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

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON FOR BOTTLE PACK (90 film-coated tablets)

1. NAME OF THE MEDICINAL PRODUCT

FABLYN 500 microgram film-coated tablets

lasofoxifene

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains lasofoxifene tartrate, equivalent to 500 microgram lasofoxifene.

3. LIST OF EXCIPIENTS

Contains lactose

See the package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

90 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For oral use.

Read the package leaflet before use.

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

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Sealed pack.

Do not use if box has been opened.

8. EXPIRY DATE

EXP:

9. SPECIAL STORAGE CONDITIONS

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Pfizer Limited

Ramsgate Road

Sandwich

Kent

CT13 9NJ

United Kingdom

12. MARKETING AUTHORISATION NUMBER

EU/0/00/000/000

13. BATCH NUMBER

Lot:

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

FABLYN

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON FOR BLISTER PACK (30 film-coated tablets)

1. NAME OF THE MEDICINAL PRODUCT

FABLYN 500 microgram film-coated tablets

lasofoxifene

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains lasofoxifene tartrate, equivalent to 500 microgram lasofoxifene.

3. LIST OF EXCIPIENTS

Contains lactose

See the package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

30 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For oral use.

Read the package leaflet before use.

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

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Sealed pack.

Do not use if box has been opened.

8. EXPIRY DATE

EXP:

9. SPECIAL STORAGE CONDITIONS

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Pfizer Limited

Ramsgate Road

Sandwich

Kent

CT13 9NJ

United Kingdom

12. MARKETING AUTHORISATION NUMBER

EU/0/00/000/000

13. BATCH NUMBER

Lot:

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

FABLYN

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON FOR BLISTER PACK (7 film-coated tablets)

1. NAME OF THE MEDICINAL PRODUCT

FABLYN 500 microgram film-coated tablets

lasofoxifene

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains lasofoxifene tartrate, equivalent to 500 microgram lasofoxifene.

3. LIST OF EXCIPIENTS

Contains lactose

See the package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

7 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For oral use.

Read the package leaflet before use.

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

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Sealed pack.

Do not use if box has been opened.

8. EXPIRY DATE

EXP:

9. SPECIAL STORAGE CONDITIONS

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Pfizer Limited

Ramsgate Road

Sandwich

Kent

CT13 9NJ

United Kingdom

12. MARKETING AUTHORISATION NUMBER

EU/0/00/000/000

13. BATCH NUMBER

Lot:

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

FABLYN

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON FOR BLISTER PACK (28 film-coated tablets)

1. NAME OF THE MEDICINAL PRODUCT

FABLYN 500 microgram film-coated tablets

lasofoxifene

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains lasofoxifene tartrate, equivalent to 500 microgram lasofoxifene.

3. LIST OF EXCIPIENTS

Contains lactose

See the package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

28 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For oral use.

Read the package leaflet before use.

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

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Sealed pack.

Do not use if box has been opened.

8. EXPIRY DATE

EXP:

9. SPECIAL STORAGE CONDITIONS

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Pfizer Limited

Ramsgate Road

Sandwich

Kent

CT13 9NJ

United Kingdom

12. MARKETING AUTHORISATION NUMBER

EU/0/00/000/000

13. BATCH NUMBER

Lot:

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

FABLYN

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER - 28 tablets

1. NAME OF THE MEDICINAL PRODUCT

FABLYN 500 microgram film-coated tablets

lasofoxifene

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Pfizer

3. EXPIRY DATE

EXP:

4. BATCH NUMBER

Lot:

5. OTHER

Mon

Tue

Wed

Thu

Fri

Sat

Sun

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

BOTTLE LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

FABLYN 500 microgram film-coated tablets

lasofoxifene

For oral use

2. METHOD OF ADMINISTRATION

Read the package leaflet before use.

3. EXPIRY DATE

EXP:

4. BATCH NUMBER

Lot:

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

90 film-coated tablets

6. OTHER

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER - 7 tablets

1. NAME OF THE MEDICINAL PRODUCT

FABLYN 500 microgram film-coated tablets

lasofoxifene

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Pfizer

3. EXPIRY DATE

EXP:

4. BATCH NUMBER

Lot:

5. OTHER

Mon

Tue

Wed

Thu

Fri

Sat

Sun

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER - 30 tablets

1. NAME OF THE MEDICINAL PRODUCT

FABLYN 500 microgram film-coated tablets

lasofoxifene

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Pfizer

3. EXPIRY DATE

EXP:

4. BATCH NUMBER

Lot:

5. OTHER

B. PACKAGE LEAFLET

PACKAGE LEAFLET: INFORMATION FOR THE USER

FABLYN 500 microgram film-coated tablets
lasofoxifene

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

In this leaflet:

1. WHAT FABLYN IS AND WHAT IT IS USED FOR

FABLYN is used to treat osteoporosis in women after the menopause (postmenopausal osteoporosis) who are likely to break bones, especially in the spine, hips and wrists. It belongs to a group of medicines called Selective Estrogen Receptor Modulators (SERM).

In women with postmenopausal osteoporosis, FABLYN reduces the risk of both fractures of the spine (vertebral fractures) and non-spine fractures (non-vertebral fractures), but not hip fractures.

2. BEFORE YOU TAKE FABLYN

Do not take FABLYN
- if you are allergic (hypersensitive) to lasofoxifene or any of the other ingredients of FABLYN.
- if you currently have or previously had blood clots, for example in your veins, lungs or eyes (deep vein thrombosis, pulmonary embolism or retinal vein thrombosis).
- if you have any vaginal bleeding. This must be investigated by your doctor **before starting treatment**.
- if you could still become pregnant.
- if you are pregnant or breast-feeding.

Take special care with FABLYN

- **if you are immobile for some time**, such as, needing to be admitted to a hospital or having to stay in bed while recovering from an operation or an illness, as these may increase your risk of blood clots (deep vein thrombosis, pulmonary embolism or retinal vein thrombosis). **Your doctor may recommend that you stop treatment at least 3 weeks prior to this time.** Treatment with FABLYN can be restarted as soon as you regain your mobility and in consultation with your doctor.

- if you are taking FABLYN, you should walk around or exercise your legs and feet at regular intervals when traveling long distances. This is because sitting for a long time in the same position may prevent good blood circulation and may increase your risk of blood clots.

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

The following are reasons why this medicine may not be suitable for you. **You should talk to your doctor before starting to take FABLYN :**

- if you have or have had breast cancer.
- if you experience any unexplained breast abnormality.
- if you have severe liver disease.
- if you have severe kidney disease.

Taking other medicines

Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription. If you are taking estrogen replacement therapy (ERT) or hormone replacement therapy (HRT), FABLYN may not be suitable for you.

Taking FABLYN with food and drink

FABLYN can be taken with or without food and drink.

Pregnancy and breast-feeding

FABLYN is only for women after the menopause and must not be taken by women who can still become pregnant.

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

Driving and using 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.

Important information about some of the ingredients of FABLYN

FABLYN contains lactose. If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicine.

3. HOW TO TAKE FABLYN

Always take FABLYN exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure. The usual dose is one tablet each day.

Swallow the tablet whole. You may take it with or without food.

If you wish, you may take it with water or another beverage of choice.

Your doctor may also advise you to take Calcium and Vitamin D supplements while you are treated with FABLYN if your daily intakes are not considered sufficient.

If you take more FABLYN than you should

If you take more tablets than you should, tell your doctor or pharmacist.

If you forget to take FABLYN

Do not take a double dose to make up for a forgotten tablet. Take your next tablet and continue as before.

If you stop taking FABLYN

You should talk to your doctor before stopping FABLYN.

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

4. POSSIBLE SIDE EFFECTS

Like all medicines, FABLYN can cause side effects, although not everybody gets them.

Most of the side effects that occurred during studies were mild.

These side effects may occur with certain frequencies, which are defined as follows:

- Very common: affects more than 1 user in 10
- Common: affects 1 to 10 users in 100
- Uncommon: affects 1 to 10 users in 1,000
- Rare: affects 1 to 10 users in 10,000
- Very rare: affects less than 1 user in 10,000
- Not known: frequency cannot be estimated from the available data

Very common side effects:

- Muscle cramps

Common side effects:

- Hot flush
- Constipation
- Pressure in the lower abdomen
- Vaginal discharge
- Excessive sweating

Uncommon side effects:

- Urinary tract infection, burning on urination, urgent need to urinate, urinary incontinence
- Abdominal pain or pressure, pain in the back, neck, joints or chest
- Tiredness, abnormal or excessive bleeding commonly from the nose
- Diabetes (typical symptoms are excessive thirst, frequent urination)
- Burning sensation, dizziness, numbness, memory impairment, impaired or partial loss of movement of a limb, headache, restless legs syndrome (an irresistible urge to move legs to stop an uncomfortable or odd sensations)
- Abnormal or irregular beating of the heart, increased heart rate
- Swelling of hands, arms, feet or legs, limb pain
- Cough, difficulty breathing, stuffy nose, runny nose
- Dry mouth, flatulence (excessive amount of air or gases in the stomach or the intestine), stomach ache
- Dry eye, hair loss, skin rash, night sweats, itching, feeling hot, weight gain
- Breast stiffening, breast pain, vaginal bleeding, genital itching

Rare side effects:

- Infection in the ear, eye, respiratory tract or skin, diarrhea, blood in stools
- Change in appetite
- Abnormal dreams, mood swings
- Dizziness, altered sense of taste, seizures, migraine, weakness of arms or legs, sciatica (pain felt in the lower back, buttock, and/or various parts of the leg and foot; typically on one side of the body)
- Impaired vision, pain in eyes, itchy eyes, swollen eyelids, redness of the eyes, ear pain
- Lip lesions, change of bowel habits, difficulty swallowing, mouth ulcer, heart burn, mouth pain, anal pain
- Jaundice (yellowing of the skin and eyes), changes in blood tests of liver function
- Dry skin, unusual hair texture, nail disorder, skin rash, skin darkening, altered shape of fingers, skin lesion
- Painful urination, blood in urine
- Breast discharge, breast lump, vaginal pain, varicose vein
- Decreased pulse in feet, bruising

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. HOW TO STORE FABLYN

Keep out of the reach and sight of children.

Do not use FABLYN after the expiry date which is stated on the blister or bottle label and on the carton after "EXP:". The expiry date refers to the last day of that month.

This medicine does not require any special storage conditions.

6. FURTHER INFORMATION

What FABLYN contains

- The active substance is lasofoxifene. Each film-coated tablet contains lasofoxifene tartrate, equivalent to 500 micrograms of lasofoxifene.

- The other ingredients are lactose anhydrous; microcrystalline cellulose; croscarmellose sodium; silica, colloidal anhydrous; magnesium stearate; sunset yellow FCF aluminium lake (E110); hypromellose; lactose monohydrate; titanium dioxide (E171) and triacetin.

What FABLYN looks like and contents of the pack

FABLYN tablets are triangular, peach coloured, film-coated tablets marked with "Pfizer" on one side and "OPR 05" on the other.

The tablets are provided in blister packs containing 7, 28 or 30 tablets, and in bottle packs containing 90 tablets. Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer

The Marketing Authorisation Holder is Pfizer Limited, Ramsgate Road, Sandwich, Kent CT13 9NJ, United Kingdom.

The Manufacturer is Pfizer Manufacturing Deutschland GmbH, Heinrich Mack Strasse 35, 89257 Illertissen, Germany.

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

België/Belgique/Belgien Pfizer S.A./N.V. Tél/Tel: +32 (0)2 554 62 11	**Luxembourg/Luxemburg** Pfizer S.A. Tél: +32 (0)2 554 62 11
България Пфайзер Люксембург САРЛ, Клон България Тел.: +359 2 970 4333	**Magyarország** Pfizer Kft. Tel. + 36 1 488 37 00
Česká republika Pfizer s.r.o. Tel: +420-283-004-111	**Malta** V.J. Salomone Pharma Ltd. Tel: +356 21 22 01 74
Danmark Pfizer ApS Tlf: +45 44 20 11 00	**Nederland** Pfizer bv Tel: +31 (0)10 406 43 01
Deutschland Pfizer Pharma GmbH Tel: +49 (0) 30 55 0055-51000	**Norge** Pfizer AS Tlf: +47 67 52 61 00
Eesti Pfizer Luxembourg SARL Eesti filiaal Tel: +372 6 405 328	**Österreich** Pfizer Corporation Austria Ges.m.b.H. Tel: +43 (0)1 521 15-0
Ελλάδα Pfizer Hellas A.E. Τηλ: +30 210 6785 800	**Polska** Pfizer Polska Sp. z o.o. Tel.: +48 22 335 61 00
España Pfizer S.A. Tel: +34 91 490 99 00	**Portugal** Laboratórios Pfizer, Lda. Tel: + 351 214 235 500
France	**România**

Pfizer Tél: +33 (0)1 58 07 34 40	Pfizer România S.R.L Tel: +40 (0)21 207 28 00
Ireland Pfizer Healthcare Ireland Tel: + 1800 633 363	**Slovenija** Pfizer Luxembourg SARL Pfizer, podružnica za svetovanje s področja farmacevtske dejavnosti, Ljubljana Tel: + 386 (0)1 52 11 400
Ísland Vistor hf., Sími: + 354 535 7000	**Slovenská republika** Pfizer Luxembourg SARL, organizačná zložka Tel: +421-2-3355 5500
Italia Pfizer Italia S.r.l. Tel: +39 06 33 18 21	**Suomi/Finland** Pfizer Oy Puh/Tel: +358(0)9 43 00 40
Κύπρος GEO. PAVLIDES & ARAOUZOS LTD, Τηλ: +35722818087	**Sverige** Pfizer AB Tel: +46 (0)8 5505 2000
Latvija Pfizer Luxembourg SARL Filiāle Latvijā Tel: +371 670 35 775	**United Kingdom** Pfizer Limited Tel: +44 (0)1737 331111
Lietuva Pfizer Luxembourg SARL filialas Lietuvoje Tel. +3705 2514000	

This leaflet was last approved in {MM/YYYY}.

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

資料３－６　ミファムルチド（mifamurtide）

ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

MEPACT 4 mg powder for suspension for infusion.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One vial contains 4 mg mifamurtide*.
After reconstitution, each ml of suspension in the vial contains 0.08 mg mifamurtide.

*fully synthetic analogue of a component of *Mycobacterium sp.* cell wall.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder for suspension for infusion.

White to off-white homogeneous lyophilised powder.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

MEPACT is indicated in children, adolescents and young adults for the treatment of high-grade resectable non-metastatic osteosarcoma after macroscopically complete surgical resection. It is used in combination with post-operative multi-agent chemotherapy. Safety and efficacy have been assessed in studies of patients 2 to 30 years of age at initial diagnosis (see section 5.1).

4.2 Posology and method of administration

MEPACT treatment should be initiated and supervised by specialist physicians experienced in the diagnosis and treatment of osteosarcoma.

Posology
The recommended dose of mifamurtide for all patients is 2 mg/m^2 body surface area. It should be administered as adjuvant therapy following resection: twice weekly at least 3 days apart for 12 weeks, followed by once-weekly treatments for an additional 24 weeks for a total of 48 infusions in 36 weeks.

Paediatric patients
The safety and efficacy of MEPACT have been established in children from the age of 2 years. It is not recommended for use in children below the age of 2 due to a lack of data on efficacy and safety in this age group.

Elderly patients
None of the patients treated in the osteosarcoma studies were 65 or older and in the phase III randomised study, only patients up to age 30 years were included. Therefore, there are not sufficient data to recommend the use of MEPACT in patients >30 years of age.

Patients with impaired renal or hepatic function
The pharmacokinetics of mifamurtide in patients with renal or hepatic impairment have not been formally studied. Caution should be used in these patients because dose adjustment information is not available.

Continued monitoring of the kidney and liver function is recommended if MEPACT is used beyond completion of chemotherapy until all therapy is completed.

Method of administration
MEPACT must be reconstituted, filtered using the filter provided and further diluted prior to administration. The reconstituted, filtered and diluted suspension for infusion is a homogenous, white to off-white, opaque liposomal suspension, free of visible particles and free of foam and lipid lumps.

After reconstitution, filtering using the filter provided and further dilution, MEPACT is administered by intravenous infusion over a period of 1 hour.

MEPACT **must not** be administered as a bolus injection.

For further instructions on reconstitution, filtering using the filter provided and dilution prior to administration, see section 6.6.

4.3 Contraindications

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

Concurrent use with ciclosporin or other calcineurin inhibitors (see section 4.5).

Concurrent use with high-dose non-steroidal anti-inflammatory drugs (NSAIDs, cyclooxygenase inhibitors) (see section 4.5).

4.4 Special warnings and precautions for use

Respiratory distress
In patients with a history of asthma or other chronic obstructive pulmonary disease, consideration should be given to administration of bronchodilators on a prophylactic basis. Two patients with pre-existing asthma developed mild to moderate respiratory distress associated with the treatment. If a severe respiratory reaction occurs, administration of MEPACT should be discontinued and appropriate treatment initiated.

Neutropenia
Administration of MEPACT was commonly associated with transient neutropenia, usually when used in conjunction with chemotherapy. Episodes of neutropenic fever should be monitored and managed appropriately. MEPACT may be given during periods of neutropenia, but subsequent fever attributed to the treatment should be monitored closely. Fever or chills persisting for more than 8 hours after administration of MEPACT should be evaluated for possible sepsis.

Inflammatory response
Association of MEPACT with signs of pronounced inflammatory response, including pericarditis and pleuritis, was uncommon. It should be used with caution in patients with a history of autoimmune, inflammatory or other collagen diseases. During MEPACT administration, patients should be monitored for unusual signs or symptoms, such as arthritis or synovitis, suggestive of uncontrolled inflammatory reactions.

Cardiovascular disorders
Patients with a history of venous thrombosis, vasculitis or unstable cardiovascular disorders should be closely monitored during MEPACT administration. If symptoms are persistent and worsening, administration should be delayed or discontinued. Haemorrhage was observed in animals at very high doses. These are not expected at the recommended dose, however monitoring of clotting parameters after the first dose and once again after several doses is recommended.

Allergic reactions
Occasional allergic reactions have been associated with MEPACT treatment, including rash, shortness of breath and Grade 4 hypertension. It may be difficult to distinguish allergic reactions from exaggerated inflammatory responses, but patients should be monitored for signs of allergic reactions.

Gastrointestinal toxicity
Nausea, vomiting and loss of appetite are very common adverse reactions to MEPACT. Gastrointestinal toxicity may be exacerbated when MEPACT is used in combination with high dose, multi-agent chemotherapy and was associated with an increased use of parenteral nutrition.

4.5 Interaction with other medicinal products and other forms of interaction

Limited studies of the interaction of MEPACT with chemotherapy have been conducted. Although these studies are not conclusive, there is no evidence of interference of MEPACT with the anti-tumour effects of chemotherapy and vice versa.

It is recommended to separate the administration times of MEPACT and doxorubicin or other lipophilic medicinal products if used in the same chemotherapy regimen.

The use of MEPACT concurrently with ciclosporin or other calcineurin inhibitors is contraindicated due to their hypothesised effect on splenic macrophages and mononuclear phagocytic function (see section 4.3).

Also, it has been demonstrated *in vitro* that high-dose NSAIDs (cyclooxygenase inhibitors) can block the macrophage activating effect of liposomal mifamurtide. Therefore the use of high-dose NSAIDs is contraindicated (see section 4.3).

Because mifamurtide acts through stimulation of the immune system, the chronic or routine use of corticosteroids should be avoided during treatment with MEPACT.

In vitro interaction studies showed that liposomal and non-liposomal mifamurtide do not inhibit the metabolic activity of cytochrome P450 in pooled human liver microsomes. Liposomal and non-liposomal mifamurtide do not induce the metabolic activity or the transcription of cytochrome P450 in primary cultures of freshly isolated human hepatocytes. Mifamurtide is therefore not expected to interact with the metabolism of substances that are hepatic cytochrome P450 substrates.

In a large controlled randomised study, MEPACT used at the recommended dose and schedule with other medicinal products that have known renal (cisplatin, ifosfamide) or hepatic (high-dose methotrexate, ifosfamide) toxicities did not exacerbate those toxicities and there was no need to adjust mifamurtide dose.

4.6 Pregnancy and lactation

Pregnancy
There are no data from the use of mifamurtide in pregnant patients. Animal studies are insufficient with respect to reproductive toxicity (see section 5.3). MEPACT should not be used during pregnancy and in women not using effective contraception.

Lactation
It is unknown whether mifamurtide is excreted in human milk. The excretion of mifamurtide in milk has not been studied in animals. A decision on whether to continue/discontinue breast-feeding or to continue/discontinue therapy should be made taking into account the benefit of breast-feeding to the child and the benefit of MEPACT therapy to the woman.

4.7 Effects on ability to drive and use machines

No studies of the effects on the ability to drive and use machines have been performed. Some very common or common undesirable effects of MEPACT treatment (such as dizziness, vertigo, fatigue and blurred vision) may have an effect on the ability to drive and use machines.

4.8 Undesirable effects

Each of the 248 patients treated with MEPACT during the early phase single arm studies in patients with mostly advanced malignancies experienced at least one undesirable effect. Many of the most frequently reported undesirable effects as shown in the following summary table are thought to be related to the mechanism of action of mifamurtide. The majority of these events were reported as either mild or moderate. This profile is consistent whether summarising all early studies (n=248) or only those studies in osteosarcoma (n=51). It is likely that undesirable effects also occurred in the large randomised study, but they were not recorded because only serious and life-threatening adverse reactions were collected in that study.

Adverse reactions are classified according to system organ class and frequency. Frequency groupings are defined according to the following convention: Very common (≥1/10), common (≥1/100 to <1/10). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Table 1. Adverse reactions associated with MEPACT in ≥ 1/100 patients

Infections and infestations
Common: Sepsis, cellulitis, nasopharyngitis, catheter site infection, upper respiratory tract infection, urinary tract infection, pharyngitis, *Herpes simplex* infection
Neoplasms benign, malignant and unspecified (incl cysts and polyps)
Common: Cancer pain
Blood and lymphatic system disorders
Very common: Anaemia
Common: Leukopenia, thrombocytopenia, granulocytopenia
Metabolism and nutrition disorders
Very common: Anorexia
Common: Dehydration, hypokalaemia, decreased appetite
Psychiatric disorders
Common: Confusional state, depression, insomnia, anxiety
Nervous system disorders
Very common: Headache, dizziness
Common: Paraesthesia, hypoaesthesia, tremor, somnolence, lethargy
Eye disorders
Common: Blurred vision
Ear and labyrinth disorders
Common: Vertigo, tinnitus, hearing loss
Cardiac disorders
Very common: Tachycardia
Common: Cyanosis, palpitations
Vascular disorders
Very common: Hypertension, hypotension
Common: Phlebitis, flushing, pallor
Respiratory, thoracic and mediastinal disorders
Very common: Dyspnoea, tachypnoea, cough
Common: Pleural effusion, exacerbated dyspnoea, productive cough, haemoptysis, wheezing, epistaxis, exertional dyspnoea, sinus congestion, nasal congestion, pharyngolaryngeal pain

Gastrointestinal disorders

Very common:	Vomiting, diarrhoea, constipation, abdominal pain, nausea
Common:	Upper abdominal pain, dyspepsia, abdominal distension, lower abdominal pain

Hepatobiliary disorders

Common:	Hepatic pain

Skin and subcutaneous tissue disorders

Very common:	Hyperhidrosis
Common:	Rash, pruritis, erythema, alopecia, dry skin

Musculoskeletal and connective tissue disorders

Very common:	Myalgia, arthralgia, back pain, pain in extremity
Common:	Muscle spasms, neck pain, groin pain, bone pain, shoulder pain, chest wall pain, musculoskeletal stiffness

Renal and urinary disorders

Common:	Haematuria, dysuria, pollakiuria

Reproductive system and breast disorders

Common:	Dysmenorrhoea

General disorders and administration site conditions

Very common:	Fever, chills, fatigue, hypothermia, pain, malaise, asthenia, chest pain
Common:	Peripheral oedema, oedema, mucosal inflammation, infusion site erythema, infusion site reaction, catheter site pain, chest discomfort, feeling cold

Investigations

Common:	Weight decreased

Surgical and medical procedures

Common:	Post-procedural pain

Blood and lymphatic system disorders

Anaemia has most commonly been reported when MEPACT is used in conjunction with chemotherapeutic agents. In a randomised controlled trial, the incidence of myeloid malignancy (acute myeloid leukaemia/myelodysplastic syndrome) was the same in patients receiving MEPACT plus chemotherapy as in patients receiving only chemotherapy (approximately 2.5%).

Metabolism and nutritional disorders

Anorexia (21%) was very commonly reported in trials of MEPACT in late stage cancer patients.

Nervous system disorders

Consistent with other generalised symptoms, the most common nervous system disorders were headache (50%) and dizziness (17%).

Ear and labyrinth disorders

Although hearing loss may be attributable to ototoxic chemotherapy, like cisplatin, it is unclear whether MEPACT in conjunction with multi-agent chemotherapy may increase hearing loss.

A higher percentage of objective and subjective hearing loss was observed overall in patients who received MEPACT and chemotherapy (12 % and 7%, respectively) in the phase III study (see Section 5.1 for a description of the trial) compared to those patients that received only chemotherapy (7% and 1%). All patients received a total dose of cisplatin of 480 mg/m^2 as part of their induction (neoadjuvant) and/or maintenance (adjuvant) chemotherapy regimen.

Cardiac and vascular disorders

Mild-moderate tachycardia (50%), hypertension (26%) and hypotension (29%) were commonly reported in uncontrolled trials of MEPACT. One serious incident of subacute thrombosis was reported in early studies, but no serious cardiac events were associated with MEPACT in a large randomised controlled trial.

Respiratory disorders
Respiratory disorders, including dyspnoea (21%), cough (18%) and tachypnoea (13%) were very commonly reported, and two patients with pre-existing asthma developed mild to moderate respiratory distress associated with MEPACT treatment in a phase II study.

Gastrointestinal disorders
Gastrointestinal disorders were frequently associated with MEPACT administration, including nausea (57%) and vomiting (44%) in about half of patients, constipation (17%), diarrhoea (13%) and abdominal pain.

Skin and subcutaneous disorders
Hyperhidrosis (11%) was very common in patients receiving MEPACT in uncontrolled studies.

Musculoskeletal and connective tissue disorders
Low grade pain was common in patients receiving MEPACT, including myalgia (31%), back pain (15%), extremity pain (12%) and arthralgia (10%).

General disorders and administration site conditions
The majority of patients experience chills (89%), fever (85%) and fatigue (53%). These are typically mild to moderate, transient in nature and generally respond to palliative treatment (e.g., paracetamol for fever). Other generalised symptoms that were typically mild to moderate and very common included hypothermia (23%), malaise (13%), pain (15%), asthenia (13%) and chest pain (11%). Oedema, chest discomfort, local infusion or catheter site reactions and 'feeling cold' were less frequently reported in these patients, mostly with late stage malignant disease.

Investigations
Increase in blood urea and blood creatinine was associated with MEPACT use in one patient with osteosarcoma.

4.9 Overdose

No case of overdose has been reported. The maximum tolerated dose in phase I studies was 4-6 mg/m^2 with a high variability of adverse reactions. Signs and symptoms that were associated with higher doses and/or were dose limiting were not life-threatening, and included fever, chills, fatigue, nausea, vomiting, headache and hypo- or hypertension.

In the event of an overdose, it is recommended that appropriate supportive treatment be initiated. Supportive measures should be based on institutional guidelines and the clinical symptoms observed. Examples include paracetamol for fever, chills and headache and anti-emetics (other than steroids) for nausea and vomiting.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other cytokines and immunomodulators, ATC code: L03AX15

Mechanism of action
Mifamurtide (muramyl tripeptide phosphatidyl ethanolamine, MTP-PE) is a fully synthetic derivative of muramyl dipeptide (MDP), the smallest naturally-occurring immune stimulatory component of cell walls from *Mycobacterium sp.* It has similar immunostimulatory effects as natural MDP with the additional advantage of a longer half-life in plasma. MEPACT is a liposomal formulation specifically designed for *in vivo* targeting to macrophages by intravenous infusion.

MTP-PE is a specific ligand of NOD2, a receptor found primarily on monocytes, dendritic cells and macrophages. MTP-PE is a potent activator of monocytes and macrophages. Activation of human macrophages by MEPACT is associated with production of cytokines, including tumour necrosis factor (TNF-α), interleukin-1 (IL-1β), IL-6, IL-8, and IL-12 and adhesion molecules, including lymphocyte function-associated antigen-1 (LFA-1) and intercellular adhesion molecule-1 (ICAM-1). *In vitro*-treated human monocytes killed allogeneic and autologous tumor cells (including melanoma, ovarian, colon, and renal carcinoma), but had no toxicity towards normal cells.
In vivo administration of MEPACT resulted in the inhibition of tumour growth in mouse and rat models of lung metastasis, skin and liver cancer, and fibrosarcoma. Significant enhancement of disease-free survival was also demonstrated in the treatment of dog osteosarcoma and hemangiosarcoma with MEPACT as adjuvant therapy. The exact mechanism by which MEPACT activation of monocytes and macrophages leads to antitumour activity in animals and humans is not yet known.

Clinical safety and efficacy
The safety of liposomal mifamurtide has been assessed in more than 700 patients with various kinds and stages of cancer and in 21 healthy adult subjects (see section 4.8).

MEPACT significantly increased the overall survival of patients with newly-diagnosed resectable high-grade osteosarcoma when used in conjunction with combination chemotherapy when compared to chemotherapy alone. In a randomised phase III study of 678 patients (age range from 1.4 to 30.6 years) with newly-diagnosed resectable high-grade osetosarcoma, the addition of adjuvant MEPACT to chemotherapy either doxorubicin cisplatin and methotrexate with or without ifosfamide
resulted in a relative reduction in the risk of death of 28% (p = 0.0313, hazard ratio (HR) = 0.72 [95% confidence interval (CI): 0.53, 0.97]).

5.2 Pharmacokinetic properties

After intravenous administration in 21 healthy adult subjects mifamurtide was cleared rapidly from plasma (minutes), resulting in a very low plasma concentration of total (liposomal and free) mifamurtide. The mean AUC was 17.0 +/- 4.71 h x nM and Cmax was 15.7 +/- 3.72 nM. In separate study in 14 patients, mean serum concentration-time curves of total and free mifamurtide that were assessed after the first infusion of MEPACT and after a last infusion 11 or 12 weeks later, were almost superimposable and the mean AUC values of the free mifamurtide after the first and last infusion were similar. These data indicate that neither total nor free mifamurtide accumulated during the treatment period.

At 6 hours after injection of radiolabelled liposomes containing 6 mg mifamurtide, radioactivity was found in liver, spleen, nasopharynx, thyroid, and, to a lesser extent, in lung. The liposomes were phagocytosed by cells of the reticuloendothelial system. In 2 of 4 patients with lung metastases, radioactivity was associated with lung metastases. Mean half-life of radiolabelled material was biphasic with an α phase of about 15 minutes and a terminal half-life of approximately 18 hours.

5.3 Preclinical safety data

In sensitive species (rabbit and dog) the highest daily dose of liposomal mifamurtide that did not cause adverse effects was 0.1 mg/kg, corresponding to 1.2 and 2 mg/m^2, respectively. The no-adverse-effect level for MEPACT in animals corresponds roughly to the 2 mg/m^2 recommend dose for humans.

Data from a six month dog study of daily intravenous injections of up to 0.5 mg/kg (10 mg/m^2) MEPACT provide an 8- to 19-fold cumulative exposure safety margin for overt toxicity for the intended clinical dose in humans. Major toxic effects associated with these high daily and cumulative doses of MEPACT were mainly exaggerated pharmacological effects: pyrexia, signs of

pronounced inflammatory response manifested as synovitis, bronchopneumonia, pericarditis and inflammatory necrosis of the liver and bone marrow. The following events were also observed: haemorrhage and prolongation of coagulation times, infarcts, morphological changes in the wall of small arteries, oedema and congestion of the central nervous system, minor cardiac effects, and slight hyponatraemia. MEPACT was not mutagenic and did not cause teratogenic effects in rats and rabbits. Embryotoxic effects were observed only at maternal toxic levels.

There were no results from general toxicity studies that suggested harmful effects on male or female reproductive organs. Specific studies addressing reproductive function, perinatal toxicity and carcinogenic potential have not been performed.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

1-Palmitoyl-2-oleoyl-sn-glycero-3-phosphocholine (POPC)
1,2-Dioleoyl-sn-glycero-3-phospho-L-serine monosodium salt (OOPS)

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

Unopened vial of powder:
2 years

Reconstituted suspension:
Chemical and physical stability has been demonstrated for 6 hours up to 25°C.

From a microbiological point of view, immediate use is recommended. If not used immediately, the reconstituted, filtered and diluted solution in-use storage times and conditions prior to use of the reconstituted product are the responsibility of the user and must not be longer than 6 hours at 25°C. Do not store in a refrigerator and do not freeze the solution.

6.4 Special precautions for storage

Store in a refrigerator (2°C – 8°C). Do not freeze.
Keep the vial in the outer carton in order to protect from light.

For storage conditions of the reconstituted medicinal product, see section 6.3.

6.5 Nature and contents of container

50 ml type I glass vial with a grey butyl rubber stopper, aluminium seal and plastic flip-off cap, containing 4 mg of mifamurtide.

Each carton contains one vial and one single-use, non-pyrogenic, latex-free sterile Filter for MEPACT supplied in a PVC-grade blister.

6.6 Special precautions for disposal and other handling

MEPACT must be reconstituted, filtered using the filter provided and further diluted using aseptic technique.

Each vial should be reconstituted with 50 ml of sodium chloride 9 mg/ml (0.9 %) solution for injection. After reconstitution, each ml suspension in the vial contains 0.08 mg mifamurtide. The volume of reconstituted suspension corresponding to the calculated dose is extracted through the filter provided and further diluted with additional 50 ml sodium chloride 9 mg/ml (0.9 %) solution for injection according to the detailed instructions shown below.

Instructions for preparation of MEPACT for intravenous infusion

Materials provided in each package -

- MEPACT powder for suspension for infusion (vial)
- Filter for MEPACT

Materials required but not provided -

- Sodium chloride 9 mg/ml (0.9%) solution for injection, EP/USP 100 ml bag
- One single use 60 or 100 ml sterile syringe with luer lock
- Two medium (18) gauge sterile injection needles

It is recommended that the reconstitution of the liposomal suspension should be performed in a laminar flow cabinet utilising sterile gloves using aseptic technique.

The lyophilised powder should be allowed to reach a temperature between approximately 20°C – 25°C prior to reconstitution, filtering using the filter provided and dilution. This should take approximately 30 minutes.

1. The cap of the vial should be removed and the stopper cleaned using an alcohol pad.
2. The filter should be removed from the blister pack, and the cap removed from the filter spike. The spike should then be inserted into the vial septum firmly until seated. The filter luer connector cap should not be removed at this time.
3. The 100 ml sodium chloride 9 mg/ml (0.9%) solution for injection bag, needle and syringe should be unpacked (not provided in the pack).
4. The site of the sodium chloride 9 mg/ml (0.9%) solution for injection bag where the needle is going to be inserted should be swabbed with an alcohol pad.
5. Using the needle and syringe, 50 ml of sodium chloride 9 mg/ml (0.9%) solution for injection should be withdrawn from the bag.
6. After removing the needle from the syringe, the syringe should be attached to the filter by opening the filter luer connector cap (Figure 1).

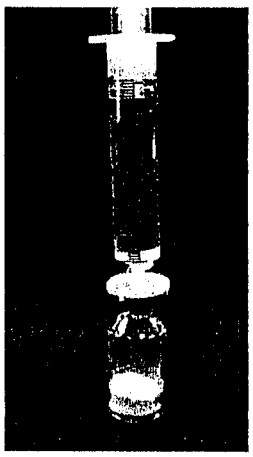

Figure 1

7. The sodium chloride 9 mg/ml (0.9%) solution for injection is added to the vial by slow, firm depression of the syringe plunger. **The filter and syringe must not be removed from the vial.**
8. The vial should be allowed to stand undisturbed for one minute to ensure thorough hydration of the dry substance.
9. **The vial should then be shaken vigorously for one minute while keeping the filter and syringe attached.** During this time the liposomes are formed spontaneously (Figure 2).

Figure 2

10. The desired dose may be withdrawn from the vial by inverting the vial and slowly pulling back on the syringe plunger (Figure 3). Each ml reconstituted suspension contains 0.08 mg mifamurtide. The volume of suspension to be withdrawn for dose quantities is calculated as follows:

    Volume to withdraw = [12.5 x calculated dose (mg)] ml

    For convenience, the following table of concordance is provided:

Dose	Volume
1.0 mg	12.5 ml
2.0 mg	25 ml
3.0 mg	37.5 ml
4.0 mg	50 ml

Figure 3

11. The syringe should then be removed from the filter and a new needle placed on the suspension-filled syringe. The bag injection site should be wiped with an alcohol pad and the suspension in the syringe should be injected into the original bag containing the remaining 50 ml of sodium chloride 9 mg/ml (0.9%) solution for injection (Figure 4).

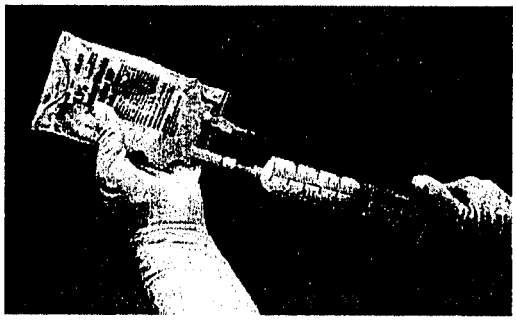

Figure 4

12. The bag should be gently swirled to mix the solution.
13. Patient identification, time and date should be added to the label on the bag containing the reconstituted, filtered and diluted liposomal suspension.
14. Chemical and physical in-use stability has been demonstrated for 6 hours at room temperature (between approximately 20°C – 25°C).
15. From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 6 hours at room temperature.
16. The liposomal suspension is infused intravenously over about one hour.

Disposal
No special requirements.

7. MARKETING AUTHORISATION HOLDER

IDM Pharma, S.A.
47 rue de Chaillot
75116 Paris
France
Tel: +33 467 55 84 62
Fax: +33 174 90 00 17

8. MARKETING AUTHORISATION NUMBER(S)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10. DATE OF REVISION OF THE TEXT

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

ANNEX II

A. MANUFACTURING AUTHORISATION HOLDER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OF THE MARKETING AUTHORISATION

A. MANUFACTURING AUTHORISATION HOLDER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

IDM Pharma, S.A.
47 rue de Chaillot
75116 Paris
France

B. CONDITIONS OF THE MARKETING AUTHORISATION

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

Medicinal product subject to restricted medical prescription (See Annex I: Summary of Product Characteristics, section 4.2).

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

Not applicable.

- **OTHER CONDITIONS**

Pharmacovigilance system
The MAH must ensure that the system of pharmacovigilance, as described in version POL/501 v1 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 POL/500 v1 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

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER PACKAGING

1. NAME OF THE MEDICINAL PRODUCT

MEPACT 4 mg powder for suspension for infusion
Mifamurtide

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each vial contains 4 mg of mifamurtide. After reconstitution, each ml of reconstituted suspension in the vial contains 0.08 mg of mifamurtide.

3. LIST OF EXCIPIENTS

Excipients: Palmitoyl-2-oleoyl-sn-glycero-3-phosphocholine (POPC),
1,2-Dioleoyl-sn-glycero-3-phospho-L-serine monosodium salt (OOPS)

4. PHARMACEUTICAL FORM AND CONTENTS

Powder for suspension for infusion
Pack of 1 vial of powder containing 4 mg mifamurtide, 1 sterile Filter for MEPACT

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use
For intravenous infusion after reconstitution, filtering using the filter provided and further dilution.

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

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator. Do not freeze.
Keep the vial in the outer carton in order to protect from light.

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

IDM Pharma, S.A.
47 rue de Chaillot
75116 Paris
France

12. MARKETING AUTHORISATION NUMBER(S)

13. BATCH NUMBER

LOT

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

VIAL LABEL

1. NAME OF THE MEDICINAL PRODUCT

MEPACT 4 mg powder for suspension for infusion
Mifamurtide

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each vial contains 4 mg of mifamurtide. After reconstitution, each ml of reconstituted suspension in the vial contains 0.08 mg of mifamurtide.

3. LIST OF EXCIPIENTS

Excipients: Palmitoyl-2-oleoyl-sn-glycero-3-phosphocholine (POPC),
1,2-Dioleoyl-sn-glycero-3-phospho-L-serine monosodium salt (OOPS)

4. PHARMACEUTICAL FORM AND CONTENTS

Powder for suspension for infusion
4 mg mifamurtide

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use
For intravenous infusion after reconstitution, filtering using the filter provided and further dilution.

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

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator. Do not freeze.
Keep the vial in the outer carton in order to protect from light.

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

IDM Pharma, S.A.
47 rue de Chaillot
75116 Paris
France

12. MARKETING AUTHORISATION NUMBER(S)

13. BATCH NUMBER

LOT

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER – FILTER FOR MEPACT

1. NAME OF THE MEDICINAL PRODUCT

Filter for MEPACT

2. NAME OF THE MARKETING AUTHORISATION HOLDER

IDM Pharma, S.A.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

LOT

5. OTHER

Store at 2°C – 40°C
Read the package leaflet before use
Single-use/non-pyrogenic/latex-free
Manufactured by ARIES s.r.l.

B. PACKAGE LEAFLET

PACKAGE LEAFLET: INFORMATION FOR THE USER

MEPACT 4 mg powder for suspension for infusion
Mifamurtide

Read all of this leaflet carefully before you start using this medicine.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor.

In this leaflet:

1. WHAT MEPACT IS AND WHAT IT IS USED FOR

MEPACT contains the active substance mifamurtide, similar to a component of the cell wall of certain bacteria. It stimulates your immune system to help your body kill tumour cells.

MEPACT is used to treat osteosarcoma (bone cancer) in children, adolescents and young adults. It is used after you have had surgery to remove the tumour and together with chemotherapy to kill remaining cancer cells to reduce the risk of cancer coming back.

2. BEFORE YOU USE MEPACT

Do not use MEPACT
- if you are allergic (hypersensitive) to mifamurtide or any of the other ingredients of MEPACT.
- if you are taking medicines containing ciclosporin or tacrolimus or high doses of NSAIDs (see "Using other medicines" below).

Take special care with MEPACT
You should tell your doctor before using MEPACT if any of the following applies to you:
- if you have or have had problems with your heart or blood vessels, like blood clots (thrombosis), bleeding (haemorrhage) or inflammation of the veins (vasculitis). You should be more closely monitored while receiving MEPACT treatment. If you have long-lasting or worsening symptoms, you should contact your doctor, as MEPACT administration may need to be delayed or discontinued.
- if you have a history of asthma or other breathing disorders. Before using MEPACT, you should discuss with your doctor whether you should take medicine for your asthma when using MEPACT.
- if you have a history of inflammatory or autoimmune disease or have been treated with corticosteroids or other medicines that may affect your immune system.

Using other medicines
Please tell your doctor if you are taking or have recently taken any other medicines, including medicines that may be obtained without a prescription. It is especially important to tell your doctor if you are taking medicines containing any of the following active substances:

- ciclosporin, tacrolimus, used after a transplant to prevent rejection of transplanted organs, or other immunosuppressants used e.g. to treat psoriasis (a skin disease).

- non-steroidal-anti-inflammatory drugs (NSAIDs), such as acetylsalicylic acid, ibuprofen, or diclofenac, used for treatment of headaches, fever or pain. You must not use MEPACT with high doses of NSAIDs.
- corticosteroids, used to treat inflammations, allergies or asthma. You must not use MEPACT with regular use of corticosteroids.

It is recommended to separate the times of administration of MEPACT and doxorubicin or other medicines if used in the same chemotherapy treatment regimen.

Pregnancy and breast-feeding
MEPACT has not been tested in pregnant women. Therefore, MEPACT should not be used during pregnancy and in women not using effective contraception. You should use effective contraception if you are being treated with MEPACT. It is important to tell your doctor if you are pregnant, think you may be pregnant, or are planning to get pregnant.

It is not known whether MEPACT passes to human milk. If you are breast-feeding, you should discuss with your doctor.

Driving and using machines
Some very common and common side effects of MEPACT treatment (such as dizziness, vertigo, fatigue and blurred vision) may affect your ability to drive and use machines.

3. HOW TO USE MEPACT

Dose and schedule
The safety and efficacy of MEPACT have been established in patients aged 2 to 30 years. The dose of MEPACT is 2 mg mifamurtide/m^2 body surface area. It will be given to you twice a week (at least three days apart) for the first 12 weeks, then once a week for 24 more weeks.

The schedule of your MEPACT treatments can be adjusted to fit with your chemotherapy schedule. It is not necessary to interrupt your schedule of MEPACT if your chemotherapy is delayed; you should complete 36 weeks (9 months) of treatment with MEPACT without an interruption.

How MEPACT is given
The freeze-dried powder has to be reconstituted into a liquid suspension, filtered using the filter provided and further diluted before use. MEPACT is then infused directly into your vein (intravenous) over about one hour. This is done by your doctor or a nurse, who will also monitor you during that time. You do not need to be hospitalised to receive MEPACT. It can also be administered as an outpatient.

If you use more MEPACT than you should
You may experience more severe side effects, including fever, chills, fatigue, nausea, vomiting, headache and hypo- or hypertension. In the event of such an overdose, contact your doctor or nearest hospital.

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

4. POSSIBLE SIDE EFFECTS

Like all medicines, MEPACT can cause side effects, although not everybody gets them.
The majority of patients experience chills, fever and fatigue. These are typically mild to moderate and transient and can usually be treated by your doctor, e.g., with paracetamol for fever.

Contact your doctor **immediately**:

- if you have continuing fever or chills more than 8 hours after your dose of MEPACT, because this may be a sign of an infection or
- if you experience rash or have any problems breathing (wheezing).

Side effects may occur with certain frequencies, which are defined as follows:
- very common: affects more than 1 user in 10
- common: affects 1 to 10 users in 100
- uncommon: affects 1 to 10 users in 1,000
- rare: affects 1 to 10 users in 10,000
- very rare: affects less than 1 user in 10,000
- not known: frequency cannot be estimated from the available data.

Very common side effects:
- fever, shaking/shivering, weakness, tiredness or general discomfort
- nausea and/or vomiting, diarrhoea or constipation
- headache or dizziness
- rapid beating of the heart
- high blood pressure or low blood pressure
- no appetite for food
- sweating
- pain, including general pain, pain in your muscles and/or joints and pain in back, chest, abdomen, arm or leg
- cough, trouble breathing or rapid breathing
- low body temperature
- low number of red blood cells

Common side effects:
- blue colour of tissues such as the skin or gums caused by too little oxygen
- perceptible increase in frequency or force of heartbeat
- swelling in arms or legs or other swelling
- chest discomfort
- upset stomach, decreased appetite or weight loss
- injection site or catheter site redness, swelling, infection or other local reaction
- rash or redness, inflammation of the skin, itching, dry skin, pale or transient red appearance
- inflammation of skin, tendons, muscles or similar tissues that support body structure
- inflammation of a vein
- upper abdominal or chest wall pain; abdominal bloating or pain
- other pain, including neck, shoulder or throat pain
- muscle spasms or stiffness
- feeling cold
- tired feeling, drowsiness or sleepiness
- burning, pricking/tingling sensation or diminished sensitivity to sensation
- (involuntary shaking movement
- dehydration
- mucosal inflammation
- nose, throat, or sinus congestion or inflammation
- infections of the upper respiratory tract (such as a cold) or the urinary tract (such as a bladder infection)
- generalised infection
- *Herpes simplex* (virus) infection
- productive cough, wheezing or exertional or exacerbated shortness of breath
- spitting of blood or nosebleed
- fluid in the lung cavity
- blood in urine, difficulty or pain in urination or frequent urination
- difficulty sleeping, depression, anxiety or confusion
- dizziness
- ears ringing

- blurred vision
- hair loss
- difficult, painful menstruation
- hearing loss

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor.

5. HOW TO STORE MEPACT

Keep out of the reach and sight of children.
Do not use MEPACT after the expiry date which is stated on the vial label and the carton.

Unopened vial
Store in a refrigerator (2°C – 8°C). Do not freeze.
Keep the vial in outer carton in order to protect from light.

Reconstituted suspension
Once reconstituted in sodium chloride 9 mg/ml (0.9%) solution, store at room temperature (approximately 20°C - 25°C) and use within 6 hours.

6. FURTHER INFORMATION

What MEPACT contains
- The active substance is mifamurtide. Each vial contains 4 mg of mifurtamide. After reconstitution with 50 ml sodium chloride 9 mg/ml (0.9%) solution for injection, each ml of suspension contains 0.08 mg of mifamurtide.
- The other ingredients are 1-Palmitoyl-2-oleoyl-sn-glycero-3-phosphocholine (POPC) and 1,2-Dioleoyl-sn-glycero-3-phospho-L-serine monosodium salt (OOPS).

What MEPACT looks like and contents of the pack
MEPACT is a white to off-white homogeneous freeze-dried powder for suspension for infusion.

MEPACT is supplied in a carton that contains
- One 50 ml vial with a grey butyl stopper, aluminium seal and plastic flip-off cap.
- One sterile Filter for MEPACT supplied in a blister.

Marketing Authorisation Holder and Manufacturer

IDM Pharma, S.A.
47 rue de Chaillot
75116 Paris
France
Tel: +33 467 55 84 62
Fax: +33 174 90 00 17

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

This leaflet was last approved in

The following information is intended for medical or healthcare professionals only:

Instructions for preparation of MEPACT for intravenous infusion

Materials provided in each package -

- 1 vial of MEPACT (mifamurtide)
- 1 Filter for MEPACT

Materials required but not provided -

- Sodium chloride 9 mg/ml (0.9%) solution for injection, EP/USP 100 ml bag
- One single use 60 or 100 ml sterile syringe with luer lock
- Two medium (18) gauge sterile injection needles

It is recommended that the reconstitution of the liposomal suspension should be performed in a laminar flow cabinet utilising sterile gloves using aseptic technique.

The lyophilised powder should be allowed to reach a temperature between approximately 20°C – 25°C prior to reconstitution, filtering using the filter provided and dilution. This should take approximately 30 minutes.

1. The cap of the vial should be removed and the stopper cleaned using an alcohol pad.
2. The filter should be removed from the blister pack, and the cap removed from the filter spike. The spike should then be inserted into the vial septum firmly until seated. The filter luer connector cap should not be removed at this time.
3. The 100 ml sodium chloride 9 mg/ml (0.9%) solution for injection bag, needle and syringe should be unpacked (not provided in the pack).
4. The site of the sodium chloride 9 mg/ml (0.9%) solution for injection bag where the needle is going to be inserted should be swabbed with an alcohol pad.
5. Using the needle and syringe, 50 ml of sodium chloride 9 mg/ml (0.9%) solution for injection should be withdrawn from the bag.
6. After removing the needle from the syringe, the syringe should be attached to the filter by opening the filter luer connector cap (Figure 1).

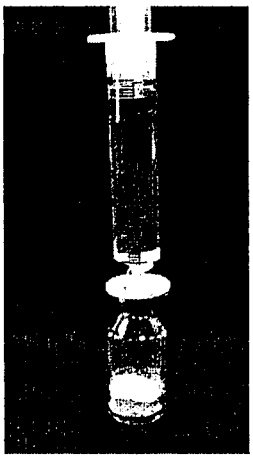

Figure 1

7. The sodium chloride 9 mg/ml (0.9%) solution for injection is added to the vial by slow, firm depression of the syringe plunger. **The filter and syringe must not be removed from the vial.**
8. The vial should be allowed to stand undisturbed for one minute to ensure thorough hydration of the dry substance.

9. **The vial should then be shaken vigorously for one minute while keeping the filter and syringe attached.** During this time the liposomes are formed spontaneously (Figure 2).

Figure 2

10. The desired dose may be withdrawn from the vial by inverting the vial and slowly pulling back on the syringe plunger (Figure 3). Each ml reconstituted suspension contains 0.08 mg mifamurtide. The volume of suspension to be withdrawn for dose quantities is calculated as follows:

    Volume to withdraw = [12.5 x calculated dose (mg)] ml

    For convenience, the following table of concordance is provided:

Dose	Volume
1.0 mg	12.5 ml
2.0 mg	25 ml
3.0 mg	37.5 ml
4.0 mg	50 ml

Figure 3

11. The syringe should then be removed from the filter and a new needle placed on the suspension-filled syringe. The bag injection site should be wiped with an alcohol pad and the suspension in the syringe should be injected into the original bag containing the remaining 50 ml of sodium chloride 9 mg/ml (0.9%) solution for injection (Figure 4).

Figure 4

12. The bag should be gently swirled to mix the solution.
13. Patient identification, time and date should be added to the label on the bag containing the reconstituted, filtered and diluted liposomal suspension.
14. Chemical and physical in-use stability has been demonstrated for 6 hours at room temperature (between approximately 20°C – 25°C).
15. From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 6 hours at room temperature.

Disposal
No special requirements.