral infarction, headache, restless legs syndrome
Rare:	Amnesia, dementia Alzheimer's type, dizziness postural, dysgeusia, epilepsy, hydrocephalus, hypogeusia, memory impairment, migraine, migraine with aura, motor neurone disease, nerve compression, paresis, presyncope, sciatica, vascular headache
Eye disorders	
Uncommon:	Dry eye
Rare:	Aphakia, chorioretinopathy, conjunctival haemorrhage, conjunctival hyperaemia, eye haemorrhage, eye pruritus, eyelid oedema, keratoconjunctivitis sicca, macular degeneration, ocular hyperaemia, pupils unequal, retinal detachment, retinal vascular disorder, retinopathy, visual acuity reduced, visual disturbance
Ear and labyrinth disorders	
Rare:	Ear discomfort, inner ear disorder, vertigo positional
Cardiac disorders	
Uncommon:	Palpitations, tachycardia
Rare:	Cardiac failure, cardiomegaly, cor pulmonale, sinus arrest, supraventricular extrasystoles, tricuspid valve incompetence
Vascular disorders	
Common:	Hot flush
Uncommon:	Deep vein thrombosis, flushing, phlebitis, thrombophlebitis, thrombophlebitis superficial, venous stasis
Rare:	Aortic aneurysm, arterial occlusive disease, capillary disorder, embolism, haematoma, haemorrhage, intermittent claudication, lymphostasis, thrombosis, vascular stenosis, venous thrombosis, venous thrombosis limb
Respiratory, thoracic and mediastinal disorders	
Uncommon:	Cough, pulmonary embolism, rhinitis allergic
Rare:	Chronic obstructive pulmonary disease, pulmonary granuloma, vasomotor rhinitis
Gastrointestinal disorders	
Common:	Constipation
Uncommon:	Abdominal pain, abdominal pain lower, abdominal pain upper, dry mouth, flatulence, gastritis, irritable bowel syndrome
Rare:	Abdominal tenderness, anal fissure, anal spasm, cheilitis, cheilosis, colitis ulcerative, duodenal ulcer, duodenitis, dysphagia, gastric polyps, inguinal hernia, mouth ulceration, oesophagitis, oral pain, rectal polyp, rectal ulcer, stomach discomfort
Hepatobiliary disorders	
Uncommon:	Cholelithiasis, hepatic steatosis
Rare:	Bile duct stone, cholecystitis, hepatitis, jaundice, liver disorder
Skin and subcutaneous tissue disorders	
Common	Hyperhidrosis
Uncommon:	Alopecia, erythema, night sweats, pruritus
Rare:	Angioedema, dry skin, hair texture abnormal, nail disorder, onychoclasis, photosensitivity reaction, pruritus generalized, rash maculo-papular, rash pruritic,

	rosacea, skin irritation, skin lesion, skin hyperpigmentation, skin oedema, urticaria
Musculoskeletal, connective tissue and bone disorders	
Very common:	Muscle spasms
Uncommon:	Back pain, neck pain, pain in extremity
Rare:	Arthropathy, bursitis, clubbing, coccydynia, costochondritis, dactylitis, exostosis, extremity contracture, haemarthrosis, joint stiffness, muscle contracture, muscle twitching, musculoskeletal discomfort, pain in jaw, periarthritis, rheumatoid arthritis, rotator cuff syndrome, tenosynovitis
Renal and urinary disorders	
Uncommon:	Micturition urgency, nocturia, pollakiuria, urethral disorder, urinary incontinence
Rare:	Calculus bladder, hypercalciuria, hypertonic bladder, nephrosclerosis, urethral haemorrhage, urinary bladder polyp, urinary tract disorder
Reproductive system and breast disorders	
Common:	Cystocele, endometrial disorder, endometrial hypertrophy* (sonographic endometrial thickness), uterine polyp, vaginal discharge, vaginal disorder
Uncommon:	Breast disorder female, breast induration, breast pain, cervix disorder, cervical dysplasia, cervical polyp, colpocele, endometrial hyperplasia** (based on investigator reporting), genital discharge, genital haemorrhage, hydrometra, metrorrhagia, postmenopausal haemorrhage, rectocele, uterine cervical erosion, uterine prolapse, vaginal haemorrhage, vaginal prolapse, vulvovaginal pruritus
Rare:	Adenomyosis, adnexa uteri cyst, adnexa uteri mass, breast discharge, breast engorgement, breast fibrosis, enlarged clitoris, fallopian tube cyst, nipple disorder, nipple pain, perineal laceration, pruritus genital, uterine cervical squamous metaplasia, uterine haemorrhage, uterine mass, vaginal erosion, vaginal inflammation, vaginal pain, vaginal wall congestion, varicose veins vulval, vulvar disorder
Congenital, familial and genetic disorders	
Rare:	Malformation venous
General disorders and administration site conditions	
Common:	Therapeutic response unexpected
Uncommon:	Chest pain, fatigue, feeling hot, oedema peripheral
Rare:	Chest discomfort, feeling drunk, hyperthermia, inflammation, mass, oedema, polyp
Investigations	
Common:	Aspartate aminotransferase increased
Uncommon:	Alanine aminotransferase increased, blood glucose increased, smear cervix abnormal, transaminases increased, weight increased
Rare:	5′ nucleotidase increased, blood albumin decreased, blood creatinine abnormal, blood triglycerides increased, blood urine present, bone density decreased, chest X-ray abnormal, electrocardiogram T wave abnormal, gamma-glutamyltransferase increased, hepatitis B surface antigen positive, high density lipoprotein decreased, low density lipoprotein increased, pedal pulse decreased, platelet count decreased, ultrasound breast abnormal, ultrasound ovary abnormal
Injury and poisoning	
Rare:	Excoriation, genital injury, limb injury, skeletal injury, soft tissue injury, spinal fracture, thoracic vertebral fracture, tooth fracture

* Endometrial hypertrophy is a MedDRA dictionary term that represents sonographic endometrial thickness findings.

** Endometrial hyperplasia events based on investigator reporting rather than histopathology findings and did not require histological confirmation.

4.9 Overdose

No case of FABLYN overdose has been reported.

Lasofoxifene has been administered to postmenopausal women at single doses as high as 100 mg (200 times the recommended unit dose) and multiple doses as high as 10 mg/day (20 times the recommended dose) for up to one year without dose-related serious adverse reactions.

There is no specific antidote for FABLYN. In the event of overdose, general supportive measures should be initiated based on the patient's signs and symptoms.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Selective Estrogen Receptor Modulator (SERM), ATC code: {not yet assigned}

Decreases in estrogen levels after menopause or oophorectomy lead to accelerated bone loss due to increased bone turnover, where bone resorption exceeds bone formation. The increased turnover causes accelerated bone loss because the compensatory increase in bone formation is not sufficient to offset increased bone resorption. In some women, these changes will eventually lead to decreased bone mass, osteoporosis, and increased risk for fractures, particularly of the spine, hip, and wrist. Vertebral fractures are the most common type of osteoporotic fracture in postmenopausal women.

Lasofoxifene is a SERM whose biological actions are largely mediated through binding to estrogen receptors. This binding results in the activation of some estrogenic pathways and a blockade of others. Lasofoxifene produces tissue and cell-specific effects in estrogen-responsive tissues.

Clinical data indicate that FABLYN has an estrogen-like agonist effect on bone as well as antagonistic effects on the breast. The effects of FABLYN on bone are manifested as reductions in the serum and urine levels of bone turnover markers, increases in bone mineral density (BMD), and decreases in incidence of fractures.

Skeletal effects:

Bone turnover

In the osteoporosis treatment trials, FABLYN therapy resulted in consistent, statistically significant suppression of bone resorption and bone formation, as reflected by changes in serum and urine markers of bone turnover (e.g., C-telopeptide and markers of bone formation: osteocalcin, procollagen type 1 N-terminal propeptide, and bone-specific alkaline phosphatase). The suppression of bone turnover markers was evident by 3 months and persisted throughout the 36-month observation period in a sub-study of the PEARL study.

5-year results from large, multinational fracture trial (PEARL)

The effects of FABLYN on fracture incidence (table 2) were examined through 5 years; and BMD and bone biomarkers in postmenopausal women with osteoporosis were examined through 3 years in the PEARL study. The study population consisted of 8,556 postmenopausal women with osteoporosis as defined by low BMD (vertebral or hip BMD at least 2.5 standard deviations below the mean value for healthy young women). Women enrolled in this study had a median age of 67 years (range 59 to 80) and a median time since menopause of 20 years. All women in the study received calcium (1,000 mg/day) and Vitamin D (400-800 IU/day).

Table 2: Fracture incidence in postmenopausal women over 5 years

	FABLYN	Placebo	Relative risk reduction (95% CI) vs. placebo
New radiographic vertebral fractures Percentage of patients with new fracture	n=2,748 5.6%	n=2,744 9.3%	41%[a] (28%, 52%)
New radiographic vertebral fracture in patients with ≥ 1 baseline fracture Percentage of patients with new fracture	n=778 8.7%	n=774 14.2%	42%[b] (21%, 57%)
New radiographic vertebral fracture in patients without any prevalent fracture at baseline Percentage of patients with new fracture	n=1,970 4.4%	n=1,970 7.4%	41%[c] (23%, 55%)
Non-vertebral fractures Percentage of patients with non-vertebral fracture	n=2,852 8.1%	n=2,852 10.4%	24%[d] (9%, 36%)
All clinical fractures Percentage of patients with clinical fracture	n=2,852 9.3%	n=2,852 12.1%	25%[e] (12%, 36%)
Abbreviations: n= number of patients; CI = Confidence Intervals [a] $p < 0.0001$; [b] $p = 0.0004$; [c] $p = 0.0002$; [d] $p = 0.0020$; [e] $p = 0.0004$			

-Radiographic vertebral fractures

FABLYN significantly decreased the incidence of new radiographic vertebral fractures (excluding worsening of previous fractures) from 9.3% for placebo to 5.6% for FABLYN (relative risk reduction = 41%, $p < 0.0001$). This decrease was observed through the first year and was maintained through 5 years.

In women with a prevalent vertebral fracture at baseline, FABLYN significantly reduced the incidence of new vertebral radiographic fractures from 14.2% for placebo to 8.7% for FABLYN (relative risk reduction = 42%, $p = 0.0004$). In women without any prevalent vertebral fractures at baseline, the incidence of new radiographic vertebral fractures was significantly reduced from 7.4% for placebo to 4.4% for FABLYN (relative risk reduction = 41%, $p = 0.0002$).

Significantly fewer women experienced multiple radiographic vertebral fractures in the FABLYN treatment group versus the placebo group throughout 5 years of dosing ($p < 0.0001$).

Significantly fewer women treated with FABLYN experienced moderate or severe vertebral fractures (as determined by the Genant scale) compared to women treated with placebo (5.2% placebo-treated women versus 3.3% FABLYN-treated women; $p = 0.0006$).

-Non-vertebral fractures

FABLYN significantly decreased the incidence of non-vertebral fractures from 10.4% for placebo to 8.1% for FABLYN (relative risk reduction = 24%, p = 0.0020). This decrease was observed through the first year and was maintained through 5 years. The reduction in the incidence of non-vertebral fractures was also observed in postmenopausal women with severe osteoporosis (defined as a baseline lumbar spine BMD T-score ≤ -2.5 + prevalent fracture or BMD T-score ≤ -3) (p = 0.0183).

-All clinical fractures

FABLYN significantly decreased the incidence of all clinical fractures from 12.1% for placebo to 9.3% for FABLYN (relative risk reduction = 25%, p = 0.0004). This decrease was observed through the first year and maintained through 5 years.

-Bone mineral density

In a 3-year substudy of the PEARL study (n=760), FABLYN significantly increased BMD (compared to placebo) at lumbar spine (3.3%), total hip (3.0%), femoral neck (3.3%), greater trochanter (3.6%), intertrochanteric area (2.6%), Ward's triangle (5.9%) and forearm (1.8%) at 3 years. FABLYN also significantly increased whole body bone mineral content (BMC), compared to placebo, at 3 years. Significant increases in BMD were observed as early as 3 months for lumbar spine and total hip.

An analysis was conducted of the subjects who were referred to their physician for consideration of treatment with an alternative osteoporosis medicinal product if one of the following was observed: a) ≥7% BMD loss at LS or ≥10% BMD loss at femoral neck at Month 12; b) ≥11% BMD loss at lumbar spine (LS) or ≥14% BMD loss at femoral neck at Month 24; c) ≥2 on-study radiographic vertebral fractures by Month 24. These referrals were significantly less frequent in the FABLYN group (0.9%) than in the placebo group (3.3%).

Results from one-year trial in Asian subjects

The effects of FABLYN on BMD in postmenopausal Japanese, Korean and Taiwanese women with osteoporosis were also examined in a one-year, randomized, placebo-controlled, double-blind osteoporosis treatment trial. The study population consisted of 497 women with osteoporosis as defined by low vertebral BMD (T-score ≤ 2.5). Women in this study had a median age of 63 years (range 44 to 79) and a median time since menopause of 13 years. All women in the study received calcium (600-1200 mg/day) and Vitamin D (400-800 IU/day).

In this study, FABLYN significantly increased spine and hip (total hip and all subcomponents of the hip) BMD by 2 to 4%. It also reduced markers of bone turnover.

Bone histomorphometry

Bone formed during two years' administration of lasofoxifene is of normal quality. To assess bone quality, bone biopsies were obtained from 71 postmenopausal women enrolled in BMD trials after 2 years of treatment. There was no evidence of osteomalacia, marrow fibrosis, cellular toxicity, woven bone or other abnormalities affecting the quality of the bone following lasofoxifene treatment.

Effects on the endometrium:

The following results of the effects of FABLYN on the endometrium through 5 years of exposure are reported from the PEARL study.

There was no difference between FABLYN- and placebo-treated women in the incidences of endometrial carcinoma and endometrial hyperplasia.

Lasofoxifene may be associated with benign endometrial effects: endometrial cystic change viewed on ultrasound and histological benign cystic atrophy (a variant of atrophic endometrium), contributing to approximately 1.5 mm increase in mean endometrial thickness. In clinical practice, these benign findings do not warrant further evaluation in women with no vaginal bleeding, in accordance with guidelines for postmenopausal women (see section 4.4).

The incidence of endometrial cystic change and endometrial thickness was analyzed in a subset of the study population (298 patients) with an annual transvaginal ultrasound (TVU) through 3 years. Placebo-treated women had a 1.9% incidence in cystic change over 3 years, whereas the FABLYN-treated women had a 20.4% incidence. All histology findings were benign. Placebo-treated women had a 0.7 mm mean decrease from baseline in endometrial thickness over 3 years, whereas the FABLYN-treated women had a 1.4 mm mean increase. The increase was observed at 12 months, and did not significantly increase through 3 years. In some cases, these findings were observed to resolve spontaneously on treatment.

In all women with a uterus at baseline, histologically benign endometrial polyps were reported in 34 of 2,302 (1.5%) FABLYN-treated women versus 18 of 2,309 (0.8%) placebo-treated women. In a subset of the study population designed to look at endometrial histology (1,080 patients) with a TVU at 3 years, histologically benign endometrial polyps were reported in 20 of 366 (5.5%) FABLYN-treated women and 12 of 360 (3.3%) placebo-treated women.

The overall incidence of vaginal bleeding was low (≤ 2.6% in all treatment groups). Vaginal bleeding was reported in 74 (2.6%) FABLYN-treated women versus 37 (1.3%) placebo-treated women. The number of subjects discontinuing treatment as a result of vaginal bleeding was low [FABLYN: 4 (0.1%), placebo: 0].

The number of hysterectomies in the FABLYN-treated group (27/2,302 patients, 1.2%) and the placebo-treated group (24/2,309 patients, 1.0%) were similar. To assess the effect of FABLYN on diagnostic uterine procedures (i.e., hysteroscopy, saline infused sonohysterogram, endometrial biopsy, polypectomy or dilation and curettage), an analysis was conducted on women without planned TVU surveillance (4,055 patients). More FABLYN-treated patients (7.0%) had a diagnostic procedure compared to placebo-treated patients (2.7%). Diagnostic uterine procedures were performed in a greater number of FABLYN-treated patients as a result of vaginal bleeding (as mandated by the protocol) and asymptomatic endometrial findings (e.g., suspected uterine polyps, endometrial thickness).

Effects on breast:

Over the 5 years of the PEARL study (involving 8,556 patients), FABLYN treatment compared to placebo reduced the risk of invasive breast cancer by 85% (placebo: 20 (0.7%), FABLYN: 3 (0.1%); HR 0.15 (CI 0.04, 0.50)), the risk of all breast cancer by 79% (placebo: 24 (0.9%), FABLYN: 5 (0.2%); HR 0.21 (CI 0.08, 0.55)), the risk of estrogen receptor (ER) positive invasive breast cancer by 83% (placebo: 18 (0.7%), FABLYN: 3 (0.1%); HR 0.17 (CI 0.05, 0.57)) and the risk of estrogen receptor (ER) positive breast cancer by 81% (placebo: 21 (0.8%), FABLYN: 4 (0.1%); HR 0.19 (CI 0.07, 0.56)). FABLYN has no effect on the risk of ER negative breast cancer or ER negative invasive breast cancers. These observations support the conclusion that lasofoxifene has no intrinsic estrogen agonist activity in breast tissue.

Effects on lipid metabolism and cardiovascular risk:

The effect of FABLYN on the lipid profile was evaluated in a 3-year substudy of the PEARL study; the substudy enrolled 1,014 postmenopausal women. Relative to placebo, FABLYN significantly decreased total cholesterol, LDL cholesterol, LDL-associated apolipoprotein B-100, and high sensitivity C-reactive protein (median changes -10.4%, -15.8%, -11.8%, -12.5%, respectively); no significant changes versus placebo were seen for HDL cholesterol or VLDL cholesterol. Statistically significant increases were seen for apolipoprotein A-1, which is associated with HDL cholesterol, and serum triglycerides (median changes vs. placebo 6.1% and 4.9%, respectively).

At 5 years in the overall study population (N=8,556), the incidence of major coronary events, including coronary death, non-fatal myocardial infarction, new ischemic heart disease, hospitalization for unstable angina, and revascularisation procedures, was significantly lower. There were 0.51 events/100 patient-years for FABLYN-treated patients compared to 0.75 events/100 patient-years in placebo-treated patients (HR 0.68; 95% CI 0.50, 0.93, p= 0.016). In the same study at 5 years, there was no increase in the risk of stroke including hemorrhagic, ischemic, embolic stroke, stroke type unspecified and transient ischemic attacks in FABLYN-treated patients. There were 0.48 events/100 patient years in the placebo group and 0.36 events/100 patient years among FABLYN-treated patients (HR = 0.75; 95% CI 0.51, 1.10, p = 0.140).

Effects on vulvar and vaginal atrophy (VVA):

The efficacy of FABLYN in the treatment of VVA was investigated in two 12-week Phase 3 studies in postmenopausal women with moderate or severe signs and symptoms of VVA, regardless of osteoporosis status (involving 889 patients). In both studies, it decreased the severity of the subject's most bothersome baseline VVA symptom, decreased vaginal pH, decreased the percentage of vaginal parabasal cells from the maturation index (MI) and increased the percentage of vaginal superficial cells from the MI. Similar results for vaginal pH and MI were observed in the PEARL study.

5.2 Pharmacokinetic properties

The disposition of lasofoxifene was evaluated in 758 subjects in conventional clinical pharmacology studies. Pharmacokinetic data from over 2,000 postmenopausal women including patients in selected osteoporosis clinical trials contributed to a population pharmacokinetic analysis.

Absorption:

Lasofoxifene is slowly absorbed from the gastrointestinal tract with maximal plasma concentrations attained on average by approximately 6 hours after dosing. Ingestion of a high fat meal does not change the oral bioavailability of lasofoxifene. FABLYN may be administered any time of day without regard to food or beverage intake.

Distribution:

The apparent volume of distribution (V/F) of lasofoxifene in postmenopausal women is approximately 1,350 l.

Lasofoxifene is highly bound to proteins in human plasma (>99%). Lasofoxifene binds to both albumin and α_1-acid glycoprotein; however, it does not affect the binding of either warfarin or propranolol.

Metabolism:

Biotransformation and disposition of lasofoxifene in humans have been determined following oral administration of ^{14}C-labeled lasofoxifene. Lasofoxifene is extensively metabolized in humans. Five metabolic pathways of lasofoxifene have been identified: direct glucuronidation; direct sulfation; hydroxylation at the phenyl tetraline moiety (with subsequent conjugative metabolism of the catechol intermediates by methylation and glucuronidation); oxidation at the pyrrolidine ring; and phenyl hydroxylation. Three metabolites of lasofoxifene were detected in plasma: the direct glucuronide conjugate, the glucuronide of a hydroxylated metabolite, and the methylated catechol.

The binding affinities of the major circulating metabolites of lasofoxifene were at least 31-fold and 18-fold less than those of lasofoxifene for the estrogen receptor alpha and the estrogen receptor beta, respectively, indicating that these metabolites are unlikely to contribute to the pharmacologic activity of lasofoxifene. Oxidation, by multiple cytochrome P450s including CYPs 2D6 and 3A4/5, and conjugation of lasofoxifene are the two primary mechanisms of elimination of lasofoxifene from the systemic circulation. The apparent oral clearance (CL/F) of lasofoxifene in postmenopausal women is approximately 6.6 l/hr.

Elimination:

Lasofoxifene has a half-life of approximately 6 days. Lasofoxifene and its metabolites are primarily excreted in feces, with a minor component of urinary excretion of active substance-related material. Following oral administration of ^{14}C-labeled lasofoxifene in solution to humans, approximately 72% of the radioactive dose was recovered by day 24 (approximately 66% in feces and 6% in urine). Less than 2% of the administered dose was recovered in the urine as unchanged lasofoxifene.

Linearity/non-linearity:

Lasofoxifene exhibits linear pharmacokinetics over a wide dose range following single-dose (up to 100 mg) and multiple-dose (up to 20 mg once daily) administration. Steady-state pharmacokinetics of lasofoxifene are consistent with expectations from its single-dose pharmacokinetics.

At steady state, the half-life of lasofoxifene in postmenopausal women is approximately 6 days, resulting in small fluctuations in concentrations over the 24-hour dosing interval.

Paediatric:

The pharmacokinetics of lasofoxifene have not been evaluated in a paediatric population.

Elderly:

No clinically meaningful differences in lasofoxifene pharmacokinetic were observed over the age range of 40 to 80 years of age based on the results of a population pharmacokinetic analysis. No dose adjustment for FABLYN is necessary in elderly patients.

Race:

In a population pharmacokinetic analysis, no discernible difference in lasofoxifene pharmacokinetics was detected in different racial groups. This analysis included 2,049 postmenopausal women consisting of 85.5% Caucasian, 8.6% Hispanic, 3.4% Asian, and 1.9% African American. The results of a phase 1 study in Japanese and Caucasian women was consistent with the population pharmacokinetic analysis and showed no discernible difference in lasofoxifene pharmacokinetics in these two populations.

Gender:

Since FABLYN is indicated for use only in postmenopausal women, no assessment of the effect of gender on lasofoxifene pharmacokinetics has been made.

Hepatically impaired patients:

Lasofoxifene was studied, as a single 0.25 mg dose, in healthy subjects and subjects with mild or moderate hepatic impairment. Plasma lasofoxifene exposure was approximately the same in healthy subjects as in subjects with mild hepatic impairment (Child-Pugh Class A) and was modestly increased (38%) in subjects with moderate hepatic impairment (Child-Pugh Class B) compared to healthy subjects. These differences are not considered to be clinically meaningful. No dose adjustment for FABLYN is necessary for patients with mild or moderate hepatic insufficiency. Subjects with severe hepatic impairment have not been studied (see section 4.4).

Renally impaired patients:

Since less than 2% of lasofoxifene is recovered in urine as unchanged active substance, a study in subjects with renal insufficiency was not conducted. In a population pharmacokinetic analysis, there were no clinically meaningful differences in lasofoxifene pharmacokinetics between postmenopausal women with estimated creatinine clearance as low as 32 ml/min and those with normal creatinine clearance. No dose adjustment for FABLYN is necessary for patients with mild or moderate renal insufficiency (see section 4.4).

5.3 Preclinical safety data

Lasofoxifene was not genotoxic in any of the battery of tests applied. In two-year carcinogenicity studies conducted in rats (≥1 mg/kg/day; 7 times systemic exposure following a human dose of 0.5 mg/day based on plasma AUC) an increased incidence of renal tubular adenoma and carcinoma in males and granulosa cell tumours of the ovary in females was noted. In the corresponding 2-year study in mice (≥2 mg/kg/day; less than systemic exposure following a human dose of 0.5 mg/day based on plasma AUC), there was an increased incidence of adrenal cortical adenoma and carcinoma, interstitial cell tumors of the testis, benign and malignant ovarian tumors and benign uterine glandular polyps. Although all of these tumours are believed to be the result of rodent-specific hormonal mechanisms, their relevance for humans is currently unknown. Based on 3- and 5-year human data in the clinical trials, the incidence of cancer during treatment with lasofoxifene was not higher than for placebo.

Lasofoxifene was not teratogenic in rats up to a dose of 10mg/kg (approximately 53 times the AUC in humans) or rabbits up to a dose of 3 mg/kg (below the level of systemic exposure in humans). Increased incidence of imperforate anus, hypoplastic tail, edema and limb flexures noted in fetuses of pregnant rats dosed at 100 mg/kg (approximately 400 times the AUC in humans) were associated with increased embryo-fetal lethality and generalized failure to thrive. In fertility studies conducted in rats with lasofoxifene, slight effects on male reproductive performance occurred at ≥10 mg/kg/day (approximately 42 times the AUC in humans) as evidenced by decreases in copulation index, implantation sites, and fetuses sired. Reduced fertility, and an increase in pre- and post-implantation loss leading to reduced litter size and prolonged gestation were observed in females treated at ≥0.01 mg/kg/day (below the level of systemic exposure in humans). In a prenatal and postnatal study in rats, at ≥0.01 mg/kg/day lasofoxifene delayed and/or disrupted parturition, increased pup mortality at birth, altered the achievement of developmental milestones, and reduced growth. Overall, the reproductive and developmental effects observed in animals are consistent with the SERM class of compounds.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:

Lactose anhydrous

Microcrystalline cellulose

Croscarmellose sodium

Silica, colloidal anhydrous

Magnesium stearate

Tablet coating:

Sunset yellow FCF aluminium lake (E110)

Hypromellose

Lactose monohydrate

Titanium dioxide (E171)

Triacetin

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

4 years

6.4 Special precautions for storage

This medicine does not require any special storage conditions.

6.5 Nature and contents of container

FABLYN film-coated tablets are supplied in PVC blisters with aluminum foil backing or HDPE bottles with polyethylene/aluminum foil lined polypropylene child-resistant closures.

Blister packs of 7, 28 or 30 tablets and bottles of 90 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Pfizer Limited

Ramsgate Road,

Sandwich,

Kent, CT13, 9NJ

United Kingdom

8. MARKETING AUTHORISATION NUMBERS

EU/0/00/000/000

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

<{DD/MM/YYYY}> <{DD month YYYY}>

10. DATE OF REVISION OF THE TEXT

{MM/YYYY}

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

ANNEX II

A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURING AUTHORISATION HOLDER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OF THE MARKETING AUTHORISATION

A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURING AUTHORISATION HOLDER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer of the biological active substance

Not applicable

Name and address of the manufacturer responsible for batch release

Pfizer Manufacturing Deutschland GmbH

Heinrich Mack Strasse 35

D-89257 Illertissen

Germany

B. CONDITIONS OF THE MARKETING AUTHORISATION

- **CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE IMPOSED ON THE MARKETING AUTHORISATION HOLDER**

Medicinal product subject to medical prescription.

- **CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**

The Marketing Authorisation Holder (MAH) shall ensure that, prior to launch, all healthcare professionals who are expected to prescribe FABLYN or order gynaecological ultrasound of patients treated with FABLYN, are provided with access to risk minimisation educational programme.

The programme shall have both electronic and printed form, which are identical in terms of content.

The programme materials shall be provided via the following means:

- Web-based
- On CD
- Printed on paper

The programme shall convey the following key messages:

- FABLYN increases risk of venous thromboembolism (VTE).
- The approaches recommended for mitigation of risk of venous thromboembolism based on the SmPC, including contraindication of FABLYN in patients with active or past history of VTE.
- FABLYN causes morphologic changes, particularly the cystic atrophy of endometrium. It results in increased mean endometrial thickness.
- Based on the clinical trials, the morphologic changes caused by FABLYN are benign and do not require further investigation unless vaginal bleeding occurs.
- References to authoritative international guidelines relevant for uterine surveillance.
- The need to stop treatment with FABLYN and investigate when unexplained uterine bleeding occurs.

The programme shall include the full text of the SmPC.

The MAH shall also provide access to educational programme for pathologists. This programme should focus on interpretation of endometrial biopsy of women treated with FABLYN. It must be in line with authoritative international guidelines and supported by evidence published in peer reviewed medical journals.

- **OTHER CONDITIONS**

Pharmacovigilance system

The MAH must ensure that the system of pharmacovigilance, as described in version version 1.1 presented in Module 1.8.1. of the Marketing Authorisation Application, is in place and functioning before and whilst the product is on the market.

Risk Management Plan

The MAH commits to performing the studies and additional pharmacovigilance activities detailed in the Pharmacovigilance Plan, as agreed in version 1.4 of the Risk Management Plan (RMP) presented in Module 1.8.2. of the Marketing Authorisation Application and any subsequent updates of the RMP agreed by the CHMP.

As per the CHMP Guideline on Risk Management Systems for medicinal products for human use, the updated RMP should be submitted at the same time as the next Periodic Safety Update Report (PSUR).

In addition, an updated RMP should be submitted

- When new information is received that may impact on the current Safety Specification, Pharmacovigilance Plan or risk minimisation activities
- Within 60 days of an important (pharmacovigilance or risk minimisation) milestone being reached
- At the request of the EMEA