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: each film-coated tablet contains 142.8 mg lactose monohydrate

For a 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”.

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**

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

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

Oral use.

**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 patients**
Bazedoxifene is not indicated for use in paediatric patients.
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.

CONBRIZA is only 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 (see section 4.8). The risk factors associated with venous thromboembolism (VTE) cases in clinical trials included: advanced age, obesity, immobilisation, surgery, major trauma and malignancy. It 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.

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).

CONBRIZA 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

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 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 Pregnancy and lactation

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.

It is not known whether bazedoxifene is excreted in human milk. Bazedoxifene is not intended for use in breast-feeding women.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive or use machines have been performed. However, in clinical trials, somnolence was reported as an adverse reaction, and patients should be advised on the potential effect on driving and using machines.

4.8 Undesirable effects

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).

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Very common ( ≥1/10); Common ( ≥1/100 to <1/10); Uncommon ( ≥1/1,000 to <1/100); Rare ( ≥1/10,000 to <1/1,000); Very Rare (<1/10,000).

Immune system disorders

Common: Hypersensitivity

Nervous system disorders

Common: Somnolence
Eye disorders

Rare: Retinal vein thrombosis*

Vascular disorders

Very common: Hot flushes
Uncommon: Deep vein thrombosis*
Superficial thrombophlebitis

Respiratory, thoracic and mediastinal disorders

Uncommon: Pulmonary embolism*

Gastrointestinal disorders

Common: Dry mouth

Skin and subcutaneous tissue disorders

Common: Urticaria

Musculoskeletal, connective tissue and bone disorders

Very common: Muscle spasms (includes leg cramps)

General disorders and administration site conditions

Common: Peripheral oedema

Investigations

Common: Increased blood triglycerides, increased alanine aminotransferase; increased aspartate aminotransferase

*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 3.23 in the bazedoxifene 20 mg group and 1.72 in placebo. The relative risk was 1.9 through the 3-year study period. The relative risk decreased over the three years studied (year 1=3.0, year 2=2.5, year 3=0.3). Other venous thromboembolic events could also occur.

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: Selective estrogen receptor modulator, ATC code: G03XC02.

Bazedoxifene belongs to a class of compounds known as selective estrogen 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 remodeling 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.

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. 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 36 months of treatment with bazedoxifene 20 mg and raloxifene 60 mg 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 36 months of treatment |
|-----------------------------------------------|-----------------|-----------------|-----------------|-----------------|
| Number of subjects                           | Number (%)a of subjects with new vertebral fracture | Number (%)a of subjects with ≥1 new vertebral fracture | Number (%)a of subjects with ≥1 new vertebral fracture |
| Bazedoxifene 20 mg                            | n=1,724         | n=1,741         | n=967           | n=981           |
| Placebo                                       | 35 (2.34%)      | 13 (1.98%)      | 22 (2.63%)      |
| Absolute risk reduction                      | 1.73%           | 1.15%           | 2.17%           |
| Relative risk reduction (95% CI)              | 42%b (11%, 62%) | 35%c            | 45%d (6%, 68%) |

a Kaplan-Meier rate estimates
b p-value=0.015
c p-value=0.22
d p-value=0.035

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 36 months (1.32% and 2.08%, respectively). The effect of bazedoxifene on BMD at other skeletal sites was similar.

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.

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 24 months (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 24 or 36 months 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
In the osteoporosis treatment study after 36 months 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. The clinical relevance of these changes has not been established. The treatment effect on lipids was similar in the osteoporosis prevention study.

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 24 months. At 36 months, 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.

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 24 months. 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 36 months. 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).

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.

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 summarized in Table 2.

<table>
<thead>
<tr>
<th></th>
<th>C&lt;sub&gt;max&lt;/sub&gt; (ng/ml)</th>
<th>t&lt;sub&gt;max&lt;/sub&gt; (h)</th>
<th>t&lt;sub&gt;1/2&lt;/sub&gt; (h)</th>
<th>AUC (ng·h/ml)</th>
<th>Cl/F (l/h/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multiple dose</td>
<td></td>
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</tr>
<tr>
<td>20 mg/day</td>
<td>6.2 ± 2.2</td>
<td>1.7 ± 1.8</td>
<td>28 ± 11</td>
<td>82 ± 37</td>
<td>4.1 ± 1.7</td>
</tr>
</tbody>
</table>

Absorption
Bazedoxifene is rapidly absorbed with a t<sub>max</sub> 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<sub>max</sub> and AUC increased by 28% and 22%, respectively. An additional study evaluating the effects of a standardized medium-fat meal on the pharmacokinetics of bazedoxifene at steady-state showed a 42% and 35%
increase in $C_{\text{max}}$ 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 (95.8% - 99.3%) to plasma proteins *in vitro*.

**Metabolism**

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 insufficiency**

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 insufficiency**

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 patients**

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 \( \geq 0.5 \text{ mg/kg/day} \) (1.5 times the human exposure). Treatment of rats at maternally toxic doses \( \geq 1 \text{ mg/kg/day} \) (\( \geq 0.3 \) 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 ovariectomized 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 estriadiol 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 \textit{in vitro} bacterial reverse mutation assay, \textit{in vitro} mammalian cell forward mutation assay at the thymidine kinase (TK\(^\pm\)) locus in L5178Y mouse lymphoma cells, \textit{in vitro} chromosome aberration assay in Chinese hamster ovary (CHO) cells, and \textit{in vivo} mouse micronucleus assay.

Bazedoxifene caused corticomedullary 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 dosages 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 ovariectomized cynomolgus monkeys, bazedoxifene, administered orally to monkeys at dosages of 0, 0.2, 0.5, 1, 5, or 25 mg/kg/day, resulted in exposures, based on surface area (mg/m²) 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:
Hypermellose
Titanium dioxide (E171)
Macrogol 400

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

Do not store above 25°C.

6.5 Nature and contents of container

PVC/Aclar blister packs of 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

Wyeth Europa Ltd.
Huntercombe Lane South
Taplow, Maidenhead
Berkshire SL6 0PH
United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

EMEA/H/C/000913/001
EMEA/H/C/000913/002
EMEA/H/C/000913/003
EMEA/H/C/000913/004

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: {DD/MM/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

C. SPECIFIC OBLIGATIONS TO BE FULFILLED BY THE MARKETING AUTHORISATION HOLDER
A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURING AUTHORISATION HOLDER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

Wyeth Medica Ireland
Little Connell
Newbridge
County Kildare
Republic of Ireland

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

Not applicable.

• OTHER CONDITIONS

The MAH must ensure that the system of pharmacovigilance, as described in version 2.0 presented in Module 1.8.1. of the Marketing Authorisation, is in place and functioning before and whilst the product is on the market.

The MAH commits to performing the studies and additional pharmacovigilance activities detailed in the Pharmacovigilance Plan, as agreed in version 2.5 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

The MAH will submit 6-monthly PSURs unless otherwise specified by the CHMP.

C. SPECIFIC OBLIGATIONS TO BE FULFILLED BY THE MARKETING AUTHORISATION HOLDER

None
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

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

### 5. Method and route(s) of administration

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

### 8. Expiry date

EXP

### 9. Special storage conditions

Do not store above 25°C.
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

Wyeth Europa Ltd.
Huntercombe Lane South
Taplow, Maidenhead
Berkshire SL6 0PH
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EMEA/H/C/000913/001 28 tablets
EMEA/H/C/000913/002 30 tablets
EMEA/H/C/000913/003 84 tablets
EMEA/H/C/000913/004 90 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
<table>
<thead>
<tr>
<th>MINIMUM PARTICULARS TO APPEAR ON BLISTERS AND STRIPS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>BLISTER</strong></td>
</tr>
<tr>
<td><strong>1. NAME OF THE MEDICINAL PRODUCT</strong></td>
</tr>
<tr>
<td>CONBRIZA 20 mg film-coated tablets</td>
</tr>
<tr>
<td>Bazedoxifene</td>
</tr>
<tr>
<td><strong>2. NAME OF THE MARKETING AUTHORISATION HOLDER</strong></td>
</tr>
<tr>
<td>Wyeth</td>
</tr>
<tr>
<td><strong>3. EXPIRY DATE</strong></td>
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<tr>
<td>EXP</td>
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<tr>
<td><strong>4. BATCH NUMBER</strong></td>
</tr>
<tr>
<td>Lot</td>
</tr>
<tr>
<td><strong>5. OTHER</strong></td>
</tr>
</tbody>
</table>
B. PACKAGE LEAFLET
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 CONBRIZA is and what it is used for
2. Before you take CONBRIZA
3. How to take CONBRIZA
4. Possible side effects
5. How to store CONBRIZA
6. Further information

1. WHAT CONBRIZA IS AND WHAT IT IS USED FOR

CONBRIZA is a medicine that belongs to a group of non-hormonal medicines called Selective Estrogen 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.

2. BEFORE YOU TAKE CONBRIZA

Do not take CONBRIZA

- if you are allergic (hypersensitive) to bazedoxifene or any of the other ingredients of CONBRIZA (see 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.

Take special care with 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 product may not be suitable for you. If any of them apply to you, talk to your doctor before you take the medicine.

**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.

**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 CONBRIZA 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 CONBRIZA, you should avoid driving or operating machines.

**Important information about some of the ingredients of CONBRIZA**

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 medicinal product.

3. **HOW TO TAKE CONBRIZA**

Always take CONBRIZA exactly as your doctor has told you. You should 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 CONBRIZA to treat osteoporosis, it must be taken daily.

- The usual dose is one tablet by mouth daily.
- You can take the tablet at any time of the day, with or without food.
- CONBRIZA 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 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 CONBRIZA, 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 have any further questions on the use or stopping the use of this product, ask your doctor or pharmacist.

4. POSSIBLE SIDE EFFECTS

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

The frequency of possible side effects listed below is defined using the following convention:
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 spasms (includes leg cramps)
- Hot flushes

**Common** side effects:
- Allergic reaction (including hypersensitivity and urticaria)
- Dry mouth
- Increase in blood triglycerides (fat found in your blood)
- Increase in liver enzymes
- Swelling of the hands, feet and legs (peripheral oedema)
- Drowsiness

**Uncommon** side effects:
- Blood clot in the leg
- Blood clot in the lungs

**Rare** side effects:
- Blood clot in the eye (retinal vein)

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 CONBRIZA**

Keep out of the reach and sight of children.

Do not use CONBRIZA 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.

6. **FURTHER 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, pre-gelatinised starch (maize), sodium starch glycolate, sodium lauryl sulfate, colloidal anhydrous silica, magnesium stearate, ascorbic acid, hypromellose, titanium dioxide (E171) and macrogol 400.

**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”. They are packed in PVC/Aclar blisters and are available in packs of 28, 30, 84 or 90 tablets.

Not all pack sizes may be marketed.

**Marketing Authorisation Holder and Manufacturer**

Marketing Authorisation Holder: Wyeth Europa Limited, Huntercombe Lane South, Taplow, Maidenhead, Berkshire SL6 0PH, United Kingdom.

Manufacturer: Wyeth Medica Ireland, Little Connell Newbridge, County Kildare, Ireland.

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

- **België/Belgique/Belgien**
  Wyeth Pharmaceuticals S.A./N.V.
  Tél/Tel:+32 10 49 47 11
  Fax:+32 10 49 48 70

- **Česká republika**
  Wyeth Whitehall Czech s.r.o.
  Tel:+420 2 67 294 111
  Fax:+420 2 67 294 199

- **Danmark**
  Wyeth Danmark
  Tlf:+45 44 88 88 05
  Fax:+45 44 88 88 06

- **Kύπρος**
  Wyeth Hellas (Cyprus Branch) AEBE
  Τηλ/+357 22 817690
  Φαξ/+357 22 751855

- **Magyarország**
  Wyeth Kft.
  Tel:+36 1 453 33 30
  Fax:+36 1 240 4632

- **Malta**
  Vivian Corporation Ltd.
  Tel:+356 21344616
  Fax:+356 21341087
This leaflet was last approved in {MM/YYYY}.

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