ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

CONBRIZA 20 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains bazedoxifene acetate equivalent to 20 mg bazedoxifene.

Excipient with known effect

Each film-coated tablet contains 142.8 mg lactose (as monohydrate).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.

White to off-white, capsule-shaped, film-coated tablet debossed on one side with “WY20”. The tablet is approximately 1.5 cm in length.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

CONBRIZA is indicated for the treatment of postmenopausal osteoporosis in women at increased risk of fracture. A significant reduction in the incidence of vertebral fractures has been demonstrated; efficacy on hip fractures has not been established.

When determining the choice of CONBRIZA or other therapies, including oestrogens, for an individual postmenopausal woman, consideration should be given to menopausal symptoms, effects on uterine and breast tissues, and cardiovascular risks and benefits (see section 5.1).

4.2 Posology and method of administration

Posology

The recommended dose of CONBRIZA is one tablet once daily, at any time of day, with or without food (see section 5.2).

Doses higher than 20 mg are not recommended because there is no demonstrable increased efficacy and higher doses may be associated with additional risk (see section 5.1).

Supplemental calcium and/or vitamin D should be added to the diet if daily intake is inadequate.

Special populations

Renal impairment
Bazedoxifene has not been sufficiently evaluated in patients with severe renal impairment; caution should be used in this population (see sections 4.4 and 5.2).

No dose adjustment is required for mild or moderate renally impaired patients.

Hepatic impairment
Safety and efficacy of bazedoxifene have not been evaluated in patients with hepatic impairment; use in this population is not recommended (see sections 4.4 and 5.2).

Elderly patients
No dose adjustment is necessary based on age (see section 5.2).

Paediatric population
There is no relevant use of bazedoxifene in the paediatric population.

Method of administration

Oral use.

4.3 Contraindications

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

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

CONBRIZA is only indicated for use in postmenopausal women. Bazedoxifene must not be taken by women of child-bearing potential (see sections 4.6 and 5.3).

Unexplained uterine bleeding.

Patients with signs or symptoms of endometrial cancer; safety in this patient group has not been adequately studied.

4.4 Special warnings and precautions for use

Use of CONBRIZA is not recommended in women at an increased risk for venous thromboembolic events. CONBRIZA is associated with an increased risk of venous thromboembolism (VTE). In clinical trials, the highest rate of VTE was observed during the first year of treatment, with a relative risk of 2.69 compared to placebo. After 3 years the relative risk was 1.63 and after a 5 year study period the relative risk was 1.50; after 7 years the relative risk was 1.51 (see sections 4.8 and 5.1). The risk factors associated with VTE cases in clinical trials included: advanced age, obesity, immobilisation, surgery, major trauma and malignancy. CONBRIZA should be discontinued prior to and during prolonged immobilisation (e.g., post-surgical recovery, prolonged bed rest), and therapy should be resumed only after the patient is fully ambulatory. In addition, women taking CONBRIZA should be advised to move about periodically during prolonged travel.

Bazedoxifene has not been studied in premenopausal women. Its safety in premenopausal women has not been established, and its use is not recommended in this population.

There is no evidence of endometrial proliferation. Any uterine bleeding during CONBRIZA therapy is unexpected and should be fully investigated.

Bazedoxifene has not been studied in women with triglyceride levels >300 mg/dl (>3.4 mmol/litre). It may increase serum triglyceride levels; therefore, caution should be exercised in patients with known hypertriglyceridaemia (see section 5.1).

The safety of CONBRIZA in patients with breast cancer has not been studied. No data are available on the concomitant use with agents used in the treatment of early or advanced breast cancer. Therefore, bazedoxifene is not recommended for treatment or prevention of breast cancer.

Bazedoxifene has not been sufficiently evaluated in patients with severe renal impairment; caution should be used in this population.

Patients with hepatic impairment showed a 4.3-fold increase in area under the curve (AUC) [on average] compared with controls. Use in this population is not recommended (see sections 4.2 and 5.2).

Excipients with known effect

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

This medicinal product contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium free'.

4.5 Interaction with other medicinal products and other forms of interaction

In a 30-day study, bazedoxifene increased hormone-binding globulin concentrations, including corticosteroid-binding globulin (CBG), sex hormone-binding globulin (SHBG) and thyroxine-binding globulin (TBG).

Bazedoxifene undergoes metabolism by uridine diphosphate glucuronosyltransferase (UGT) enzymes in the intestinal tract and liver (see section 5.2). The metabolism of bazedoxifene may be increased by concomitant use of substances known to induce UGTs, such as rifampicin, phenobarbital, carbamazepine, and phenytoin, potentially leading to decreased systemic concentrations of bazedoxifene.

Bazedoxifene undergoes little or no cytochrome P450 (CYP)-mediated metabolism. Bazedoxifene does not induce or inhibit the activities of major CYP isoenzymes. *In vitro* data suggest that bazedoxifene is unlikely to interact with co-administered medicinal products via CYP-mediated metabolism.

There were no significant pharmacokinetic interactions between bazedoxifene and the following medicinal products: ibuprofen, atorvastatin, azithromycin, or an antacid containing aluminium and magnesium hydroxide. Based on *in vitro* bazedoxifene plasma protein binding characteristics, drug interactions with warfarin, digoxin and diazepam are unlikely.

4.6 Fertility, pregnancy and lactation

Pregnancy

CONBRIZA is only for use in postmenopausal women. It is contraindicated in women of child-bearing potential (see section 4.3). There are no data from the use of bazedoxifene in pregnant women. Studies in rabbits have shown reproductive toxicity (see section 5.3). The potential risk for humans is unknown.

Breast-feeding

It is not known whether bazedoxifene is excreted in human milk. CONBRIZA is only indicated for use in postmenopausal women (see section 4.3) and should not be used during breast-feeding.

Fertility

Studies in rats have shown adverse effects on fertility (see section 5.3). The potential risk for humans is unknown.

4.7 Effects on ability to drive and use machines

CONBRIZA has minor influence on the ability to drive and use machines.

In clinical trials, somnolence was reported as an adverse reaction, and patients should be advised on the potential effect on driving and using machines.

Patients may experience visual symptoms such as visual acuity disturbance or blurred vision. If such symptoms occur, patients should avoid driving or use of machines that requires accurate visual perception until symptoms have resolved, or until they have received medical advice that it is safe to do so.

4.8 Undesirable effects

Summary of the safety profile

The safety of CONBRIZA has been evaluated in two multicentre, double-blind, randomised, placebo- and active-control, Phase 3 trials: 7,492 evaluable postmenopausal women in a three-year osteoporosis treatment trial (1,886 women received bazedoxifene 20 mg; 1,872 women received bazedoxifene 40 mg; 1,849 women received raloxifene; 1,885 women received placebo) and 1,583 evaluable postmenopausal women in a 2-year osteoporosis prevention trial (321 women received bazedoxifene 10 mg; 322 women received bazedoxifene 20 mg; 319 women received bazedoxifene 40 mg; 311 women received raloxifene; 310 women received placebo).

The majority of adverse reactions occurring during the clinical trials were mild to moderate in severity and did not lead to discontinuation of therapy.
The most frequent drug-related adverse reactions in double-blind, randomised studies were hot flushes and muscle spasms (includes leg cramps).

Tabulated list of adverse reactions

The safety data in the following table are derived from both clinical trials and spontaneous post-marketing reporting.

Adverse reactions are categorised according to the following frequencies: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

System organ class	Very common	Common	Uncommon	Frequency not known (cannot be estimated from available data)
Immune system disorders		Hypersensitivity		
Nervous system disorders		Somnolence		
Eye disorders			Retinal vein thrombosis*	Vision disorders/Ocular events[#]
Cardiac disorders				Palpitations
Vascular disorders	Hot flush		Deep vein thrombosis*, thrombophlebitis superficial	

System organ class	Very common	Common	Uncommon	Frequency not known (cannot be estimated from available data)
Respiratory, thoracic and mediastinal disorders			Pulmonary embolism*	
Gastrointestinal disorders		Dry mouth		
Skin and subcutaneous tissue disorders		Urticaria, rash, pruritus		
Musculoskeletal and connective tissue disorders	Muscle spasms (includes leg cramps)			
General disorders and administration site conditions	Oedema peripheral			
Investigations		Blood triglycerides increased, alanine aminotransferase increased, aspartate aminotransferase increased.		

Description of selected adverse reactions

*In the osteoporosis treatment trial in 7,492 evaluable subjects (mean age=66 years), the bazedoxifene-treated women had an increased risk of venous thromboembolism (deep vein thrombosis, pulmonary embolism and retinal vein thrombosis). The rate per 1,000 women-years through the 3-year study period was 2.86 in the bazedoxifene 20 mg group and 1.76 in the placebo group, and through the 5-year study period was 2.34 in the bazedoxifene 20 mg group and 1.56 in the placebo group. The rate per 1,000 women-years through the 7 year study period was 2.06 in the bazedoxifene 20 mg group and 1.36 in the placebo group. The rate of VTE was highest in the first year with a relative risk of 2.69. After 3 years the relative risk was 1.63 and after a 5 year study period the relative risk was 1.50. After 7 year study period the relative risk was 1.51 (see section 5.1). Other venous thromboembolic events could also occur.

#There have been post-marketing reports of ocular events other than retinal vein thrombosis. These reports include visual acuity reduced, blurred vision, photopsia, visual field defect, visual impairment, dry eye, eyelid oedema, blepharospasm, eye pain and eye swelling. The underlying nature of these events is uncertain. If ocular symptoms occur, patients should be advised to seek medical attention.

Reporting of suspected adverse reactions

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

4.9 Overdose

In the case of overdose, there is no specific antidote, and treatment should be symptomatic.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Sex hormones and modulators of the genital system, selective oestrogen receptor modulator, ATC code: G03XC02.

Mechanism of action

Bazedoxifene belongs to a class of compounds known as selective oestrogen receptor modulators (SERMs). Bazedoxifene acts as both an oestrogen-receptor agonist and/or antagonist, depending upon the cell and tissue type and target genes. Bazedoxifene decreases bone resorption and reduces biochemical markers of bone turnover to the premenopausal range. These effects on bone remodelling lead to an increase in bone mineral density (BMD), which in turn contributes to a reduction in the risk of fractures. Bazedoxifene functions primarily as an oestrogen-receptor antagonist in uterine and breast tissues.

Clinical efficacy

The efficacy of bazedoxifene was established in two multicentre, double-blind, randomised, placebo- and active-control, Phase 3 trials: 3-year osteoporosis treatment trial and a 2-year osteoporosis prevention trial.

Osteoporosis treatment trial
In the osteoporosis treatment study, 7,492 postmenopausal women (mean age of 66 years; range 50 to 85 years and a mean time of 19.5 years since menopause) received bazedoxifene (20 or 40 mg daily), raloxifene (60 mg daily), or placebo to evaluate the incidence of new vertebral fractures over 3 years (3-year core study). The 3-year core study was extended twice, with two 2-year double-blind, placebo-controlled extensions, resulting in a total treatment duration of up to 7 years (7-year study). A total of 3,146 subjects continued into the first 2-year extension (bazedoxifene 20 mg: n=1,047, bazedoxifene 40/20 mg: n=1,041, placebo: n=1,058). The bazedoxifene 40 mg dose was decreased to a 20 mg dose after approximately 4 years. The raloxifene group was discontinued during the first 2-year extension. A total of 1,732 subjects continued into the second 2-year extension (bazedoxifene 20 mg: n=560, bazedoxifene 40/20 mg: n=582, and placebo: n=590). All subjects were to receive 1,200 mg of elemental calcium and 400 IU of vitamin D daily.

This study included mostly Caucasian (87.3%) subjects who were either osteoporotic without baseline vertebral fracture (BMD T-score at lumbar spine [LS] or femoral neck [FN] between -2.5 and -4.0) or osteoporotic, with at least 1 mild baseline vertebral fracture. The mean LS and FN T-scores at baseline were -2.4 and -1.7, respectively.

There was a significant reduction in the incidence of new vertebral fractures after 3 years of treatment with bazedoxifene 20 mg (42%), bazedoxifene 40 mg (37%) and raloxifene 60 mg (42%) compared to placebo. The reduction in the incidence of vertebral fracture was similar among bazedoxifene and raloxifene treatment groups. The treatment effect was similar among those with and without prevalent vertebral fractures (Table 1).

Table 1: Effect of bazedoxifene on risk of vertebral fractures after 3 years of treatment				
	Number of subjects		Absolute risk reduction	Relative risk reduction (95% CI)
	Bazedoxifene 20 mg	Placebo		
Total number of subjects	n=1,724	n=1,741		
Number (%)[a] of subjects with new vertebral fracture	35 (2.34%)	59 (4.07%)	1.73%	42%[b] (11%, 62%)
Subjects with no baseline fracture	n=757	n=760		
Number (%)[a] of subjects with ≥1 new vertebral fracture	13 (1.98%)	20 (3.13%)	1.15%	35%[c]
Subjects with ≥1 baseline fracture	n=967	n=981		
Number (%)[a] of subjects with ≥1 new vertebral fracture	22 (2.63%)	39 (4.80%)	2.17%	45%[d] (6%, 68%)
[a] Kaplan-Meier rate estimates [b] p-value=0.015 [c] p-value=0.22 [d] p-value=0.035				

After 5 years of treatment, the incidence of new vertebral fractures remained lower in the bazedoxifene 20 mg group (4.49%) compared to placebo (6.82%) with a relative risk reduction of 36% (p=0.014).

After 7 years of treatment, the incidence of new vertebral fractures remained lower in the bazedoxifene 20 mg group (7.64%) compared to placebo (9.90%) with a relative risk reduction of 30% (p=0.022).

The incidence of non-vertebral osteoporosis-related fractures was similar among bazedoxifene 20 mg (5.68%), raloxifene 60 mg (5.87%), and placebo (6.26%) groups. In a post-hoc analysis, the 10-year fracture probability as an index of baseline fracture risk was determined. The mean 10-year fracture probability of a major osteoporotic fracture for the entire study population was 11%. In subjects treated with bazedoxifene, the incidence of fractures was related to the baseline fracture risk: the higher the fracture risk, the greater the benefit with bazedoxifene treatment. In subjects with 10-year fracture probabilities at or above 16%, bazedoxifene was associated with a significant decrease in the risk of all clinical fractures.

In a post-hoc analysis, the relative risk of non-vertebral fractures in bazedoxifene-treated subjects decreased with increased fracture probability. In subjects with a fracture probability of 20% or greater (n = 618), the risk of non-vertebral fractures in bazedoxifene-treated subjects was decreased by 55% (95% CI: 18-76) compared to placebo-treated subjects.

The increase in LS BMD compared with placebo with bazedoxifene 20 mg and raloxifene 60 mg was significant at 6 months (1.02% and 1.29%, respectively) and was maintained through 3 years (1.32% and 2.08%, respectively). The effect of bazedoxifene on BMD at other skeletal sites was similar. The increases in BMD relative to placebo remained statistically significant at all skeletal sites throughout the 5 years of treatment with bazedoxifene. After 7 years of treatment with bazedoxifene the increases in BMD relative to placebo remained statistically significant at the femoral neck, femoral trochanter, and total hip. The increase from baseline in lumbar spine BMD at 7 years in the bazedoxifene 20 mg group was not statistically greater than in the placebo group.

Discontinuation from the study was required when excessive bone loss or incident vertebral fractures occurred. Such discontinuation was statistically significant more frequently in the placebo group (4.0%) than in the bazedoxifene 20 mg (2.8%) or raloxifene 60 mg (2.1%) groups.

Osteoporosis prevention trial
The prevention study (1,583 subjects; mean age, 58 years; mean years since menopause, 11) compared BMD effects of bazedoxifene (10, 20, or 40 mg daily), raloxifene (60 mg daily), and placebo. All subjects received calcium supplementation daily; most received 600 mg calcium (e.g., Caltrate™) daily, while some received up to 1,200 mg daily. This study included subjects who had a LS or FN neck BMD T-score no less than -2.5. The median T-score ranged from -0.6 to -1.4, depending on the skeletal site.

BMD was preserved in bazedoxifene 20 mg and raloxifene 60 mg-treated subjects, while significant loss in BMD was observed in patients receiving placebo. The increase in LS BMD with bazedoxifene 20 mg and raloxifene 60 mg, compared with placebo, was significant at 6 months (1.14% and 1.26%, respectively) and was maintained through 2 years (1.41% and 1.49%, respectively). The effect of bazedoxifene on BMD at other skeletal sites was similar.

Clinical safety

Assessment of bone histomorphometry and bone turnover
In the osteoporosis treatment study in 7,492 postmenopausal women (mean age = 66 years), 121 bone biopsies were obtained from iliac crest after the administration of fluorochrome label from the subjects in bazedoxifene, raloxifene and placebo groups (bazedoxifene 20 mg = 28; bazedoxifene 40 mg = 29, raloxifene 60 mg = 32, placebo = 32) after approximately 2 or 3 years of treatment. Histological assessment of bone biopsies from all treatment groups revealed formation of normal lamellar bone in all treated subjects. There was no evidence of osteomalacia, peritrabecular or marrow fibrosis, cellular toxicity or woven bone in any of the bone-biopsy specimens in any of the treatment groups. Histomorphometric assessment revealed normal mineralisation, as evidenced by the presence of normal osteoid thickness, normal mineralisation lag time, and mineral apposition rate.

In the osteoporosis treatment study, bazedoxifene 20 mg and raloxifene 60 mg therapy resulted in a significant reduction of serum markers of bone resorption (C-telopeptide) and bone formation (osteocalcin), when compared to placebo, indicating a reduction in bone turnover. Median reductions from baseline over 25% for C-telopeptide and osteocalcin were observed with bazedoxifene therapy. Similar reductions in the rate of bone turnover have been observed in the osteoporosis prevention study.

Effects on lipid metabolism and cardiovascular system
In the osteoporosis treatment study after 3 years of treatment, bazedoxifene 20 mg and raloxifene 60 mg exhibited significant reductions in serum total cholesterol, low-density lipoprotein (LDL) cholesterol and a significant increase in high-density lipoprotein (HDL) cholesterol compared to placebo. The median percent change from baseline of total cholesterol, LDL cholesterol and HDL cholesterol with bazedoxifene 20 mg were –3.75%, –5.36% and 5.10%, respectively, and were similar to that observed with raloxifene 60 mg. The effect on triglycerides in the bazedoxifene 20 mg and raloxifene 60 mg groups was similar to placebo. This lipid profile was maintained throughout the 7 years of treatment. The treatment effect on lipids was similar in the osteoporosis prevention study. The clinical relevance of these changes has not been established.

In the osteoporosis treatment trial in 7,492 subjects (mean age = 66 years), the bazedoxifene-treated women had an increased risk of VTE (deep vein thrombosis, pulmonary embolism and retinal vein thrombosis) (see section 4.8). The highest rate of VTE per 1,000 women-years of follow up was observed during the first year: 4.64 in the bazedoxifene 20 mg group and 1.73 in the placebo group (relative risk 2.69).The rate per 1,000 women-years at 3 years was 2.86 in the bazedoxifene 20 mg group and 1.76 in the placebo group (relative risk 1.63). The rate per 1,000 women-years at 5 years was 2.34 in the bazedoxifene 20 mg group and 1.56 in the placebo group (relative risk 1.50). After 7 years the rate per 1,000 women-years was 2.06 in the bazedoxifene 20 mg group and 1.36 in the placebo group (relative risk 1.51).

Cerebrovascular effects
In the 3 year core study the rate per 1,000 women-years for ischaemic strokes was similar between the 20 mg bazedoxifene (1.98) and placebo (2.2) groups and higher in the 40 mg bazedoxifene (2.72) group. The rate per 1,000 women years for transient ischaemic attacks (TIA) was similar between the 20 mg bazedoxifene (1.1) and placebo (0.88) groups and higher in the 40 mg bazedoxifene (1.59) group.

After 5 years of treatment the rate per 1,000 women-years for ischaemic strokes was similar between the 20 mg bazedoxifene (1.87) and the placebo (2.02) groups. The rate per 1,000 women years for TIA was higher for the 20 mg bazedoxifene group (0.94) compared to placebo (0.62).

After 7 years of treatment, the rate per 1,000 women-years for ischaemic strokes was the same for the 20 mg bazedoxifene (1.78) and the placebo (1.78) groups. The rate per 1,000 women years for TIA was higher for the bazedoxifene 20 mg group (0.96) compared to placebo (0.55).

Effects on the uterus
In the osteoporosis treatment study, transvaginal ultrasonography (TVU) showed minimal changes in endometrial thickness in placebo (-0.08 mm, n=131), bazedoxifene 20 mg (-0.07 mm, n=129), and raloxifene 60 mg (0.16 mm, n=110) treated groups after 2 years. At 3 years, there were no cases of endometrial cancer and 1 case (0.1%) of endometrial hyperplasia in the bazedoxifene 20 mg-treated subjects. There was 1 case (0.1%) of endometrial cancer, 1 case of sarcoma (0.1%), and 1 case (0.1%) of endometrial hyperplasia in the raloxifene 60 mg-treated subjects. There were 3 cases (0.2%) of endometrial cancer and 1 case (0.1%) of endometrial hyperplasia in the placebo group. Endometrial polyps were diagnosed in 10 subjects in the bazedoxifene 20 mg, 17 subjects in the raloxifene 60 mg, and 11 subjects in the placebo treatment groups through month 36.

After 5 years of treatment, the endometrial thickness in the bazedoxifene 20 mg group did not change and remained similar to placebo; there were no cases of endometrial cancer in the bazedoxifene 20 mg group compared to 6 cases in the placebo group ($p<0.05$).

After 7 years of treatment, the endometrial thickness in the bazedoxifene 20 mg group did not change and remained similar to placebo; there were no cases of endometrial cancer in the bazedoxifene 20 mg group compared to 7 cases in the placebo group ($p<0.008$).

In the osteoporosis prevention study, TVU showed minimal changes from baseline in endometrial thickness in placebo (-0.24 mm, n=154), bazedoxifene 20 mg (-0.06 mm, n=158) and raloxifene 60 mg (0.01 mm, n=154) treated groups after 2 years. No cases of hyperplasia or endometrial malignancy were identified in any bazedoxifene- or raloxifene-treated subjects.

Effects on the breast
In the osteoporosis treatment study, the incidence of breast-related adverse events in the bazedoxifene group was similar to placebo at 3 years. There were 5 cases of breast cancer per 4,591 person-years of follow-up in the bazedoxifene 20 mg group (1.09 per 1,000), 7 cases of breast cancer per 4,526 person-years of follow-up in the raloxifene 60 mg group (1.55 per 1,000), and 8 cases of breast cancer per 4,604 person-years of follow-up in the placebo group (1.74 per 1,000). After 5 years of treatment, there were 9 cases of breast cancer in the bazedoxifene 20 mg group (1.40 per 1,000 women-years) and 10 cases in the placebo group (1.56 per 1,000 women-years). After 7 years of treatment, there were 13 cases of breast cancer in the bazedoxifene 20 mg group (1.78 per 1,000 women-years) and 11 cases in the placebo group (1.50 per 1,000 women-years).

In the osteoporosis prevention study, the incidence of breast-related adverse events (breast tenderness, pain, breast cancer, benign breast neoplasm) in the bazedoxifene 20 mg and raloxifene 60 mg groups was similar to placebo.

In the breast-density study, an ancillary study of the osteoporosis treatment study, 444 postmenopausal women (mean age = 59 years) with osteoporosis from all 4 treatment groups, were evaluated for mammographic breast density changes at 24 months. Mean changes in mammographic breast density

in the bazedoxifene 20 mg group were significantly reduced from baseline (-1.45 percentage points, $p<0.05$) while no changes were observed in the placebo group (-0.15 percentage points).

Effects on thyroid and ovarian malignancies
In the osteoporosis treatment study in 7,492 postmenopausal women (mean age, 66 years), among 1,886 subjects treated with bazedoxifene (20 mg), there were 5 cases of thyroid cancer (0.69 per 1,000) and among 1,885 subjects treated with placebo, there was 1 case of thyroid cancer (0.14 per 1,000) after 7 years of treatment. There were no cases on thyroid cancer in the 40 mg treatment group up to 5 years.

In the osteoporosis treatment study in 7,492 postmenopausal women (mean age, 66 years), among 1,886 subjects treated with bazedoxifene (20 mg), there were 5 cases of ovarian cancer (0.69 per 1,000) and among 1,885 subjects treated with placebo, there were 0 cases of ovarian cancer after 7 years of treatment. There was one case of ovarian cancer in the 40 mg treatment group up to 5 years.

5.2 Pharmacokinetic properties

The mean pharmacokinetic parameters of bazedoxifene after multiple doses in healthy postmenopausal ambulatory women who were naturally postmenopausal or who had undergone bilateral oophorectomy are summarised in Table 2.

Table 2. Mean ± SD pharmacokinetic parameters of bazedoxifene (n=23)

	C_{max} (ng/ml)	t_{max} (h)	$t_{½}$ (h)	AUC (ng•h/ml)	Cl/F (l/h/kg)
Multiple dose 20 mg/day	6.2 ± 2.2	1.7 ± 1.8	28 ± 11	82 ± 37	4.1 ± 1.7

Absorption

Bazedoxifene is rapidly absorbed with a t_{max} of approximately 2 hours and exhibits a linear increase in plasma concentrations for single doses from 0.5 mg up to 120 mg and multiple daily doses from 1 mg to 80 mg. The absolute bioavailability of bazedoxifene is approximately 6%.

When single doses of 20 mg bazedoxifene were administered with a high-fat meal, C_{max} and AUC increased by 28% and 22%, respectively. An additional study evaluating the effects of a standardised medium-fat meal on the pharmacokinetics of bazedoxifene at steady-state showed a 42% and 35% increase in C_{max} and AUC, respectively, when 20 mg bazedoxifene was administered with food. Because these changes are not considered clinically relevant, bazedoxifene can be administered without regard to meals.

Distribution

Following intravenous administration of a 3 mg dose of bazedoxifene, the volume of distribution is 14.7 ± 3.9 l/kg. Bazedoxifene is highly bound (98% - 99%) to plasma proteins *in vitro*.

Biotransformation

The metabolic disposition of bazedoxifene in postmenopausal women has been determined following oral administration of 20 mg of radio-labelled bazedoxifene. Bazedoxifene is extensively metabolised in women. Glucuronidation is the major metabolic pathway. Little or no cytochrome P450-mediated metabolism is evident. Bazedoxifene-5-glucuronide is the major circulating metabolite. The concentrations of this glucuronide are approximately 10-fold higher than those of unchanged active substance in plasma.

Elimination

Bazedoxifene is eliminated with a half-life of approximately 30 hours. Steady-state concentrations are achieved by the second week of once-daily administration. The apparent oral clearance of

bazedoxifene is approximately 4 to 5 l/h/kg. The major route of excretion of radio-labelled bazedoxifene is the faeces, and less than 1% of the dose is eliminated in urine.

Special populations

Hepatic impairment
The disposition of a single 20 mg dose of bazedoxifene was compared in patients with hepatic impairment [Child-Pugh Class A (n=6), B (n=6), and C (n=6)] and subjects with normal hepatic function (n=18). On average, patients with hepatic impairment showed a 4.3-fold increase in AUC compared with controls. Safety and efficacy have not been evaluated further in patients with hepatic insufficiency. Use in this patient population is not recommended (see sections 4.2 and 4.4).

Renal impairment
Limited clinical data (n=5) are available in subjects with moderate renal impairment (CrCl < 50 ml/min). A single 20 mg dose of bazedoxifene was administered to these subjects. Negligible amounts of bazedoxifene were eliminated in urine. Impaired renal function showed little or no influence on bazedoxifene pharmacokinetics, and no dosing adjustment is required.

Elderly patients
The pharmacokinetics of a 20 mg single-dose of bazedoxifene were evaluated in a study in 26 healthy postmenopausal women. On average, compared to women 51 to 64 years of age (n=8), women 65 to 74 years of age (n=8) showed a 1.5-fold increase in AUC, and women >75 years of age (n=8) showed a 2.3-fold increase in AUC. This increase was most likely attributed to age-related changes in hepatic function. No dose adjustment is necessary based on age.

Paediatric population
The pharmacokinetics of bazedoxifene have not been studied in the paediatric population.

Race
No pharmacokinetic differences based on ethnic group were observed.

5.3 Preclinical safety data

In rabbit studies, abortion and an increased incidence of heart (ventricular septal defect) and skeletal system (ossification delays, misshapen or misaligned bones, primarily of the spine and skull) anomalies in the foetuses were present at maternally toxic doses of ≥0.5 mg/kg/day (1.5 times the human exposure). Treatment of rats at maternally toxic doses ≥1 mg/kg/day (≥0.3 times the human exposure) resulted in reduced numbers of live foetuses and/or reductions in foetal body weights. No foetal developmental anomalies were observed.

Female rats were administered daily doses of 0.3 to 30 mg/kg (0.03 to 8 times the human exposure) prior to and during mating with untreated males. Oestrous cycles and fertility were adversely affected in all bazedoxifene-treated female groups.

The effects of bazedoxifene treatment on bone, uterus, and mammary gland were assessed in ovariectomised rats (0.15 to 1.5 mg/kg/day) and non-human primates [*Cynomolgus macaques*] (0.2 to 25.0 mg/kg/day). In rats, treatment with bazedoxifene for approximately one year partially prevented the effects of ovariectomy on numerous skeletal parameters (bone mineral content, bone mineral density, and architecture). Additionally, uterine wet weights were reduced compared with untreated animals and histologic evaluation demonstrated little to no difference from the untreated controls. In monkeys, treatment with bazedoxifene for 18 months resulted in the partial preservation of cortical and cancellous bone mass as determined by BMD measurements. The partial preservation of bone mass was achieved by reductions in the ovariectomy-induced increases in bone turnover, evaluated by biochemical markers of bone turnover and histomorphometric indices measured in cancellous and cortical bone. Importantly, in both species, the administration of bazedoxifene had no deleterious effects on bone quality. Like the rodent results, bazedoxifene treatment in non-human primates

resulted in uterine and mammary gland atrophy without other histological differentiation from untreated animals.

Repeated-dose studies in normally cycling rodents and cynomolgus monkeys revealed a marked stimulation of ovarian follicle growth without ovulation, leading to partly haemorrhagic-ovarian cysts and markedly elevated estradiol levels. This pharmacological effect of bazedoxifene can also be expected in pre-menopausal women, but is considered clinically irrelevant in post-menopausal women.

In 6-month carcinogenicity studies in transgenic mice, there was an increased incidence of benign, ovarian granulosa-cell tumours in female mice given 150 or 500 mg/kg/day. Systemic exposure (AUC) to bazedoxifene in these groups was 35 and 69 times that in postmenopausal women administered 20 mg/day for 14 days.

In a 2-year carcinogenicity study in rats, an increased incidence of benign, ovarian granulosa-cell tumours was observed in female rats at dietary concentrations of 0.03 and 0.1%. Systemic exposure (AUC) of bazedoxifene in these groups was 2.6 and 6.6 times that observed in postmenopausal women administered 20 mg/day for 14 days.

The observation of benign, ovarian granulosa-cell tumours in female mice and rats administered bazedoxifene is a class effect of SERMs, related to its pharmacology in rodents when treated during their reproductive lives, when their ovaries are functional and responsive to hormonal stimulation.

Bazedoxifene was not genotoxic or mutagenic in a battery of tests, including *in vitro* bacterial reverse mutation assay, *in vitro* mammalian cell forward mutation assay at the thymidine kinase (TK±) locus in L5178Y mouse lymphoma cells, *in vitro* chromosome aberration assay in Chinese hamster ovary (CHO) cells, and *in vivo* mouse micronucleus assay.

Bazedoxifene caused corticomedullar nephrocalcinosis and enhanced spontaneous chronic progressive nephropathy (CPN) in male rats. Urine parameters were pathologically changed. In long-term studies renal tumours (adenomas and carcinomas) were observed at all doses tested, most likely as a consequence of this chronic renal damage. In the 2-year carcinogenicity study, bazedoxifene, administered orally in the diet to rats at doses of 0, 0.003%, 0.01%, 0.03%, or 0.1%, resulted in exposures, based on surface area (mg/m^2) of approximately 0.6 to 23 times and 0.9 to 31 times in males and females, respectively, the clinical dose of 20 mg. Since chronic progressive nephropathy and corticomedullar nephrocalcinosis are most likely rat-specific nephropathies, these findings are presumably not relevant for humans.

In an 18-month bone efficacy study in aged ovariectomised cynomolgus monkeys, bazedoxifene, administered orally to monkeys at doses of 0, 0.2, 0.5, 1, 5, or 25 mg/kg/day, resulted in exposures, based on surface area (mg/m^2) of approximately 0.2 to 24 times the clinical dose of 20 mg. Renal cell carcinomas were observed in this study. These tumours are considered as spontaneous renal cell carcinomas that are known to occur in nonhuman primates and are unlikely to be relevant to humans.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core
Lactose monohydrate
Microcrystalline cellulose
Pregelatinised starch (maize)
Sodium starch glycolate
Sodium lauryl sulfate

Colloidal anhydrous silica
Magnesium stearate
Ascorbic acid

Film coating
Hypromellose
Titanium dioxide (E171)
Macrogol 400

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

18 months.

6.4 Special precautions for storage

Do not store above 25°C.

6.5 Nature and contents of container

PVC/Aclar blister packs of 7, 28, 30, 84, and 90 film-coated tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Pfizer Europe MA EEIG
Boulevard de la Plaine 17
1050 Bruxelles
Belgium

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/09/511/001
EU/1/09/511/002
EU/1/09/511/003
EU/1/09/511/004
EU/1/09/511/005

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 17 April 2009

Date of latest renewal: 17 April 2014

10. DATE OF REVISION OF THE TEXT

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

ANNEX II

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

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

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

Pfizer Ireland Pharmaceuticals Unlimited Company
Little Connell
Newbridge
County Kildare
Ireland

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to medical prescription.

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

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

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON TEXT

1. NAME OF THE MEDICINAL PRODUCT

CONBRIZA 20 mg film-coated tablets
bazedoxifene

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains bazedoxifene acetate equivalent to 20 mg bazedoxifene.

3. LIST OF EXCIPIENTS

Also contains lactose.
See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablet

7 film-coated tablets
28 film-coated tablets
30 film-coated tablets
84 film-coated tablets
90 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use.

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

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 25ºC.

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 Europe MA EEIG
Boulevard de la Plaine 17
1050 Bruxelles
Belgium

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/09/511/001 28 tablets
EU/1/09/511/002 30 tablets
EU/1/09/511/003 84 tablets
EU/1/09/511/004 90 tablets
EU/1/09/511/005 7 tablets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

CONBRIZA

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN

NN

MINIMUM PARTICULARS TO APPEAR ON BLISTERS AND STRIPS

BLISTER

1. NAME OF THE MEDICINAL PRODUCT

CONBRIZA 20 mg film-coated tablets
bazedoxifene

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Pfizer Europe MA EEIG

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

B. PACKAGE LEAFLET

Package Leaflet: Information for the patient

CONBRIZA 20 mg film-coated tablets
bazedoxifene

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

What is in this leaflet:

1. What CONBRIZA is and what it is used for

CONBRIZA contains the active substance bazedoxifene, and is a medicine that belongs to a group of non-hormonal medicines called Selective Oestrogen Receptor Modulators (SERMs). It is used for the treatment of osteoporosis in women after they have reached menopause, when they are at an increased risk of fractures. It works by slowing or stopping the thinning of bone in these women. This medicine should not be used for the treatment of osteoporosis in men.

2. What you need to know before you take CONBRIZA

Do not take CONBRIZA

- if you are allergic to bazedoxifene or any of the other ingredients of this medicine (listed in section 6).
- if you have or have had a blood clot (for example, in the blood vessels in your legs, lungs, or eyes).
- if you are pregnant or could still become pregnant. This medicine may cause harm to your unborn child if taken during pregnancy.
- if you have any unexplained vaginal bleeding. This must be investigated by your doctor.
- if you have active uterine cancer.

Warnings and precautions

Talk to your doctor or pharmacist before taking CONBRIZA

- as it may increase your risk of getting blood clots. While very infrequent, these clots can cause serious medical problems, disability or death. Speak with your doctor to see if you are at increased risk for blood clots.
- if you are immobile (unable to move) for some time, such as being wheel-chair bound, sitting for a prolonged period of time or having to stay in bed while recovering from an operation or illness. If you are traveling on long trips, you should walk around or exercise your legs and feet

at regular intervals. 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. If you need to remain immobile for an extended period of time or are scheduled to have surgery, it is important for you to talk to your doctor about ways you can reduce the risk of blood clots.
- if you are pre-menopausal. CONBRIZA has only been studied in women who have reached menopause, and therefore is not recommended.
- if you have had increased levels of triglycerides (a type of fat found in your blood) in the past.
- if you have liver or severe kidney problems.
- if you have any vaginal bleeding while you take CONBRIZA, you should speak with your doctor.
- if you are suffering from breast cancer, as there is insufficient experience with this medicine use in women with this disease.

The above are some reasons why this medicine may not be suitable for you. If any of them apply to you, talk to your doctor before you take the medicine.

Other medicines and CONBRIZA

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

Pregnancy and breast-feeding

CONBRIZA is for use only by postmenopausal women. It must not be taken by women who are pregnant or who could still have a baby. Do not take this medicine if you are breast-feeding, because it is not known whether it is excreted in mother's milk.

Driving and using machines

If you feel drowsy after taking this medicine, you should avoid driving or operating machines.

You may notice problems with your eyesight such as blurred vision while taking this medicine. If this happens, you should avoid driving or operating machines until your doctor tells you that it is safe to do so.

CONBRIZA contains lactose and sodium

This medicine contains lactose (a type of sugar). If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicine. This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially ‘sodium-free’.

3. How to take CONBRIZA

Always take this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure. You should continue taking this medicine as long as your doctor tells you to. In order for this medicine to treat osteoporosis, it must be taken daily.

- The recommended dose is one tablet by mouth daily. Taking more than one tablet daily is not more effective and may carry additional risks.
- You can take the tablet at any time of the day, with or without food.
- This medicine should be taken with an adequate amount of calcium and vitamin D. Consult your doctor to see if your dietary calcium and vitamin D intake is adequate and whether you need calcium and vitamin D supplementation. If you take supplemental calcium and/or vitamin D, it may be taken at the same time as this medicine.

If you take more CONBRIZA than you should

Tell your doctor or pharmacist if you accidentally take more CONBRIZA than you should.

If you forget to take CONBRIZA

If you forget to take a tablet, take it as soon as you remember. However, if it is almost time to take your next dose of this medicine, skip the dose you missed and only take your next scheduled dose. Do not take a double dose to make up for a forgotten tablet.

If you stop taking CONBRIZA

If you decide to stop taking this medicine before finishing the prescribed course of treatment, you should talk to your doctor first.

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

4. Possible side effects

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

Serious side effects – Stop taking CONBRIZA and see a doctor immediately

Uncommon (may affect up to 1 in 100 people):

- If you have signs of a blood clot in the legs or lungs, such as painful swelling and redness of the legs, sudden chest pain, or difficulty in breathing;
- If you have signs of a blood clot in the eye (retinal vein), such as one sided visual disturbance or visual impairment or blurring or loss of vision in one eye.
- If you get any of the problems listed under '**Do not take CONBRIZA'**

Not known (frequency cannot be estimated from the available data):

- If you have other events affecting the eye and/or vision (seeing sparks or flashes of light, narrowing of visual field, and swelling of eye or eyelid)

Other side effects

Some patients have experienced the following side effects while taking CONBRIZA:

Very common (may affect more than 1 in 10 people):

- Muscle spasms (includes leg cramps)
- Hot flushes
- Swelling of the hands, feet and legs (peripheral oedema)

Common (may affect up to 1 in 10 people):

- Allergic reaction (including hypersensitivity and urticaria)
- Rash, itching
- Dry mouth
- Increase in blood triglycerides (fat found in your blood)
- Increase in liver enzymes
- Drowsiness

Not known (frequency cannot be estimated from the available data):

- Palpitations (awareness of your heart beat)
- Dry eye, eye pain, visual acuity reduced, visual impairment, blepharospasm (abnormal, involuntary blinking or spasm of the eyelids).

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

5. How to store CONBRIZA

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

Do not use this medicine after the expiry date which is stated on the carton and blister after EXP. The expiry date refers to the last date of that month.

Do not store above 25°C.

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

6. Contents of the pack and other information

What CONBRIZA contains

- The active substance is bazedoxifene. Each film-coated tablet contains bazedoxifene acetate equivalent to 20 mg bazedoxifene.
- The other ingredients are lactose monohydrate, microcrystalline cellulose, pregelatinised starch (maize), sodium starch glycolate, sodium lauryl sulfate, colloidal anhydrous silica, magnesium stearate, ascorbic acid, hypromellose, titanium dioxide (E171) and macrogol 400 (see section 2 “CONBRIZA contains lactose and sodium”).

What CONBRIZA looks like and contents of the pack

CONBRIZA is supplied as a white to off-white, capsule-shaped, film-coated tablet marked with “WY20”. The tablet is approximately 1.5 cm in length. They are packed in PVC/Aclar blisters and are available in packs of 7, 28, 30, 84 or 90 tablets.

Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer

Marketing Authorisation Holder
Pfizer Europe MA EEIG, Boulevard de la Plaine 17, 1050 Bruxelles, Belgium.

Manufacturer
Pfizer Ireland Pharmaceuticals Unlimited Company, Little Connell, Newbridge, County Kildare, Ireland.

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

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

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