

NEW ZEALAND DATA SHEET

1. PRODUCT NAME

Duavive[®] 0.45mg/20mg modified-release tablet

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Duavive (conjugated estrogens/bazedoxifene), pairs conjugated estrogens with bazedoxifene, a selective estrogen receptor modulator (SERM).

Each modified-release tablet contains 0.45 mg of conjugated estrogens (CE) and bazedoxifene acetate equivalent to 20 mg of bazedoxifene.

Excipient(s) with known effect

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

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

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

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Duavive is indicated for the treatment of estrogen 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 Dose and method of administration

Dose

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

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.

Duavive may be given at any time of day, without regard to meals. Tablets should be swallowed whole. Tablets should not be chewed, crushed or broken.

Dose dispensing is not appropriate for this product.

Special populations

Elderly

Duavive has not been studied in women over 75 years of age. In 224 women included in clinical trials, between 65 and 75 years of age, no dosage adjustment was required (see section 5.2).

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 section 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 section 4.3, 4.4 and 5.2)).

Paediatric population

There is no relevant use of Duavive in the paediatric population.

Method of Administration

The recommended dose for Duavive is CE 0.45 mg/bazedoxifene 20 mg taken as a single oral tablet, once daily.

4.3 Contraindications

Hypersensitivity to the active substances or to any of the excipients listed in DESCRIPTION.

Known, suspected, or past history of breast cancer.

Known, past or suspected estrogen-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 section 4.4).

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 estrogens or selective estrogen receptor modulators (SERMs).

Duavive has not been studied in the treatment of premature menopause.

Medical examination/follow-up

Before initiating or reinstating 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 estrogen-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 estrogens are administered alone for prolonged periods. The reported increase in endometrial cancer risk among estrogen-only users varies from 2- to 12-fold greater compared with non-users, depending on duration of treatment and estrogen dose. After stopping treatment, risk may remain elevated for at least 10 years. Women taking Duavive should not take additional estrogens 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 estrogen-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 estrogen-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 estrogen-progestogen 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 estrogen-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 estrogens 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 estrogens, 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 estrogen-only therapy. Randomised controlled data found no increased risk of CAD in hysterectomised women using estrogen-only therapy.

Ischaemic stroke

Estrogen-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).

Gallbladder disease

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 estrogens has been reported (see section 4.8).

Hypertriglyceridaemia

Women with pre-existing hypertriglyceridaemia should be followed closely during treatment with estrogens, since rare cases of large increases of plasma triglycerides leading to pancreatitis have been reported with estrogen 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.

Impaired liver function and past history of cholestatic jaundice

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

Fluid retention

Estrogens 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 estrogens components of Duavive will be increased. Use in this population is not recommended (see section 4.2).

Dementia

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

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

Other conditions

Estrogens 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).

Duavive contains lactose, sucrose, glucose (in polydextrose and maltitol solution component of Opaglos 2 Clear) and sorbitol (in polydextrose component of Opaglos 2 Clear). 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 medicines and other forms of interactions

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

Cytochrome P450

In vitro and *in vivo* studies have shown that estrogens 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/bazedoxifene 20 mg.

The metabolism of estrogens 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 estrogens. Clinically, an increased metabolism of estrogens may lead to decreased effect and changes in the uterine bleeding profile.

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

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.

Uridine Diphosphate Glucuronosyltransferase (UGT)

Bazedoxifene undergoes metabolism by 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 rifampin, 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).

Ibuprofen

The pharmacokinetics of bazedoxifene and ibuprofen are not significantly altered when the drugs are co-administered.

Atorvastatin

Concomitant administration of bazedoxifene (40 mg daily) and atorvastatin (20 mg, single-dose) to healthy postmenopausal women did not affect the pharmacokinetics of bazedoxifene, atorvastatin or its active metabolites.

Azithromycin

The pharmacokinetics of bazedoxifene were not significantly altered when co-administered with azithromycin.

Aluminium and Magnesium hydroxide

There was no clinically relevant pharmacokinetic interaction of antacids containing aluminium and magnesium hydroxide with bazedoxifene.

Drugs highly bound to plasma proteins

Based on *in vitro* bazedoxifene plasma protein-binding characteristics, interactions with warfarin, digoxin or diazepam are unlikely.

4.6 Fertility, pregnancy and lactation

Fertility

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

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. Estrous cycles and fertility were adversely affected in all bazedoxifene-treated female groups. The potential risk for humans is unknown.

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 fetuses and/or reductions in fetal body weights. No fetal developmental anomalies were observed. The potential risk for humans is unknown.

Pregnancy

Australian Pregnancy Category D

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 fetal exposure to estrogens indicate no teratogenic or fetotoxic effects.

Lactation

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

4.7 Effects on ability to drive and use machinery

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

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).

Adverse Reactions Observed with CE/bazedoxifene

Table 1 below lists the adverse reactions observed with CE/bazedoxifene (n=3,168) in placebo-controlled clinical trials.

Table 1: Adverse Reactions Observed with CE/bazedoxifene

System organ class	Frequency of occurrence of adverse reactions			
	Very common ($\geq 1/10$),	Common ($\geq 1/100$ to $< 1/10$)	Uncommon ($\geq 1/1,000$ to $< 1/100$)	Rare ($\geq 1/10,000$ to $< 1/1,000$)
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 estrogens alone is represented by several studies. Any increased risk to users of estrogen-only therapy is substantially lower than that seen in users of estrogen–progestogen 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 in Table 2 and Table 3.

Table 2: US WHI Estrogen 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 Estrogen 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.

Table 3: Million Women Study (Estradiol Only Arm) – Estimated Additional Risk of Breast Cancer after 5 Years Use

Age range (years)	Additional cases per 1,000 never-users of HRT over a 5 year period*	Risk ratio [#]	Additional cases per 1,000 ET users over 5 years (95% CI)
Estradiol only			
50-65	9-12	1.2	1-2 (0-3)

* 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 annual risk of endometrial cancer is about 5 in every 10,000 women with a uterus not using HRT.

In women with a uterus, use of estrogen-only HRT is not recommended because it increases the risk of endometrial cancer (see section 4.4). Depending on the duration of estrogen-only use and estrogen 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 estrogen-only use (see section 4.4). Endometrial hyperplasia may be a precursor to endometrial cancer.

Ovarian cancer

Long-term use of estrogen-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.

Estrogens 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 in Table 4.

Table 4: WHI Studies Estrogen 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 estrogen-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 estrogen-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 estrogen 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 (see Table 5).

Table 5: 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

Although the following are not considered adverse reactions for Duavive, they are adverse reactions that have been observed with CE (Table 6) and/or bazedoxifene (Table 7) monotherapy and may possibly occur with Duavive.

Table 6: Adverse Reactions that have been Observed with CE Monotherapy

System organ class	Frequency of occurrence of adverse reactions			
	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)
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	
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; ischemic colitis; vomiting	
Skin and subcutaneous tissue disorders	Alopecia	Hirsutism; rash; pruritus; chloasma		Erythema multiforme; erythema nodosum

System organ class	Frequency of occurrence of adverse reactions			
	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)
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)			Increase in blood pressure

Table 7: Adverse Reactions That Have Been Observed with Bazedoxifene Monotherapy

System organ class	Frequency of occurrence of adverse reactions				
	Very common	Common	Uncommon	Rare	Not Known
Immune system disorders		Hypersensitivity			
Nervous system disorders		Somnolence			
Eye disorders			Retinal vein thrombosis		
Cardiac disorders					Palpitations
Vascular disorders	Hot flush		Deep vein thrombosis; superficial thrombophlebitis		
Respiratory, thoracic and mediastinal disorders			Pulmonary embolism		
Gastrointestinal disorders		Dry mouth			
Skin and subcutaneous tissue disorders		Urticaria; rash**; pruritis			
Musculoskeletal and connective tissue disorders	Muscle spasms*				
General disorders and administration	Oedema peripheral				

System organ class	Frequency of occurrence of adverse reactions				
	Very common	Common	Uncommon	Rare	Not Known
site conditions					
Investigations		Blood triglycerides increased, alanine aminotransferase increased; aspartate aminotransferase increased			

* Includes leg cramps.

** Rash includes: maculopapular rash, petechial rash, pruritic rash, purpuric rash, pustular rash, rash, vesiculobullous rash.

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 medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions <https://nzphvc.otago.ac.nz/reporting/>.

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

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5. PHARMACOLOGICAL PROPERTIES

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

5.1 Pharmacodynamic properties

Mechanism of action

Duavive pairs CE with the selective estrogen receptor modulator (SERM), bazedoxifene; this pairing is defined as a tissue selective estrogen complex (TSEC). The active ingredients of CE are primarily the sulphate esters of estrone, equilin sulphates and 17 α / β -estradiol which

demonstrate tissue selective estrogen receptor agonist activity. These substitute for the loss of estrogen production in menopausal women, and alleviate menopausal symptoms. As estrogens promote the growth of the endometrium, unopposed estrogens increase the risk of endometrial hyperplasia and cancer. The addition of bazedoxifene, acting as an estrogen receptor antagonist in the uterus, greatly reduces the estrogen-induced risk of endometrial hyperplasia in non-hysterectomised women.

Clinical efficacy and safety

Relief of Estrogen 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, amenorrhoea 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, amenorrhoea 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

Elderly (≥ 65 years)

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 pharmacokinetics of CE/bazedoxifene have not been evaluated in a paediatric population.

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 (baseline adjusted for total estrone) and bazedoxifene are summarised in Table 8.

Table 8: Mean ± SD Steady-State (ss) Pharmacokinetic Parameters (n=24)

	C_{max} (ng/mL)	T_{max} (hr)	AUC_{ss} (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

C_{max} – maximum observed concentration

t_{max} – time to C_{max}

AUC – area under the concentration-time curve from time 0 to 24 hours

Absorption

After a single dose of CE/bazedoxifene, 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/bazedoxifene 20 mg were administered with a high-fat meal, bazedoxifene C_{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. Estrogen 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/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 *in vitro*, but does not bind to sex hormone binding globulin (SHBG).

The distribution of exogenous estrogens is similar to that of endogenous estrogens. Estrogens are widely distributed in the body and are generally found in higher concentrations in the sex hormone target organs. Estrogens 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 estrogens are metabolised in the same manner as endogenous estrogens. Circulating estrogens exist in a dynamic equilibrium of metabolic interconversions. 17 β -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 estrogens exists as sulfate conjugates, especially estrone sulfate, which serves as a circulating reservoir for the formation of more active estrogens.

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

The clearance of bazedoxifene is 0.4 \pm 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).

Body mass index (BMI)

In a clinical study, BMI was shown to have minimal impact on the relative systemic exposures of CE and bazedoxifene. A single dose of CE 0.45 mg/bazedoxifene 20 mg was administered to 12 obese (BMI ≥ 30 kg/m²) and 12 non-obese (BMI < 30 kg/m²) postmenopausal women. In obese subjects, the systemic exposures of baseline-adjusted total estrone, total equilin, and bazedoxifene were 21%, 32%, and 13% lower, respectively, compared to non-obese subjects.

5.3 Preclinical safety data

Genotoxicity

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

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.

Carcinogenicity

Carcinogenicity 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 ovariectomised 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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

In addition to the active ingredients, each Duavive tablet also contains the following inactive ingredients:

Conjugated estrogens tablet core: lactose, microcrystalline cellulose, powdered cellulose, hypromellose, magnesium stearate, calcium phosphate. Inert filler coating: sucrose, microcrystalline cellulose, hypromellose, macrogol 400.

Bazedoxifene active coating: sucrose, hypromellose, sucrose palmitate, ascorbic acid, Opadry[®] Pink, Opaglos[®] Clear, and Opacode[®] black ink.

6.2 Incompatibilities

None stated.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Store below 25°C.

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

After opening the blister pouch, use within 60 days.

6.5 Nature and contents of container

The tablets are provided in PVC/Aclar/PVC/Al blister packs containing 7 or 28 tablets. Not all presentations may be available.

6.6 Special precautions for disposal

Any unused product or waste material should be disposed of in accordance with local requirements.

7. MEDICINE SCHEDULE

Prescription Medicine.

8. SPONSOR

Pfizer New Zealand Limited
P O Box 3998
Auckland, New Zealand.

Toll Free Number: 0800 736 363.

9. DATE OF FIRST APPROVAL

19 May 2016.

10. DATE OF REVISION OF THE TEXT

25 February 2018.

Summary table of changes (25 February 2018)

Section changed	Summary of new information
All	Reformat NZ DS to EU SmPC format
Section 5.2	Editorial changes to make it clear that the percentage change for estone and equalin is based on 'baseline-adjusted total' estone levels, and 'total' equalin levels, respectively.