ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS
1. **NAME OF THE MEDICINAL PRODUCT**

DUAVIVE 0.45 mg/20 mg modified-release tablets

2. **QUALITATIVE AND QUANTITATIVE COMPOSITION**

Each modified-release tablet contains 0.45 mg of conjugated oestrogens and bazedoxifene acetate equivalent to 20 mg bazedoxifene.

Excipients with known effect:

Each modified-release tablet contains 96.9 mg sucrose (includes 0.7 mg sucrose as sucrose monopalmitate), 59.8 mg lactose (as monohydrate) and 0.2 mg maltitol liquid.

For the full list of excipients, see section 6.1.

3. **PHARMACEUTICAL FORM**

Modified-release tablet.

Pink, oval-shaped, modified-release tablet of 12 mm printed on one side with “0.45/20”.

4. **CLINICAL PARTICULARS**

4.1 **Therapeutic indications**

DUAVIVE is indicated for:

Treatment of oestrogen deficiency symptoms in postmenopausal women with a uterus (with at least 12 months since the last menses) for whom treatment with progestin-containing therapy is not appropriate.

The experience treating women older than 65 years is limited.

4.2 **Posology and method of administration**

**Posology**

For initiation and continuation of treatment of postmenopausal symptoms, the lowest effective dose for the shortest duration (see also section 4.4) should be used.

The recommended dose for DUAVIVE is 0.45 mg conjugated oestrogens (CE) and 20 mg bazedoxifene taken as a single oral tablet, once daily.

If a tablet is forgotten, it should be taken as soon as the patient remembers. Therapy should then be continued as before. If more than one tablet has been forgotten, only the most recent tablet should be taken, the patient should not take double the usual dose to make up for missed tablets.
Special populations

Elderly population
DUAVIVE has not been studied in women over 75 years of age. Based on available data no dosage adjustment is necessary based on age (see section 5.2). The experience treating women older than 65 years is limited.

Renal impairment
The pharmacokinetics of CE/bazedoxifene have not been evaluated in patients with renal impairment. Use in this population is therefore not recommended (see sections 4.4 and 5.2).

Hepatic impairment
The safety and efficacy of CE/bazedoxifene have not been evaluated in patients with hepatic impairment. Use in this population is contraindicated (see sections 4.3, 4.4 and 5.2).

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

Method of administration

Oral use.

DUAVIVE may be taken at any time of day, without regard to meals (see section 5.2). Tablets should be swallowed whole.

4.3 Contraindications

- Hypersensitivity to the active substances or to any of the excipients listed in section 6.1.
- Known, suspected, or past history of breast cancer.
- Known, past or suspected oestrogen-dependent malignant tumours (e.g., endometrial cancer).
- Undiagnosed genital bleeding.
- Untreated endometrial hyperplasia.
- Active or past history of venous thromboembolism (e.g., deep venous thrombosis, pulmonary embolism, and retinal vein thrombosis).
- Known thrombophilic disorders (e.g., protein C, protein S, or antithrombin deficiency, see section 4.4).
- Active or past history of arterial thromboembolic disease (e.g., myocardial infarction, stroke).
- Acute liver disease or a history of liver disease as long as liver function tests have failed to return to normal.
- DUAVIVE is only indicated for use in postmenopausal women and must not be taken by women of childbearing potential (see sections 4.6 and 5.3).
- Porphyria.

4.4 Special warnings and precautions for use

For the treatment of postmenopausal symptoms, DUAVIVE should only be initiated for symptoms that adversely affect quality of life. In all cases, a careful appraisal of the risks and benefits should be undertaken at least annually, and treatment should only be continued as long as the benefit outweighs the risk.

Women taking DUAVIVE should not be taking progestins, additional oestrogens or selective oestrogen receptor modulators (SERMs).

DUAVIVE has not been studied in the treatment of premature menopause.
Medical examination/follow-up

Before initiating or reinstituting treatment with DUAVIVE, a complete personal and family medical history should be taken. Physical (including pelvic and breast) examination should be guided by this and by the contraindications and warnings for use. During treatment, periodic check-ups are recommended of a frequency and nature adapted to the individual woman. Women should be advised what changes in their breasts should be reported to their doctor or nurse (see ‘Breast cancer’ below). Investigations, including appropriate imaging tools, e.g., mammography, should be carried out in accordance with currently accepted screening practices, modified to the clinical needs of the individual.

Conditions which need supervision

If any of the following conditions are present, have occurred previously, and/or have been aggravated during pregnancy or previous hormone treatment, the patient should be closely supervised. It should be taken into account that these conditions may recur or be aggravated during treatment with DUAVIVE, in particular:

- Leiomyoma (uterine fibroids) or endometriosis
- Risk factors for thromboembolic disorders (see below)
- Risk factors for oestrogen-dependent tumours, e.g., 1™ degree heredity for breast cancer
- Hypertension
- Liver disorders (e.g., liver adenoma)
- Diabetes mellitus with or without vascular involvement
- Cholelithiasis
- Migraine or (severe) headache
- Systemic lupus erythematosus
- A history of endometrial hyperplasia (see below)
- Epilepsy
- Asthma
- Otosclerosis

Reasons for immediate withdrawal of therapy

Therapy should be discontinued in case a contraindication is discovered (e.g., venous thromboembolism, stroke, and pregnancy) and in the following situations:

- Jaundice or deterioration in liver function
- Significant increase in blood pressure
- New onset of migraine-type headache

Endometrial hyperplasia and carcinoma

In women with an intact uterus, the risk of endometrial hyperplasia and carcinoma is increased when oestrogens are administered alone for prolonged periods. The reported increase in endometrial cancer risk among oestrogen-only users varies from 2- to 12-fold greater compared with non-users, depending on duration of treatment and oestrogen dose. After stopping treatment, risk may remain elevated for at least 10 years. Women taking DUAVIVE should not take additional oestrogens as this may increase the risk of endometrial hyperplasia and endometrial carcinoma.

The addition of bazedoxifene in DUAVIVE reduces the risk of endometrial hyperplasia, which may be a precursor of endometrial carcinoma.

Break-through bleeding and spotting may occur during treatment. If break-through bleeding or spotting appears after some time on therapy, or continues after treatment has been discontinued, the
reason should be investigated, which may include endometrial biopsy to exclude endometrial malignancy.

**Breast cancer**

The overall evidence suggests a possible increased risk of breast cancer in women taking oestrogen-only therapy that is dependent on the duration of therapy.

The Women’s Health Initiative (WHI) trial found no increase in the risk of breast cancer in hysterectomised women using oestrogen-only therapy.

Observational studies have mostly reported a small increase in risk of having breast cancer diagnosed that is substantially lower than that found in users of oestrogen-progestagen combinations (see section 4.8). The excess risk becomes apparent within a few years of use but returns to baseline within a few (at most five) years after stopping treatment.

The effect of DUAVIVE on the risk of breast cancer is unknown.

**Ovarian cancer**

Ovarian cancer is much rarer than breast cancer. Long-term (at least 5-10 years) use of oestrogen-only therapy has been associated with a slightly increased risk of ovarian cancer (see section 4.8).

The effect of DUAVIVE on the risk of ovarian cancer is unknown.

**Venous thromboembolism (VTE)**

In clinical trials of up to 2 years duration in postmenopausal women with CE/bazedoxifene, cases of VTE have been reported (see section 4.8). Should a VTE event occur or be suspected, DUAVIVE should be discontinued immediately.

SERMs (including bazedoxifene) and oestrogens individually increase the risk of VTE (see section 4.8).

Hormone therapy is associated with a 1.3-3 fold risk of developing VTE. The occurrence of such an event is more likely in the first year of HRT than later (see section 4.8).

Patients with known thrombophilic states have an increased risk of VTE and hormone therapy may add to this risk. DUAVIVE is contraindicated in these patients (see section 4.3).

Generally recognised risk factors for VTE include, use of oestrogens, older age, major surgery, prolonged immobilisation, obesity (BMI > 30 kg/m²), pregnancy/postpartum period, systemic lupus erythematosus (SLE), and cancer. There is no consensus about the possible role of varicose veins in VTE. As in all postoperative patients, prophylactic measures need be considered to prevent VTE following surgery. If prolonged immobilisation is to follow elective surgery temporarily stopping DUAVIVE 4 to 6 weeks earlier is recommended. Treatment should not be restarted until the woman is completely mobilised. In addition, women taking DUAVIVE should be advised to move about periodically during travel involving prolonged immobilisation.

In women with no personal history of VTE but with a first-degree relative with a history of thrombosis at young age, screening may be offered after careful counselling regarding its limitations (only a proportion of thrombophilic defects are identified by screening). If a thrombophilic defect is identified which segregates with thrombosis in family members or if the defect is ‘severe’ (e.g., antithrombin, protein S, or protein C deficiencies or a combination of defects) hormone therapy is contraindicated.

Women already on chronic anticoagulant treatment require careful consideration of the benefit risk of use of hormone therapy.
If VTE develops after initiating therapy, or is suspected, DUAVIVE should be discontinued immediately. Women should be told to contact their doctors immediately when they are aware of a potential thromboembolic symptom (e.g., painful swelling of a leg, sudden pain in the chest, dyspnoea).

Coronary artery disease (CAD)

There is no evidence from randomised controlled trials of protection against myocardial infarction in women with or without existing CAD who received oestrogen-only therapy. Randomised controlled data found no increased risk of CAD in hysterectomised women using oestrogen-only therapy.

Ischaemic stroke

Oestrogen-only therapy is associated with an up to 1.5-fold increase in risk of ischaemic stroke. The relative risk does not change with age or time since menopause. However, as the baseline risk of stroke is strongly age-dependent, the overall risk of stroke in women who use hormone therapy will increase with age (see section 4.8).

The effect of DUAVIVE on the risk of stroke is unknown.

Should a stroke occur or be suspected, DUAVIVE should be discontinued immediately (see section 4.3).

Other conditions

- Oestrogens may cause fluid retention, and therefore patients with cardiac or renal dysfunction should be carefully monitored when being treated with DUAVIVE.

- Patients with terminal renal insufficiency should be closely monitored, since it is expected that the level of circulating oestrogens components of DUAVIVE will be increased. Use in this population is not recommended (see sections 4.2 and 5.2).

- Women with pre-existing hypertriglyceridaemia should be followed closely during treatment with oestrogens, since rare cases of large increases of plasma triglycerides leading to pancreatitis have been reported with oestrogen therapy in this condition. CE/bazedoxifene has not been studied in women with baseline triglyceride levels >300 mg/dL (>3.4 mmol/L). In clinical trials of up to 2 years duration, CE/bazedoxifene was associated with an increase from baseline in the concentration of serum triglycerides of approximately 16% at month 12 and 20% at month 24. Annual monitoring of serum triglyceride levels should therefore be considered.

- CE/bazedoxifene has not been studied in patients with impaired liver function (see sections 4.2 and 5.2) or history of cholestatic jaundice. Oestrogens may be poorly metabolised in women with impaired liver function. For women with a history of cholestatic jaundice associated with past oestrogen use or with pregnancy, caution should be exercised, and in the case of recurrence, DUAVIVE should be discontinued.

- Cases (<1%) of cholecystitis have been reported in CE/bazedoxifene clinical trials. A 2 to 4-fold increase in the risk of gallbladder disease requiring surgery in postmenopausal women receiving oestrogens has been reported (see section 4.8).

- Oestrogens increase thyroid binding globulin (TBG), leading to increased circulating total thyroid hormone, as measured by protein-bound iodine (PBI), T4 levels (by column or by radioimmunoassay) or T3 levels (by radio-immunoassay). T3 resin uptake is decreased, reflecting the elevated TBG. Free T4 and free T3 concentrations are unaltered. Other binding proteins may be elevated in serum, i.e. corticoid binding globulin (CBG), sex-hormone-binding globulin (SHBG) leading to increased circulating corticosteroi
biological active hormone concentrations are unchanged. Other plasma proteins may be increased (angiotensinogen/renin substrate, alpha-1 antitrypsin, ceruloplasmin).

Oestrogen therapy use does not improve cognitive function. There is some evidence of increased risk of probable dementia in women who start using continuous oestrogen-only therapy after the age of 65.

The effect of DUAVIVE on the risk of dementia is unknown.

DUAVIVE contains lactose, sucrose, glucose (in polydextrose and maltitol liquid) and sorbitol (in polydextrose). Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency, fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed with DUAVIVE. Results from interaction studies with CE or bazedoxifene are summarised below.

Conjugated oestrogens

The metabolism of oestrogens may be increased by concomitant use of substances known to induce drug-metabolising enzymes, specifically cytochrome P450 enzymes, such as anticonvulsants (e.g., phenobarbital, phenytoin, carbamazepine) and antiinfectives (e.g., rifampicin, rifabutin, nevirapine, efavirenz). Ritonavir and nelfinavir, although known as strong inhibitors, by contrast exhibit inducing properties when used concomitantly with steroid hormones. Herbal preparations containing St John’s wort (Hypericum perforatum) may induce the metabolism of oestrogens. Clinically, an increased metabolism of oestrogens may lead to decreased effect and changes in the uterine bleeding profile.

Inhibitors of CYP3A4, such as erythromycin, clarithromycin, ketoconazole, itraconazole, ritonavir and grapefruit juice, may increase plasma concentrations of oestrogens and may result in adverse reactions.

Bazedoxifene

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. A reduction in bazedoxifene exposure may be associated with an increased risk of endometrial hyperplasia. If break-through bleeding or spotting appears after some time on therapy, or continues after treatment has been discontinued, the reason should be investigated, which may include endometrial biopsy to exclude endometrial malignancy (see section 4.4).

Bazedoxifene undergoes little or no cytochrome P450 (CYP)-mediated metabolism. Bazedoxifene does not induce or inhibit the activities of major CYP isoenzymes, and 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 and azithromycin or an antacid containing aluminium and magnesium hydroxide. Based on in vitro bazedoxifene plasma protein-binding characteristics, interactions with warfarin, digoxin or diazepam are unlikely.
4.6 Fertility, pregnancy and lactation

Pregnancy

DUAVIVE is only for use in postmenopausal women, and is contraindicated in women who are or may become pregnant (see section 4.3). There are no data from the use of DUAVIVE in pregnant women. If pregnancy occurs during treatment with DUAVIVE, it should be withdrawn immediately.

The results of most epidemiological studies to date relevant to inadvertent foetal exposure to oestrogens indicate no teratogenic or foetotoxic effects.

In studies conducted in rabbits, bazedoxifene alone has shown reproductive toxicity (see section 5.3). The potential risk for humans is unknown.

Breast-feeding

DUAVIVE is contraindicated during breast-feeding (see section 4.3). It is not known whether bazedoxifene is excreted in human milk. Detectable amounts of oestrogens have been identified in the milk of mothers receiving CE. Oestrogen administration to breast-feeding mothers has been shown to decrease the quantity and quality of the milk.

Fertility

No studies were performed on animals to evaluate the effects on reproduction with the CE/bazedoxifene combination.

Studies in rats with bazedoxifene 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

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

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

In patients receiving bazedoxifene monotherapy there have been post-marketing reports of 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 CE/bazedoxifene was evaluated in 4,868 post-menopausal women who participated in 5 Phase 3 trials. Among these, 1,585 women were treated with CE 0.45 mg/bazedoxifene 20 mg and 1,241 received placebo. Long-term exposure to CE/bazedoxifene for up to 2 years was evaluated; 3,322 women were exposed to CE/bazedoxifene for at least 1 year, and 1,999 women were exposed for 2 years.

The most commonly reported adverse event is abdominal pain, occurring in more than 10% of patients in clinical trials.

Serious venous thromboembolic events may occur rarely (less than 1 case per 1,000 patients).
Tabulated list of adverse reactions

The table below lists the adverse reactions observed with CE/bazedoxifene (n = 3,168) in placebo-controlled clinical trials. Adverse reactions were categorised as very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100) or rare (≥ 1/10,000 to < 1/1,000).

<table>
<thead>
<tr>
<th>System organ class</th>
<th>Frequency of occurrence of adverse reactions</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Very common</td>
</tr>
<tr>
<td>Infections and infestations</td>
<td>Vulvovaginal candidiasis</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>Abdominal pain</td>
</tr>
<tr>
<td>Hepatobiliary disorders</td>
<td></td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td>Muscle spasms</td>
</tr>
<tr>
<td>Investigations</td>
<td>Blood triglycerides increased</td>
</tr>
</tbody>
</table>

Description of selected adverse reactions

**Breast cancer risk**

Breast cancer risk associated with the use of oestrogens alone is represented by several studies. Any increased risk to users of oestrogen-only therapy is substantially lower than that seen in users of oestrogen–progestagen combinations. The level of risk is dependent on duration of use (see section 4.4). Results of the largest randomised placebo-controlled trial (WHI-study) and largest epidemiological study (MWS) are presented.

**US WHI Oestrogen only (ET) arm – additional risk of breast cancer after 5 years use**

<table>
<thead>
<tr>
<th>Age range (years)</th>
<th>Incidence per 1,000 women in placebo arm over 5 years</th>
<th>Risk ratio &amp; 95% CI</th>
<th>Additional cases per 1,000 ET users over 5 years (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>50-79</td>
<td>21</td>
<td>0.8 (0.7-1.0)</td>
<td>-4 (-6 – 0)*</td>
</tr>
</tbody>
</table>

*WHI study in women with no uterus, which did not show an increase in risk of breast cancer

**Million women study (Estradiol only arm) – estimated additional risk of breast cancer after 5 years use**

<table>
<thead>
<tr>
<th>Age range (years)</th>
<th>Additional cases per 1,000 never-users of HRT over a 5 year period*</th>
<th>Risk ratio*</th>
<th>Additional cases per 1,000 ET users over 5 years (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>50-65</td>
<td>9-12</td>
<td>1.2</td>
<td>1-2 (0-3)</td>
</tr>
</tbody>
</table>

* Taken from baseline incidence rates in developed countries

* Overall risk ratio. The risk ratio is not constant but will increase with increasing duration on use.
Endometrial cancer risk

Postmenopausal women with a uterus
The endometrial cancer risk is about 5 in every 1,000 women with a uterus not using HRT.

In women with a uterus, use of oestrogen-only HRT is not recommended because it increases the risk of endometrial cancer (see section 4.4). Depending on the duration of oestrogen-only use and oestrogen dose, the increase in risk of endometrial cancer in epidemiology studies varied from 5 to 55 extra cases diagnosed in every 1,000 women between the ages of 50 and 65 years.

DUAVIVE contains bazedoxifene, which reduces the risk of endometrial hyperplasia that can occur with oestrogen-only use (see section 4.4). Endometrial hyperplasia may be a precursor to endometrial cancer.

Ovarian cancer

Long-term use of oestrogen-only HRT has been associated with a slightly increased risk of ovarian cancer. In the Million Women Study 5 years of HRT resulted in 1 extra case per 2,500 users.

Risk of venous thromboembolism

In the bazedoxifene osteoporosis treatment trial (mean age = 66.5 years), the VTE 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. After 7 years, the VTE rate per 1,000 women-years was 2.06 in the bazedoxifene 20 mg group and 1.36 in the placebo group.

Oestrogens are known to increase the risk of VTE (see section 4.4). The occurrence of such a reaction is more likely in the first year of treatment. The data from the largest randomised trial are summarised below:

WHI studies oestrogen only arm – additional risk of VTE over 5 years’ use

<table>
<thead>
<tr>
<th>Age range (years)</th>
<th>Incidence per 1,000 women in placebo arm over 5 years</th>
<th>Risk ratio &amp; 95%CI</th>
<th>Additional cases per 1,000 ET users</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral oestrogen-only*</td>
<td>7</td>
<td>1.2 (0.6-2.4)</td>
<td>1 (-3-10)</td>
</tr>
<tr>
<td>*study in women with no uterus</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Risk of ischaemic stroke

The use of oestrogen-only therapy is associated with an up to 1.5 fold increased relative risk of ischaemic stroke. This relative risk is not dependent on age or on duration of use, but as the baseline risk is strongly age-dependent, the overall risk of stroke in women who use oestrogen therapy will increase with age (see section 4.4). The additional risk of ischaemic stroke over five years of use was assessed in the largest randomised trial in women without a uterus (WHI) from 50-59 years of age.

WHI Studies combined – Additional risk of ischaemic stroke* over 5 years use

<table>
<thead>
<tr>
<th>Age range (years)</th>
<th>Incidence per 1,000 women in placebo arm over 5 years</th>
<th>Risk ratio &amp; 95%CI</th>
<th>Additional cases per 1,000 HRT users over 5 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>50-59</td>
<td>8</td>
<td>1.3 (1.1-1.6)</td>
<td>3 (1-5)</td>
</tr>
</tbody>
</table>

*no differentiation was made between ischaemic and haemorrhagic stroke.
Adverse reactions reported with CE and/or bazedoxifene monotherapy

Adverse reactions were categorized as 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) or not known (cannot be estimated from available data).

Adverse reactions that have been observed with CE monotherapy.

<table>
<thead>
<tr>
<th>System organ class</th>
<th>Frequency of occurrence of adverse reactions</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Common</td>
</tr>
<tr>
<td>Infections and infestations</td>
<td>Vaginitis</td>
</tr>
<tr>
<td>Neoplasms benign, malignant and unspecified (incl. cysts and polyps)</td>
<td></td>
</tr>
<tr>
<td>Immune system disorders</td>
<td>Hypersensitivity</td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td>Glucose intolerance;</td>
</tr>
<tr>
<td></td>
<td>Exacerbation of porphyria; hypocalcaemia (in patients with disease that can predispose to severe hypocalcaemia)</td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td>Dementia; depression; mood altered; changes in libido</td>
</tr>
<tr>
<td></td>
<td>Irritability</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>Migraine; headache; dizziness; nervousness</td>
</tr>
<tr>
<td></td>
<td>Exacerbation of epilepsy</td>
</tr>
<tr>
<td></td>
<td>Exacerbation of chorea</td>
</tr>
<tr>
<td>Eye disorders</td>
<td>Intolerance to contact lenses</td>
</tr>
<tr>
<td>Cardiac disorders</td>
<td></td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td>Myocardial infarction</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>Exacerbation of asthma</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>Alopecia</td>
</tr>
<tr>
<td></td>
<td>Hirsutism; rash; pruritus; chloasma</td>
</tr>
<tr>
<td></td>
<td>erythema multiforme; erythema nodosum</td>
</tr>
<tr>
<td>System organ class</td>
<td>Frequency of occurrence of adverse reactions</td>
</tr>
<tr>
<td>------------------------------------------</td>
<td>-------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td></td>
<td>Common</td>
</tr>
<tr>
<td><strong>Musculoskeletal and connective tissue disorders</strong></td>
<td>Arthralgia; leg cramps</td>
</tr>
<tr>
<td><strong>Reproductive system and breast disorders</strong></td>
<td>Breast pain, tenderness, enlargement, discharge; leucorrhoea</td>
</tr>
<tr>
<td><strong>Investigations</strong></td>
<td>Changes in weight (increase or decrease)</td>
</tr>
</tbody>
</table>

Adverse reactions that have been observed with bazedoxifene monotherapy.

<table>
<thead>
<tr>
<th>System organ class</th>
<th>Frequency of occurrence of adverse reactions</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Very common</td>
</tr>
<tr>
<td><strong>Immune system disorders</strong></td>
<td>Hypersensitivity</td>
</tr>
<tr>
<td><strong>Nervous system disorders</strong></td>
<td>Somnolence</td>
</tr>
<tr>
<td><strong>Eye disorders</strong></td>
<td>Retinal vein thrombosis</td>
</tr>
<tr>
<td><strong>Cardiac disorders</strong></td>
<td>Palpitations</td>
</tr>
<tr>
<td><strong>Vascular disorders</strong></td>
<td>Hot flush</td>
</tr>
<tr>
<td><strong>Respiratory, thoracic and mediastinal disorders</strong></td>
<td>Pulmonary embolism</td>
</tr>
<tr>
<td><strong>Gastrointestinal disorders</strong></td>
<td>Dry mouth</td>
</tr>
<tr>
<td><strong>Skin and subcutaneous tissue disorders</strong></td>
<td>Urticaria</td>
</tr>
<tr>
<td><strong>Musculoskeletal and connective tissue disorders</strong></td>
<td>Muscle spasms (includes leg cramps)</td>
</tr>
<tr>
<td><strong>General disorders and administration site conditions</strong></td>
<td>Peripheral oedema</td>
</tr>
<tr>
<td>System organ class</td>
<td>Frequency of occurrence of adverse reactions</td>
</tr>
<tr>
<td>--------------------</td>
<td>---------------------------------------------</td>
</tr>
<tr>
<td></td>
<td>Very common</td>
</tr>
<tr>
<td>Investigations</td>
<td>Blood triglycerides increased, alanine aminotransferase increased; aspartate aminotransferase increased</td>
</tr>
</tbody>
</table>

Post-marketing experience

In patients receiving bazedoxifene monotherapy 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 case of overdose of DUAVIVE, there is no specific antidote, and the treatment should reflect the symptoms.

Symptoms of overdose of oestrogen-containing medicinal products in adults and children may include nausea, vomiting, breast tenderness, dizziness, abdominal pain, drowsiness/fatigue; withdrawal bleeding may occur in females.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: not yet assigned. ATC code: not yet assigned

Mechanism of action

DUAVIVE pairs CE with the selective oestrogen receptor modulator (SERM), bazedoxifene, which is defined as a tissue selective oestrogen complex (TSEC). The active ingredients of CE are primarily the sulphate esters of estrone, equilin sulphates and 17α/β- estradiol. These substitute for the loss of oestrogen production in menopausal women, and alleviate menopausal symptoms. As oestrogens promote the growth of the endometrium, unopposed oestrogens increase the risk of endometrial hyperplasia and cancer. The addition of bazedoxifene, acting as an oestrogen receptor antagonist in the uterus, greatly reduces the oestrogen-induced risk of endometrial hyperplasia in non-hysterectomised women.
Clinical trial information

Relief of oestrogen-deficiency symptoms and bleeding patterns

Relief of menopausal symptoms was achieved during the first few weeks of treatment. In a 12-week study, CE 0.45 mg/bazedoxifene 20 mg significantly reduced the number and severity of hot flushes compared to placebo at weeks 4 and 12.

In one study, amenorrhea was reported in 97% of the women who received CE 0.45 mg/bazedoxifene 20 mg during months 10 to 12. Irregular bleeding and/or spotting was reported in the CE 0.45 mg/bazedoxifene 20 mg group by 7% of women during the first 3 months of treatment and by 3% of women during months 10 to 12.

In another study, amenorrhea was reported in 95% of the women who received CE 0.45 mg/bazedoxifene 20 mg during months 10 to 12. Irregular bleeding and/or spotting was reported in the CE 0.45 mg/ bazedoxifene 20 mg group by 6% of women during the first 3 months of treatment and by 5% of women during months 10 to 12.

Breast density

CE 0.45 mg/bazedoxifene 20 mg demonstrated similar changes in mammographic breast density compared to placebo over 1 year of treatment.

Effects on bone mineral density (BMD)

In a 1 year study, CE 0.45 mg/bazedoxifene 20 mg showed a significant difference from baseline in lumbar spine BMD (+1.52%) at Month 12 compared to placebo. This change in BMD was similar to that shown with bazedoxifene 20 mg alone (+1.35%) and less than that seen with CE 0.45 mg/ medroxyprogesterone 1.5 mg (+2.58%) in the same study.

Elderly population

CE/bazedoxifene has not been studied in women aged 75 years or older. Of the total number of women in Phase 3 clinical trials who received CE/bazedoxifene 20 mg, 2.4% (n=77) were aged ≥65 years. No overall differences in safety or effectiveness were observed between women aged >65 years and younger women, but greater sensitivity of some older individuals cannot be ruled out.

Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with DUAVIVE in all subsets of the paediatric population for the conditions ‘treatment of oestrogen deficiency symptoms in postmenopausal women’ (see section 4.2).

5.2 Pharmacokinetic properties

Pharmacokinetic studies for CE/bazedoxifene were conducted in healthy postmenopausal women who were naturally postmenopausal or who had undergone bilateral oophorectomy.

Following multiple doses of CE 0.45 mg/bazedoxifene 20 mg, the mean steady state pharmacokinetic parameters for CE and bazedoxifene (baseline adjusted for total estrone) are summarised below.

<table>
<thead>
<tr>
<th></th>
<th>Cmax (ng/mL)</th>
<th>Tmax (hr)</th>
<th>AUCss (ng·hr/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bazedoxifene</td>
<td>6.9 ± 3.9</td>
<td>2.5 ± 2.1</td>
<td>71 ± 34</td>
</tr>
<tr>
<td>Baseline-adjusted total estrone</td>
<td>2.6 ± 0.8</td>
<td>6.5 ± 1.6</td>
<td>35 ± 12</td>
</tr>
</tbody>
</table>
Absorption

After a single dose of CE/bazedoxifene, bazedoxifene and baseline-adjusted total estrone were absorbed with a t\text{max} of approximately 2 hours and 8.5 hours, respectively. When single doses of CE 0.625 mg/bazedoxifene 20 mg were administered with a high-fat meal, bazedoxifene C\text{max} was unaffected, but AUC increased by approximately 25%. Food had little or no effect on the exposure of CE.

CE/bazedoxifene can be administered with or without food.

Following administration of bazedoxifene alone, 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 was observed. The absolute bioavailability of bazedoxifene is approximately 6%.

CE are soluble in water and are well-absorbed from the gastrointestinal tract after release from the medicinal product formulation. Oestrogen dose proportionality was assessed in two studies of CE. Dose-proportional increases in both AUC and C\text{max} were observed across the dose range from 0.3 mg to 0.625 mg of CE for total (conjugated plus unconjugated) equilin, total estrone adjusted for baseline, and unconjugated estrone adjusted for baseline.

Distribution

The distribution of CE and bazedoxifene after administration of CE/bazedoxifene has not been studied.

Following intravenous administration of a 3 mg dose of bazedoxifene alone, the volume of distribution is 14.7 ±3.9 l/kg. Bazedoxifene is highly bound (98% - 99%) to plasma proteins \textit{in vitro}, but does not bind to sex hormone binding globulin (SHBG).

The distribution of exogenous oestrogens is similar to that of endogenous oestrogens. Oestrogens are widely distributed in the body and are generally found in higher concentrations in the sex hormone target organs. Oestrogens circulate in the blood largely bound to SHBG and albumin.

Biotransformation

The metabolic disposition of CE and bazedoxifene, after administration of CE/bazedoxifene, has not been studied.

Exogenous oestrogens are metabolised in the same manner as endogenous oestrogens. Circulating oestrogens exist in a dynamic equilibrium of metabolic interconversions. 17\beta-estradiol is converted reversibly to estrone, and both can be converted to estriol, which is the major urinary metabolite. In postmenopausal women, a significant proportion of the circulating oestrogens exists as sulfate conjugates, especially estrone sulfate, which serves as a circulating reservoir for the formation of more active oestrogens.

The metabolic disposition of bazedoxifene in postmenopausal women has been determined following oral administration of 20 mg of radiolabeled 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 bazedoxifene in plasma.

Elimination

After a single dose of CE/bazedoxifene, baseline-adjusted total estrone (representing CE) is eliminated with a half-life of approximately 17 hours. Bazedoxifene is eliminated with a half-life of
approximately 30 hours. Steady-state concentrations are achieved by the second week of once-daily administration.

CE components, 17β-estradiol, estrone, and estriol are excreted in the urine, along with glucuronide and sulfate conjugates.

The clearance of bazedoxifene is 0.4 ±0.1 L/h/kg based on IV administration. The major route of excretion of radiolabeled bazedoxifene is the faeces, and less than 1% of the dose is eliminated in urine.

Special populations

**Elderly**
The pharmacokinetics of CE/bazedoxifene have not been evaluated in women over 75 years of age. 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 2.6-fold increase in AUC. This increase is most likely attributable to age-related changes in hepatic function.

**Renal impairment**
The pharmacokinetics of CE/bazedoxifene have not been evaluated in patients with renal impairment. Limited clinical data (n=5) for bazedoxifene are available in subjects with moderate renal impairment (creatinine clearance <50 ml/min). A single 20 mg dose of bazedoxifene was administered to these subjects. Negligible (<1%) amounts of bazedoxifene are eliminated in urine. Impaired renal function showed little or no influence on bazedoxifene pharmacokinetics.

**Hepatic impairment**
The pharmacokinetics of CE/bazedoxifene have not been evaluated in women with hepatic impairment.

The disposition of a single 20 mg dose of bazedoxifene was compared in women 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, women with hepatic impairment showed a 4.3-fold increase in AUC compared with controls. Safety and efficacy have not been evaluated further in women with hepatic insufficiency. Use of CE/bazedoxifene in this population is contraindicated (see sections 4.2, 4.3 and 4.4).

5.3 **Preclinical safety data**

Carcinogenicity, mutagenicity, and impairment of fertility studies with CE/bazedoxifene have not been conducted. The following data are based on the findings in studies with bazedoxifene.

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 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. Since chronic progressive nephropathy and corticomedullar nephrocalcinosis are most likely rat-specific nephropathies, these findings are presumably not relevant for humans. 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 exposure ratios of 0.05 to 4 in males and 0.26 to 6.61 times in females respectively. In addition, based on surface area (mg/m²) dose ratios resulted in approximately 0.6 to 22 times and 1.0 to 29 times in males and females, respectively, the clinical dose of 20 mg.

Renal cell carcinomas were observed in an 18-month bone efficacy study in aged ovariectomized cynomolgus monkeys. These tumours are considered as spontaneous renal cell carcinomas that are known to occur in aged nonhuman primates and are unlikely to be relevant to humans. Bazedoxifene, administered orally to monkeys at dosages of 0, 0.2, 0.5, 1, 5, or 25 mg/kg/day, resulted in exposure ratios of 0.05 to 16.3 times, and dose ratios, based on surface area (mg/m²), of approximately 0.2 to 24 times the clinical dose of 20 mg, respectively.

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. Reproductive toxicity and impairment of fertility studies with CE/bazedoxifene have not been conducted. The following data are based on the findings in studies with bazedoxifene.

In rabbit studies with bazedoxifene, 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 fetuses were present at maternally toxic dosages of ≥ 0.5 mg/kg/day (1.5 times the human exposure). Treatment of rats with bazedoxifene at maternally toxic dosages ≥ 1 mg/kg/day (≥ 0.4 times the human dose based on body surface area) 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 dosages of 0.3 to 30 mg/kg (0.15 to 14.6 times the human dose based on body surface area, mg /m² [20 mg/kg dosage in humans is 12.3 mg/m²]) prior to and during mating with untreated males. Oestrous cycles and fertility were adversely affected in all bazedoxifene-treated female groups.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Conjugated oestrogens tablet core

Lactose monohydrate
Microcrystalline cellulose
Powdered cellulose
Hypropemellose 2208 (100,000 mPa•s)
Magnesium stearate
Calcium phosphate

Inert filler coating

Sucrose
Microcrystalline cellulose
Hydroxypropylcellulose
Hypromellose 2910 (6 mPa•s) (E464)
Hypromellose 2910 (15 mPa•s)
Macrogol 400

Bazedoxifene active coating
Sucrose
Hypromellose 2910 (3 mPa•s)
Sucrose monopalmitate
Ascorbic acid

Colour coating
Hypromellose 2910 (6 mPa•s)
Titanium dioxide (E171)
Macrogol 400
Iron oxide red (E172)

Clear coating
Hydroxyethylcellulose
Povidone (E1201)
Polydextrose (E1200)
Maltitol liquid
Poloxamer 188

Printing ink
Iron oxide black (E172)
Isopropyl alcohol
Propylene glycol (E1520)
Hypromellose 2910 (6 mPa•s)

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
3 years
After opening the blister pouch, use within 60 days.

6.4 Special precautions for storage
Do not store above 25ºC.
Store in the original package in order to protect from moisture.

6.5 Nature and contents of container
UPVC/ Monochlorotrifluoroethylene blister packs containing 28 modified-release tablets.

6.6 Special precautions for disposal
No special requirements for disposal.
7. MARKETING AUTHORISATION HOLDER

Pfizer Ltd
Ramsgate Road
Sandwich
Kent CT13 9NJ
United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/14/960/001

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 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
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 AUTHORIZATION

- Periodic Safety Update Reports

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation. Subsequently, the marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and 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 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
OUTER CARTON AND BLISTER POUCH

1. NAME OF THE MEDICINAL PRODUCT

DUAVIVE 0.45 mg/20 mg modified-release tablets
Conjugated oestrogens/bazedoxifene

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each modified-release tablet contains 0.45 mg of conjugated oestrogens and bazedoxifene acetate equivalent to 20 mg bazedoxifene

3. LIST OF EXCIPIENTS

Also contains: lactose, sucrose, polydextrose and maltitol liquid. See package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

28 modified-release tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Swallow tablet whole.
Oral use
Read the package leaflet before 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 25°C.

Store in the original package in order to protect from moisture.

After opening the blister pouch, use within 60 days.

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Pfizer Limited
Ramsgate Road
Sandwich
Kent CT13 9NJ
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/14/960/001 28 tablets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

DUA VIVE 0.45/20 mg
MINIMUM PARTICULARS TO APPEAR ON BLISTERS AND STRIPS

BLISTER

1. NAME OF THE MEDICINAL PRODUCT

DUAVIVE 0.45 mg/20 mg modified-release tablets
Conjugated oestrogens/bazedoxifene

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Pfizer

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER
B. PACKAGE LEAFLET
Package leaflet: Information for the patient

DUAVIVE 0.45 mg/20 mg modified-release tablets
Conjugated oestrogens/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 DUAVIVE is and what it is used for
2. What you need to know before you take DUAVIVE
3. How to take DUAVIVE
4. Possible side effects
5. How to store DUAVIVE
6. Contents of the pack and other information

1. What DUAVIVE is and what it is used for

DUAVIVE is a medicine that contains two active substances called conjugated oestrogens and bazedoxifene. Conjugated oestrogens is a medicine that belongs to a group of medicines called hormone replacement therapy (HRT). Bazedoxifene belongs to a group of non-hormonal medicines called selective estrogen receptor modulators (SERMs).

DUAVIVE is used in postmenopausal women who still have their uterus (womb) with at least 12 months since their last natural period.

DUAVIVE is used for:

Relief of symptoms occurring after menopause

During the menopause, the amount of the oestrogen produced by a woman’s body drops. This can cause symptoms such as hot face, neck and chest ("hot flushes"). DUAVIVE alleviates these symptoms after menopause. You will only be prescribed this medicine if your symptoms seriously hinder your daily life and your doctor determines that other types of HRT are not appropriate for you.

2. What you need to know before you take DUAVIVE

Medical history and regular check-ups

The use of DUAVIVE carries risks, which need to be considered when deciding whether to start taking it, or whether to carry on taking it.

There is no experience in treating women with a premature menopause (due to ovarian failure or surgery) with DUAVIVE.
Before you start taking this medicine, your doctor will ask you about your own and your family’s medical history. Your doctor may decide to perform a physical examination. This may include an examination of your breasts and/or an internal examination, if necessary, or if you have any special concerns. Tell your doctor if you have any medical problems or illnesses.

Once you have started this medicine you should see your doctor for regular check-ups (at least once a year). During these check-ups, discuss with your doctor the benefits and risks of continuing with DUAVIVE. You are advised to:

- go for regular breast screening and cervical smear tests, as recommended by your doctor.
- regularly check your breasts for any changes such as dimpling of the skin, changes in the nipple, or any lumps you can see or feel.

Do not take DUAVIVE

- If you are allergic to conjugated estrogens, bazedoxifene or any of the other ingredients of this medicine (listed in section 6).
- If you have or have ever had breast cancer, or if you are suspected of having it.
- If you have or have had cancer which is sensitive to oestrogens, such as cancer of the womb lining (endometrium), or if you are suspected of having it.
- If you have recently had any unexplained vaginal bleeding.
- If you have excessive thickening of the womb lining (endometrial hyperplasia) that is not being treated.
- If you have or have ever had a blood clot in a vein (thrombosis), such as in the legs (deep venous thrombosis), the lungs (pulmonary embolism) or eyes.
- If you have a blood clotting disorder (such as protein C, protein S, or antithrombin deficiency).
- If you have or recently have had a disease caused by blood clots in the arteries, such as a heart attack, stroke or angina.
- If you have or have ever had liver disease and your liver function tests have not returned to normal.
- If you are pregnant or could still become pregnant or you are breast feeding.
- If you have a rare blood problem called porphyria, which is passed down in families (inherited).

If you are not sure about any of the points above, talk to your doctor before taking this medicine. If any of the above conditions appear for the first time while taking this medicine, stop taking it at once and consult your doctor immediately.

Warnings and precautions

Tell your doctor if you have ever had any of the following problems, as these may return or become worse during treatment with DUAVIVE. If so, you should see your doctor more often for check-ups:

- fibroids inside your womb
- growth of womb lining outside your womb (endometriosis) or a history of excessive growth of the womb lining (endometrial hyperplasia)
- increased risk of developing blood clots [see “Blood clots in a vein (thrombosis)”]
- increased risk of getting a oestrogen-sensitive cancer (such as having a mother, sister or grandmother who has had breast cancer)
- high blood pressure
- a liver disorder, such as a benign liver tumour
- diabetes
- gallstones
- migraine or severe headaches
- a rare disease of the immune system that affects many organs of the body (systemic lupus erythematosus, SLE)
- seizures (epilepsy)
- asthma
- a disease affecting the eardrum and hearing (otosclerosis)
- a high level of fat in your blood (triglycerides)
- fluid retention due to cardiac or kidney problems

Children and adolescents

This medicine is not for use in children and adolescents below 18 years old.

Stop taking DUAVIVE and see a doctor immediately

If you notice any of the following:
- any of the conditions mentioned under ‘Do not take DUAVIVE’
- yellowing of your skin or the whites of your eyes (jaundice). These may be signs of a liver disease
- a large increase in your blood pressure (symptoms may be headache, tiredness, dizziness)
- migraine-like headaches which happen for the first time
- if you become pregnant
- you notice signs of a blood clot, such as painful swelling and redness of the legs, sudden chest pain, or difficulty in breathing. For more information, see ‘Blood clots in a vein (thrombosis)’

DUAVIVE and cancer

Excessive thickening of the lining of the womb (endometrial hyperplasia) and cancer of the lining of the womb (endometrial cancer)

Your product contains two medicines, conjugated oestrogens and bazedoxifene and is used to treat women with a uterus (womb).

When you take DUAVIVE do not take additional oestrogens as this may increase the risk of endometrial hyperplasia.

If you have any unexpected vaginal bleeding, you must contact your doctor as soon as possible.

Breast cancer

Evidence suggests that taking oestrogen-only HRT possibly increases the risk of breast cancer. The extra risk depends on how long you take HRT. The additional risk becomes clear within a few years. However, it returns to normal within a few years (at most 5) after stopping treatment. For women who are using oestrogen-only HRT for 5 years, little or no increase in breast cancer risk is shown.

The effect of DUAVIVE on the risk of breast cancer is unknown.

Regularly check your breasts. See your doctor as soon as possible if you notice any changes, such as:
- dimpling of the skin
- changes in the nipple
- any lumps you can see or feel

Ovarian cancer

Ovarian cancer is rare. A slightly increased risk of ovarian cancer has been reported in women taking HRT for at least 5 to 10 years.

For women aged 50 to 69 who are not taking HRT, on average about 2 women in 1,000 will be diagnosed with ovarian cancer over a 5-year period. For women who have been taking HRT for 5 years, there will be between 2 and 3 cases per 1,000 users (i.e. up to 1 extra case). Talk to your doctor if you have any concerns.

The effect of DUAVIVE on the risk of ovarian cancer is unknown.
**DUAVIVE and your heart or circulation**

**Blood clots in a vein (thrombosis)**
DUAVIVE may increase the risk of blood clots.

Oestrogen-only and bazedoxifene monotherapy increase the risk of blood clots in the veins (also called deep vein thrombosis, or DVT), especially during the first year of taking these medicines.

Blood clots can be serious, and if one travels to the lungs, it can cause chest pain, breathlessness, collapse or even death.

You are more likely to get a blood clot in your veins as you get older and if any of the following applies to you. Inform your doctor if any of the following applies to you:

- you are unable to walk for a long time because of major surgery, injury or illness (see also section 3, if you need to have surgery)
- you are seriously overweight (BMI >30 kg/m²)
- you have any blood clotting problem that needs long-term treatment with a medicine used to prevent blood clots
- if any of your close relatives has ever had a blood clot in the leg, lung or another organ
- you have systemic lupus erythematosus (SLE).
- you have cancer.

**If any of these things apply to you,** talk to your doctor to see if you should take this medicine.

**Heart disease (heart attack)**
There is no evidence that HRT will prevent a heart attack. Randomised controlled data found no increased risk of coronary artery disease in hysterectomised women using oestrogen-only therapy.

**Stroke**
The risk of having a stroke is about 1.5 times higher in HRT users than in non-users. The number of extra cases of stroke due to use of HRT will increase with age.

For women in their 50s who are not taking HRT, on average, 8 in 1,000 would be expected to have a stroke over a 5-year period. For women in their 50s who are taking HRT, there will be 11 cases in 1,000 users, over 5 years (i.e., 3 extra cases).

The effect of DUAVIVE on the risk of stroke is unknown.

Other things that can increase the risk of stroke include:

- getting older
- high blood pressure
- smoking
- drinking too much alcohol
- an irregular heartbeat

If you are worried about any of these things, talk to your doctor to see if you should take this medicine.

**Other conditions**
If you have any of the following your doctor may want to monitor you:

- kidney problems
- pre-existing high level of fat in your blood (triglycerides)
- liver problems
- asthma
- seizures (epilepsy)
- migraine
- systemic lupus erythematosus (SLE – a rare disease of the immune system that affects many organs of the body)
- fluid retention

Oestrogen therapy will not prevent memory loss. There is some evidence of a higher risk of memory loss in women who start using oestrogen therapy after the age of 65. Speak to your doctor for advice.

**Other medicines and DUAVIVE**

Tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription, herbal medicines or other natural products.

Other medicines may influence the effects of DUAVIVE, or DUAVIVE may affect other medicines. In particular tell your doctor if you are taking:

- an anticonvulsant (used in the treatment of epilepsy; for example phenobarbital, phenytoin, carbamazepine)
- an anti-infective (for example rifampicin, rifabutin, nevirapine, efavirenz, erythromycin, ketoconazole, ritonavir, nelfinavir, clarithromycin, itraconazole)
- herbal remedies containing St. John’s wort (*Hypericum perforatum*)

**DUAVIVE with drink**

Do not take this medicine with grapefruit or grapefruit juice, as it may increase the chance of side effects.

**Pregnancy and breast-feeding**

This medicine is for use only by postmenopausal women. Do not take this medicine if you are pregnant, or if you think you might be pregnant. Do not take this medicine if you are breast-feeding.

**Driving and using machines**

DUAVIVE has no known effect on the ability to drive or use machines.

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

The bazedoxifene component of this medicine has been reported to cause problems with eyesight such as blurred vision. If this happens, you should avoid driving or operating machines until your doctor tells you that it is safe to do so.

**DUAVIVE contains lactose, sucrose, polydextrose and maltitol liquid**

This medicine contains lactose (as monohydrate), sucrose, glucose (in polydextrose and maltitol liquid) and sorbitol (in polydextrose) (types of sugars). If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before using this medicinal product.

**3. How to take DUAVIVE**

Your doctor will aim to prescribe the lowest dose to treat your symptom for as short as necessary. Speak to your doctor if you think this dose is too strong or not strong enough.

Always take this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure. You should continue taking this medicine for as long as your doctor tells you. In order for this medicine to work, it should be taken daily as prescribed.
The recommended dose is one tablet once daily. Swallow the tablet whole with a glass of water.
You can take the tablet at any time of the day, with or without food; however, it is advisable to
take your tablet at the same time each day as this will help to remind you to take your medicine.

**If you are having an operation**

If you are going to have surgery, tell the surgeon you are taking DUAVIVE. You may need to stop
taking DUAVIVE about 4 to 6 weeks before the operation, to reduce the risk of a blood clot (see
section 2, Blood clots in a vein). Ask your doctor when you can start taking this medicine again.

**If you take more DUAVIVE than you should**

Call your doctor or pharmacist.
If you take too many tablets you may have nausea (feel sick) or vomit. You may experience breast
tenderness, dizziness, abdominal pain, drowsiness/fatigue or experience a short period of vaginal
bleeding.

**If you forget to take DUAVIVE**

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

**If you stop taking DUAVIVE**

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 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.

**Stop taking DUAVIVE and see a doctor immediately if you get any of the following serious side
effects:**

**Uncommon** (may affect 1 in 100 people):
- If you have signs of a blood clot, such as painful swelling and redness of the legs, sudden chest
  pain or difficulty in breathing, loss of vision, pain and swelling of the eye especially if sudden.
- If you begin to get migraine-like headaches, or severe headaches

**Rare** (may affect up to 1 in 1,000 people):
- A severe allergic reaction - symptoms may include sudden wheezing and chest pain or tightness,
  swelling of the eyelids, face, lips, mouth, tongue or throat, difficulty breathing, collapse
- If you have swelling of the eyes, nose, lips, mouth, tongue or throat, difficulty in breathing,
  severe dizziness or fainting, skin rash (symptoms of angioedema)
- If you have symptoms of pancreatitis which may include severe upper abdominal pain which
  may spread to your back, accompanied by abdominal swelling, fever, nausea and vomiting
- Abrupt onset of abdominal pain and passage of bright red blood in the stool, with or without
  diarrhoea due to sudden blockage of an artery supplying the intestines (ischemic colitis)
- A heart attack - symptoms will usually include pain, including chest pain spreading to the jaw,
  neck and upper arm. You may feel sweaty, breathless, fatigued, nauseous and faint in addition to
  the pain
Very rare (may affect up to 1 in 10,000 people):
- If you have a large rise in your blood pressure (symptoms may be headache, tiredness, dizziness)
- Erythema multiforme: symptoms may include skin rash with pink-red blotches especially on palms of hands or soles of feet which may blister. You may also have ulcers in the mouth, eyes or genitals and have a fever

Other side effects

Very common (may affect more than 1 in 10 people)
- Abdominal pain (stomach ache)

Common (may affect 1 in 10 people):
- Muscle spasms (including leg cramps)
- Constipation
- Diarrhoea
- Nausea
- Thrush (vaginal yeast infection)
- Increases in your triglyceride levels (fatty substances in the blood)

Uncommon (may affect 1 in 100 people):
- Gall bladder disease (e.g. gallstones, inflammation of the gall bladder (cholecystitis))

The following side effects have been observed when either conjugated oestrogens and/or bazedoxifene (the active ingredients in this medicine) has been used alone and may occur also with this medicine:

Very common (may affect more than 1 in 10 people)
- Hot flushes
- Muscle cramps

Common (may affect 1 in 10 people):
- Breast pain, breast tenderness, swollen breasts
- Discharge from the nipples
- Joint pain
- Visible swelling of the face or ankles
- Alopecia (hair loss)
- Changes in weight (increase or decrease)
- Increases in liver enzymes (identified in routine liver function testing)
- Dry mouth
- Drowsiness
- Hives (urticaria)

Uncommon (may affect up to 1 in 100 people):
- Vaginal inflammation
- Vaginal discharge
- Cervical erosion found on medical examination
- Blood clot in the leg veins
- Blood clot in the lungs
- Nausea (feeling sick)
- Headache
- Migraine
- Dizziness
Changes in mood
Feeling nervous
Depression
Memory loss (dementia)
Changes in your interest in sex (increased or decreased libido)
Discolouration of the skin on the face or other parts of the body
Rash
Itching
Increase in hair growth
Difficulty wearing contact lenses

**Rare** (may affect up to 1 in 1,000 people):
- Pelvic pain
- Blood clot in a vein at the back of the eye (retinal vein) which may lead to loss of vision
- Changes in breast tissue
- Vomiting
- Feeling irritable
- An effect on the way in which your blood sugar (glucose) levels are controlled including increased glucose levels in the blood
- A worsening of asthma
- A worsening of epilepsy (seizures)
- Growth of benign meningioma, a non-cancerous tumour of the membranes around the brain or spinal cord

**Very rare** (may affect up to 1 in 10,000 people):
- Painful red bumps on the skin
- A worsening of chorea (an existing neurological disorder characterised by involuntary spasmodic movements of the body)
- Enlargement of hepatic haemangiomas, a benign (non-cancerous) tumour of the liver
- Low levels of blood calcium (hypocalcaemia); frequently there will be no symptoms to suggest that your blood calcium is low, but when hypocalcaemia is severe you may feel tired, generally unwell, depressed and become dehydrated. This may be accompanied by bone pain and abdominal pain. Kidney stones may develop and cause severe pain in the mid-back region (renal colic).
- Worsening of porphyria, a rare blood disorder which is passed down in families (inherited).

**Not known** (frequency cannot be estimated from the available data):
- Palpitations (awareness of your heart beat)
- Blurred vision and minor changes to vision

**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 DUAVIVE**

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.
Store in the original package in order to protect from moisture.

After opening the blister pouch, use within 60 days.

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 DUAVIVE contains

The active substances are conjugated oestrogens and bazedoxifene. Each tablet contains 0.45 mg of conjugated oestrogens and bazedoxifene acetate equivalent to 20 mg bazedoxifene.

The other ingredients are: lactose monohydrate, sucrose, sucrose monopalmitate, polydextrose (E1200) and maltitol liquid (see section 2), microcrystalline cellulose, powdered cellulose, hydroxypropylcellulose, hydroxyethylcellulose, magnesium stearate, ascorbic acid, hypromellose (E464), povidone (E1201), poloxamer 188, calcium phosphate, titanium dioxide (E171), macrogol 400, iron oxide red (E172), iron oxide black (E172), isopropyl alcohol and propylene glycol (E1520).

What DUAVIVE looks like and contents of the pack

The DUAVIVE 0.45 mg/20 mg modified-release tablet is a pink, oval-shaped, tablet marked on one side with “0.45/20”.

The tablets are provided in UPVC/Monochlorotrifluorethylene blister packs containing 28 tablets.

Marketing Authorisation Holder

Pfizer Limited, Ramsgate Road, Sandwich, Kent CT13 9NJ, United Kingdom.

Manufacturer

Pfizer Ireland Pharmaceuticals, Little Connell, Newbridge, County Kildare, Ireland.
For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

<table>
<thead>
<tr>
<th>Country</th>
<th>Contact Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>België/Belgique/Belgien Luxembourg/Luxemburg</td>
<td>Pfizer S.A./N.V. Tél/Tel: +32 (0)2 554 62 11</td>
</tr>
<tr>
<td>Latvijā</td>
<td>Pfizer Luxembourg SARL filiāle Latvijā Tel.: + 371 670 35 775</td>
</tr>
<tr>
<td>България</td>
<td>Pfizer Luxemburg SARL filial Latvija Tel.: +359 2 970 4333</td>
</tr>
<tr>
<td>Lietuva</td>
<td>Pfizer Luxembourg SARL filialas Lietuvoje Tel. + 370 52 51 4000</td>
</tr>
<tr>
<td>Česká Republika</td>
<td>Pfizer s.r.o. Tel: +420-283-004-111</td>
</tr>
<tr>
<td>Magyarország</td>
<td>Pfizer Kft Tel: +36 1 488 3700</td>
</tr>
<tr>
<td>Danmark</td>
<td>Pfizer ApS Tlf: +45 44 201 100</td>
</tr>
<tr>
<td>Malta</td>
<td>Vivian Corporation Ltd. Tel: +35621 344610</td>
</tr>
<tr>
<td>Eesti</td>
<td>Pfizer Luxembourg SARL Eesti filiaal Tel.: +372 6 405 328</td>
</tr>
<tr>
<td>Nederland</td>
<td>Pfizer BV Tel: +31 (0)10 406 43 01</td>
</tr>
<tr>
<td>Norge</td>
<td>Pfizer AS Tlf: +47 67 526 100</td>
</tr>
<tr>
<td>España</td>
<td>Pfizer, S.L. Tél: +34914909900</td>
</tr>
<tr>
<td>Österreich</td>
<td>Pfizer Corporation Austria Ges.m.b.H. Tel: +43 (0)1 521 15-0</td>
</tr>
<tr>
<td>Polska</td>
<td>Pfizer Polska Sp. z o.o. Tel:+48 22 335 61 00</td>
</tr>
<tr>
<td>Portugal</td>
<td>Laboratórios Pfizer, Lda. Tel: (+351) 21 423 55 00</td>
</tr>
<tr>
<td>România</td>
<td>Pfizer Romania S.R.L Tel: +40 (0) 21 207 28 00</td>
</tr>
<tr>
<td>Slovenija</td>
<td>Pfizer Luxembourg SARL Pfizer, podružnica za svetovanje s področja farmacevtske dejavnosti, Ljubljana Tel.: + 386 (0) 1 52 11 400</td>
</tr>
</tbody>
</table>
Íslând
Icepharma hf
Simi: +354 540 8000

Slovenská Republika
Pfizer Luxembourg SARL,
organizačná zložka
Tel: + 421 2 3355 5500

Italia
Pfizer Italia S.r.l.
Tel: +39 06 33 18 21

Suomi/Finland
Pfizer Oy
Puh/Tel: +358 (0)9 430 040

Κύπρος
Pfizer Hellas (Cyprus Branch) A.E.
Τηλ.: +357 22 817690

Sverige
Pfizer AB
Tel:+46 (0)8 550 520 00

United Kingdom
Pfizer Limited,
Tel: +44 (0) 1304 616161

This leaflet was last revised in

Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site: