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), 62.9 mg lactose (as monohydrate), 0.2 mg maltitol liquid, 0.0176 mg glucose, and 0.0088 mg sorbitol

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 the 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 should be used (see section 4.4).

The recommended dose is 0.45 mg conjugated oestrogens (CE) and 20 mg bazedoxifene (BZA) 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

CE/BZA 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/BZA 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/BZA 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 CE/BZA in the paediatric population.

Method of administration

Oral use.

CE/BZA 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.
- CE/BZA must not be taken by women of childbearing potential, or breast-feeding women (see sections 4.6 and 5.3).
- Porphyria.

4.4 Special warnings and precautions for use

For the treatment of postmenopausal symptoms, CE/BZA 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 CE/BZA should not be taking progestins, additional oestrogens or selective oestrogen receptor modulators (SERMs).

DUAVIVE (CE/BZA) has not been studied in the treatment of premature menopause.

Medical examination/follow-up

Before initiating or reinstituting treatment with CE/BZA, 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 precautions 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 CE/BZA, in particular:

- Leiomyoma (uterine fibroids) or endometriosis
- Risk factors for thromboembolic disorders (see below)
- Risk factors for oestrogen-dependent tumours, e.g., 1st 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 CE/BZA should not take additional oestrogens as this may increase the risk of endometrial hyperplasia and endometrial carcinoma.

The addition of bazedoxifene in CE/BZA 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 shows an increased risk of breast cancer in women taking oestrogen-only HRT that is dependent on the duration of taking HRT.

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 in oestrogen only users diagnosed that is lower than that found in users of oestrogen-progestagen combinations (see section 4.8).

Results from a large meta-analysis showed that after stopping treatment, the excess risk will decrease with time and the time needed to return to baseline depends on the duration of prior HRT use. When HRT was taken for more than 5 years, the risk may persist for 10 years or more.

An observational study with an average follow-up time of 22 months showed that the risk of breast cancer among users of CE/BZA might be in the same range as among users of oestrogen-progestin combination hormone therapy. The long-term effect of CE/BZA on the risk of breast cancer remains unknown (see section 5.1).

Ovarian cancer

Ovarian cancer is much rarer than breast cancer.

Epidemiological evidence from a large meta-analysis suggests a slightly increased risk in women taking oestrogen-only Hormone Replacement Therapy (HRT), which becomes apparent within 5 years of use and diminishes over time after stopping.

Some other studies, including the WHI trial, suggest that use of combined HRTs may be associated with a similar or slightly smaller risk (see section 4.8).

The effect of CE/BZA 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/BZA, cases of VTE have been reported (see section 4.8). Should a VTE event occur or be suspected, CE/BZA 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. CE/BZA 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/m^2), 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 CE/BZA 4 to 6 weeks earlier is recommended. Treatment should not be restarted until the woman is completely mobilised. In addition, women taking CE/BZA 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, CE/BZA 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).

An observational study with an average follow-up time of 10-11 months showed that the risk of stroke among users of CE/BZA might be in the same range as among users of oestrogen-progestin combination hormone therapy. The long-term effect of CE/BZA on the risk of stroke remains unknown (see section 5.1).

Should a stroke occur or be suspected, CE/BZA 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 CE/BZA.
- Patients with terminal renal insufficiency should be closely monitored, since it is expected that the level of circulating oestrogens components of CE/BZA 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/BZA 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/BZA 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/BZA 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, CE/BZA should be discontinued.
- 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). Patients treated with CE/BZA should be monitored carefully for signs of development of gallbladder disease.

- 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 corticosteroids and sex steroids, respectively. Free or 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 CE/BZA on the risk of dementia is unknown.

Excipients content

This medicinal product contains lactose, sucrose, glucose (in polydextrose and maltitol liquid) and sorbitol (in polydextrose).

Lactose, sucrose and glucose

Patients with rare hereditary problems of galactose intolerance, total lactase deficiency, fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicinal product.

Sorbitol

This medicinal product contains sorbitol which may affect the bioavailability of other concomitantly administered medicinal products. The additive effect of all sources of sorbitol from other concomitantly administered medicinal products and dietary sources should be taken into account.

4.5 Interaction with other medicinal products and other forms of interaction

Results from a clinical drug-drug interaction study conducted with CE/BZA and from interaction studies with CE or bazedoxifene monotherapy are summarised below.

Conjugated oestrogens

In vitro and *in vivo* studies have shown that oestrogens are partially metabolised by cytochrome P450 enzymes, including CYP3A4. However, in a clinical drug-drug interaction study, repeat administration of 200 mg itraconazole, a strong CYP3A4 inhibitor, had minimal impact on the pharmacokinetics of CE (as measured by estrone and equilin) and bazedoxifene when administered with a single dose of CE 0.45 mg/BZA 20 mg.

The metabolism of oestrogens may be increased by concomitant use of substances known to induce drug-metabolising enzymes, such as anticonvulsants (e.g., phenobarbital, phenytoin, carbamazepine) and anti-infectives (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.

Effect of HRT with oestrogens on other medicinal products

Hormone contraceptives containing oestrogens have been shown to significantly decrease plasma concentrations of lamotrigine when co-administered due to induction of lamotrigine glucuronidation. This may reduce seizure control. Although the potential interaction between hormone replacement therapy and lamotrigine has not been studied, it is expected that a similar interaction exists, which may lead to a reduction in seizure control among women taking both medicinal products together.

Bazedoxifene

The metabolism of bazedoxifene may be increased by concomitant use of substances known to induce uridine diphosphate glucuronosyltransferases (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 (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.

4.6 Fertility, pregnancy and lactation

Pregnancy

CE/BZA 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 CE/BZA in pregnant women. If pregnancy occurs during treatment with CE/BZA, 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

CE/BZA 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/BZA 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

CE/BZA 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 most commonly reported adverse reaction 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/BZA (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).

System organ class	Frequency of occurrence of adverse reactions			
	Very common	Common	Uncommon	Rare
Infections and infestations		Vulvovaginal candidiasis		
Vascular disorders				Venous thromboembolic events (including, pulmonary embolism, retinal vein thrombosis, deep vein thrombosis and thrombophlebitis)
Gastrointestinal disorders	Abdominal pain	Constipation; diarrhoea; nausea		
Hepatobiliary disorders			Cholecystitis	
Musculoskeletal and connective tissue disorders		Muscle spasms		
Investigations		Blood triglycerides increased		

Description of selected adverse reactions

Breast cancer risk

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

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

Age range (years)	Incidence per 1,000 women in placebo arm over 5 years	Risk ratio & 95% CI	Additional cases per 1,000 ET users over 5 years (95% CI)
CE Oestrogen only			
50-79	21	0.8 (0.7-1.0)	-4 (-6 – 0)*

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

Largest meta-analysis of prospective epidemiological studies

Estimated additional risk of breast cancer after 5 years' use in women with BMI 27 (kg/m^2)

Age at start HRT (years)	Incidence per 1,000 never-users of HRT over a 5 year period (50-54 years)*	Risk ratio	Additional cases per 1,000 HRT users after 5 years
Oestrogen only			
50	13.3	1.2	2.7

* Taken from baseline incidence rates in England in 2015 in women with BMI 27

Note: Since the background incidence of breast cancer differs by EU country, the number of additional cases of breast cancer will also change proportionately.

Estimated additional risk of breast cancer after 10 years' use in women with BMI 27 (kg/m^2)

Age at start HRT (years)	Incidence per 1,000 never-users of HRT over a 10 year period (50-59 years)*	Risk ratio	Additional cases per 1,000 HRT users after 10 years
Oestrogen only			
50	26.6	1.3	7.1

* Taken from baseline incidence rates in England in 2015 in women with BMI 27
Note: Since the background incidence of breast cancer differs by EU country, the number of additional cases of breast cancer will also change proportionately.

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.

CE/BZA 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

Use of oestrogen-only HRT has been associated with a slightly increased risk of having ovarian cancer diagnosed (see section 4.4).

A meta-analysis from 52 epidemiological studies reported an increased risk of ovarian cancer in women currently using HRT compared to women who have never used HRT (RR 1.43, 95% CI 1.31-1.56). For women aged 50 to 54 years taking 5 years of HRT, this results in about 1 extra case per 2,000 users. In women aged 50 to 54 who are not taking HRT, about 2 women in 2,000 will be diagnosed with ovarian cancer over a 5-year period.

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

Age range (years)	Incidence per 1,000 women in placebo arm over 5 years	Risk ratio & 95%CI	Additional cases per 1,000 ET users
Oral oestrogen-only*			
50-59	7	1.2 (0.6-2.4)	1 (-3-10)

*study in women with no uterus

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

Age range (years)	Incidence per 1,000 women in placebo arm over 5 years	Risk ratio & 95%CI	Additional cases per 1,000 HRT users over 5 years
50-59	8	1.3 (1.1-1.6)	3 (1-5)

**no differentiation was made between ischaemic and haemorrhagic stroke.*

Adverse reactions reported with CE and/or bazedoxifene monotherapy

Adverse reactions were categorised 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

System organ class	Frequency of occurrence of adverse reactions			
	Common	Uncommon	Rare	Very rare
Infections and infestations		Vaginitis		
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)			Growth potentiation of benign meningioma; fibrocystic breast disease	Enlargement of hepatic haemangiomas
Immune system disorders		Hypersensitivity	Angioedema; anaphylactic/anaphylactoid reactions; urticaria	
Metabolism and nutrition disorders			Glucose intolerance	Exacerbation of porphyria; hypocalcaemia (in patients with disease that can predispose to severe hypocalcaemia)
Psychiatric disorders		Dementia; depression; mood altered; changes in libido	Irritability	

System organ class	Frequency of occurrence of adverse reactions			
	Common	Uncommon	Rare	Very rare
Nervous system disorders		Migraine; headache; dizziness; nervousness	Exacerbation of epilepsy	Exacerbation of chorea
Eye disorders		Intolerance to contact lenses		
Cardiac disorders			Myocardial infarction	
Respiratory, thoracic and mediastinal disorders			Exacerbation of asthma	
Gastrointestinal disorders		Nausea	Pancreatitis; ischaemic colitis; vomiting	
Skin and subcutaneous tissue disorders	Alopecia	Hirsutism; rash; pruritus; chloasma		Erythema multiforme; erythema nodosum
Musculoskeletal and connective tissue disorders	Arthralgia; leg cramps			
Reproductive system and breast disorders	Breast pain, tenderness, enlargement, discharge; leucorrhoea	Change in cervical ectropion and secretion	Pelvic pain	
Investigations	Changes in weight (increase or decrease)			Increases in blood pressure

Adverse reactions that have been observed with bazedoxifene monotherapy

System organ class	Frequency of occurrence of adverse reactions			
	Very common	Common	Uncommon	Not known
Immune system disorders		Hypersensitivity		
Nervous system disorders		Somnolence		
Eye disorders			Retinal vein thrombosis	Visual acuity reduced, blurred vision, photopsia, visual field defect, visual impairment, dry eye, eyelid oedema, blepharospasm, eye pain and eye swelling
Cardiac disorders				Palpitations
Vascular disorders	Hot flush		Deep vein	

System organ class	Frequency of occurrence of adverse reactions			
	Very common	Common	Uncommon	Not known
			thrombosis, thrombophlebitis superficial	
Respiratory, thoracic and mediastinal disorders			Pulmonary embolism	
Gastrointestinal disorders		Dry mouth		
Skin and subcutaneous tissue disorders		Urticaria, rash, pruritus		
Musculoskeletal and connective tissue disorders	Muscle spasms (includes leg cramps)			
General disorders and administration site conditions	Oedema peripheral			
Investigations		Blood triglycerides increased, alanine aminotransferase increased; aspartate aminotransferase increased		

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

There is no specific antidote. In case of overdose it is recommended that the patient be monitored for any signs or symptoms of adverse reactions and appropriate symptomatic treatment be instituted immediately.

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: Sex hormones and modulators of the genital system; oestrogens, combinations with other drugs; ATC code: G03CC07

Mechanism of action

CE/BZA pairs CE with the selective oestrogen receptor modulator (SERM), BZA, 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 efficacy and safety

CE/BZA was evaluated in 4,868 postmenopausal women who participated in 5 phase 3 trials. Among these, 1,585 women were treated with CE 0.45 mg/BZA 20 mg and 1,241 received placebo. Long-term exposure to CE/BZA for up to 2 years was evaluated; 3,322 women were exposed to CE/BZA for at least 1 year, and 1,999 women were exposed for 2 years.

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/BZA 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/BZA 20 mg during months 10 to 12. Irregular bleeding and/or spotting was reported in the CE 0.45 mg/BZA 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 96% of the women who received CE 0.45 mg/BZA 20 mg during months 10 to 12. Irregular bleeding and/or spotting was reported in the CE 0.45 mg/BZA 20 mg group by 8% of women during the first 3 months and by 4% of women during months 10 to 12.

Breast density

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

Risk of Breast Cancer

In an observational study of new users from five large US insurance claims databases with an average follow-up time of 22 months, the incidence rate of breast cancer among users of CE/BZA was 27.21/10,000 person-years (95% CI: 19.91, 34.51) based on 55 cases. The incidence rate among users of oestrogen-progestin combination hormone therapy was 36.33/10,000 person-years (95% CI: 30.42, 42.24) based on 231 cases. The long-term effect of CE/BZA on the risk of breast cancer remains unknown.

Risk of stroke

In an observational study of new users from five large US insurance claims databases with an average follow-up time of 10-11 months, the incidence rate of stroke among users of CE/BZA was 14.04/10,000 person-years (95% CI: 1.03, 27.05) based on 15 cases. The incidence rate among users of oestrogen-progestin combination hormone therapy was 13.36/10,000 person-years (95% CI: 7.11, 19.61) based on 41 cases. The long-term effect of CE/BZA on the risk of stroke remains unknown.

Effects on bone mineral density (BMD)

In a 1 year study, CE 0.45 mg/BZA 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

Of the total number of women in phase 3 clinical trials who received CE/BZA 20 mg, 2.4% (n=77) were aged ≥65 years. No overall differences in safety or efficacy 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 CE/BZA in all subsets of the paediatric population in the 'treatment of oestrogen deficiency symptoms in postmenopausal women' (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

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

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

Mean ± SD Steady-State Pharmacokinetic Parameters (n=24)

	C_{max} (ng/mL)	T_{max} (hr)	AUCss (ng·hr/mL)
Bazedoxifene	6.9 ± 3.9	2.5 ± 2.1	71 ± 34
Baseline-adjusted total estrone	2.6 ± 0.8	6.5 ± 1.6	35 ± 12

Absorption

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

CE/BZA can be administered with or without food.

Following administration of BZA 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 BZA 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_{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/BZA has not been studied.

Following intravenous administration of a 3 mg dose of BZA alone, the volume of distribution is 14.7 ±3.9 l/kg. BZA is highly bound (98% - 99%) to plasma proteins *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 BZA, after administration of CE/BZA, has not been studied.

Circulating oestrogens exist in a dynamic equilibrium of metabolic interconversions. 17β-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 BZA. BZA 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 BZA in plasma.

Elimination

After a single dose of CE/BZA, baseline-adjusted total estrone (representing CE) is eliminated with a half-life of approximately 17 hours. BZA 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 BZA is 0.4 ±0.1 L/h/kg based on intravenous administration. The major route of excretion of radiolabeled BZA is the faeces, and less than 1% of the dose is eliminated in urine.

Special populations

Elderly
The pharmacokinetics of CE/BZA have not been evaluated in women over 75 years of age.
The pharmacokinetics of a 20 mg single dose of BZA 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/BZA have not been evaluated in patients with renal impairment. Limited clinical data (n=5) for bazedoxifene monotherapy are available in subjects with moderate renal impairment (creatinine clearance <50 ml/min). A single 20 mg dose of BZA was administered to these subjects. Negligible (<1%) amounts of BZA are eliminated in urine. Impaired renal function showed little or no influence on bazedoxifene pharmacokinetics.

Hepatic impairment
The pharmacokinetics of CE/BZA 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/BZA in this population is contraindicated (see sections 4.2, 4.3 and 4.4).

Body mass index (BMI)
In a pharmacokinetic study (n=24) BMI appeared to have little impact on systemic exposure to CE and BZA.

5.3 Preclinical safety data

Carcinogenicity, mutagenicity, and impairment of fertility studies with CE/BZA 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 elicited male rat-specific nephropathies (corticomedullar nephrocalcinosis and enhanced spontaneous chronic progressive nephropathy) and associated adenomas and carcinomas at exposure ratios of 0.05 to 4 times, and dose ratios, based on surface area (mg/m^2), of approximately 0.6 to 22 times the clinical dose of 20 mg. These findings are considered rat-specific and presumably not relevant in humans. Renal cell carcinomas were observed in an 18-month bone efficacy study in aged ovariectomised cynomolgus monkeys at exposure ratios of 0.05 to 16.3 times, and dose ratios, based on surface area (mg/m^2), of approximately 0.2 to 24 times the clinical dose of 20 mg. These tumours are known to occur in aged nonhuman primates and were considered spontaneous in the aged monkeys and irrelevant to humans.

BZA 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/BZA have not been conducted. The following data are based on the findings in studies with BZA.

In rabbit studies with BZA, 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 BZA 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 /m^2 [20 mg/kg dosage in humans is 12.3 mg/m^2]) 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
Hypromellose 2208 (100,000 mPa•s) (E464)
Magnesium stearate
Calcium phosphate

Inert filler coating

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

Bazedoxifene active coating

Sucrose
Hypromellose 2910 (3 mPa•s) (E464)
Sucrose monopalmitate
Ascorbic acid

Colour coating

Hypromellose 2910 (6 mPa•s) (E464)
Titanium dioxide (E171)
Macrogol (400)
Red Iron oxide (E172)

Clear coating

Hydroxyethylcellulose
Povidone (E1201)
Polydextrose (E1200) (contains glucose and sorbitol)
Maltitol liquid
Poloxamer 188

Printing ink

Black Iron oxide (E172)
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

PVC/Aclar/PVC blister packs containing 28 modified-release tablets. Each blister pack is sealed in an aluminium foil blister pouch with an oxygen absorber.

6.6 Special precautions for disposal

No special requirements for disposal.

7. MARKETING AUTHORISATION HOLDER

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

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/14/960/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 16 December 2014
Date of latest renewal: 11 November 2019

10. DATE OF REVISION OF THE TEXT

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

ANNEX II

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

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

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

Pfizer Ireland Pharmaceuticals Unlimited Company
Little Connell
Newbridge
County Kildare
Ireland

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to medical prescription.

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

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

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

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

- **Risk management plan (RMP)**

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

An updated RMP should be submitted:

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

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

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

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

Read the package leaflet before use.
Swallow tablet whole.
Oral use

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

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP
After opening the blister pouch, use within 60 days.

9. SPECIAL STORAGE CONDITIONS

Do not store above 25ºC.

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

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

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

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/14/960/001 28 tablets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

DUAVIVE 0.45/20 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE INTERMEDIATE PACKAGING

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

Read the package leaflet before use.
Swallow tablet whole.
Oral use

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

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP
After opening the blister pouch, use within 60 days.

9. SPECIAL STORAGE CONDITIONS

Do not store above 25ºC.

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

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

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

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/14/960/001 28 tablets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

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

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 oestrogen receptor modulators (SERMs).

DUAVIVE is used in postmenopausal women who still have their uterus (womb) and have not had a natural period in the last 12 months.

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 oestrogens, 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 (retinal vein thrombosis).
- 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

Talk to your doctor before taking this medicine 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

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)
This medicine contains 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 shows that taking oestrogen-only hormone replacement therapy (HRT) increases the risk of breast cancer. The extra risk depends on how long you use HRT. The additional risk becomes clear within 3 years of use. After stopping HRT the extra risk will decrease with time, but the risk may persist for 10 years or more if you have used HRT for more than 5 years.

The effect of DUAVIVE on the risk of breast cancer might be in the same range as with oestrogen-progestin combination HRT.

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-much rarer than breast cancer. The use of oestrogen-only HRT has been associated with a slightly increased risk of ovarian cancer.

The risk of ovarian cancer varies with age. For example, in women aged 50 to 54 who are not taking HRT, about 2 women in 2,000 will be diagnosed with ovarian cancer over a 5-year period. For women who have been taking HRT for 5 years, there will be about 3 cases per 2,000 users (i.e. about 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.

Since 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 promptly:

- if 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)
- if you are seriously overweight (BMI >30 kg/m^2)
- if 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
- if you have systemic lupus erythematosus (SLE).
- if you have cancer.

If any of these conditions apply to you, talk to your doctor before you 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 might be in the same range as with oestrogen-progestin combination HRT.

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 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 Blood clots in a vein). Ask your doctor when you can start taking this medicine again.

In case of doubt, talk to your doctor before you take this medicine.

Other conditions

If you have any of the following your doctor should 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.

Children and adolescents

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

Other medicines and DUAVIVE

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

Some medicines may interfere with the effect of DUAVIVE. This might lead to irregular bleeding. This applies to the following medicines:
- Medicines for epilepsy (such as phenobarbital, phenytoin and carbamazepine);
- Medicines for tuberculosis (such as rifampicin, rifabutin);
- Medicines for HIV infection (such as nevirapine, efavirenz, ritonavir and nelfinavir);
- Herbal remedies containing St John's Wort (Hypericum perforatum)

DUAVIVE can affect the way some other medicines work:
- A medicine for epilepsy (lamotrigine), as this could increase the frequency of seizures

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 a minor 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, maltitol liquid, glucose and sorbitol

If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before using this medicinal product.
This medicine contains 0.0088 mg sorbitol in each tablet.

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.

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.

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.

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 begin to get migraine-like headaches, or severe headaches

Rare: may affect up to 1 in 1,000 people

- Signs of a blood clot, such as painful swelling and redness of the legs, sudden chest pain or difficulty in breathing.
- Signs of a blood clot in the eye (retinal vein), such as one sided visual disturbance including loss of vision, pain and swelling of the eye especially if sudden.
- 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
- Swelling of the eyes, nose, lips, mouth, tongue or throat, difficulty in breathing, severe

dizziness or fainting, skin rash (symptoms of angioedema)
- 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 (ischaemic 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
- 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

Not known: frequency cannot be estimated from the available data
- Other ocular reactions (seeing sparks or flashes of light, narrowing of visual field, and swelling of eye or eye lid)

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
- Visible swelling of the face, hands, legs, feet or ankles (peripheral oedema)

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

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
- Blood clot in a vein at the back of the eye (retinal vein) which may lead to loss of vision
- 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
- Increase in hair growth
- Difficulty wearing contact lenses

Rare: may affect up to 1 in 1,000 people

- Pelvic pain
- 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)
- Dry eye, eye pain, visual acuity reduced, visual impairment, blepharospasm (abnormal, involuntary blinking or spasm of the eyelids)

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

5. How to store 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, containing glucose and sorbitol) 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), red iron oxide (E172), black iron oxide (E172) 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 modified-release tablets are provided in PVC/Aclar/PVC blister packs containing 28 tablets. Each blister pack is sealed in an aluminium foil blister pouch with an oxygen absorber.

Marketing Authorisation Holder

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Manufacturer

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Other sources of information

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