SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Tridestra

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Tridestra tablet (white):
Estradiol valerate 2 mg
Excipient with known effect
82 mg lactose (as monohydrate).

Tridestra tablet (light blue, sometimes spotted):
Estradiol valerate 2 mg
Medroxyprogesterone acetate 20 mg
Excipient with known effect
143 mg lactose (as monohydrate).

Tridestra tablet (yellow):
Placebo
Excipient with known effect
82 mg lactose (as monohydrate).

For the full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Tablets, oral.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Tridestra is indicated in adult women for:

i) Hormone replacement therapy (HRT) for oestrogen deficiency symptoms in peri- and post-menopausal women.

ii) Prevention of osteoporosis in postmenopausal women at high risk of future fractures who are intolerant of, or contraindicated for, other medicinal products approved for the prevention of osteoporosis. Please also refer to section 4.4

The experience of treating women older than 65 years is limited.

4.2 Posology and method of administration

Tridestra is a cyclic HRT that produces a vaginal bleed every 3 months. The bleeding occurs during treatment when the yellow (placebo) tablets are taken and is similar to the monthly bleed experienced during the normal menstrual cycle.

Method of administration
Tridestra consists of 91 tablets in a blister pack bearing calendar markings. Dosage is according to the calendar pack. One tablet should be taken daily without a break between packs.

The dosage during days 1 to 70 (inclusive) of the cycle is 2 mg estradiol valerate (white tablets). From day 71 to day 84 (inclusive) it is 2 mg of estradiol valerate and 20 mg of medroxyprogesterone acetate (light blue, sometimes spotted tablets). From day 85 to day 91 (inclusive) a placebo preparation (yellow tablets) is taken when a menstrual like bleed occurs.

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

Women with amenorrhoea who are not taking HRT or who are switching to Tridestra from continuous combined HRT product, may start treatment on any day.

Women who are still having periods may start treatment 5 days after the start of the period.

Women who are switching from a cyclic or continuous sequential HRT product to Tridestra treatment may start one week after completion of the cycle (28 days) ie at the end of a withdrawal bleed.

If the patient has forgotten to take one tablet, it should be taken within 12 hours otherwise the forgotten tablet should be discarded and the usual tablet taken the following day. Missing a dose may increase the likelihood of breakthrough bleeding and spotting.

Unless there is a previous diagnosis of endometriosis, it is not recommended to add a progestagen in hysterectomised women.

4.3 Contraindications

- Known, past or suspected breast cancer
- Known or suspected oestrogen-dependent malignant tumours (e.g. endometrial cancer)
- Undiagnosed genital bleeding
- Untreated endometrial hyperplasia
- Previous idiopathic or current venous thromboembolism (deep venous thrombosis (DVT), pulmonary embolism)
- Known thrombophilic disorders (e.g. protein C, protein S or antithrombin defiency, see section 4.4)
- Active or recent arterial thromboembolic disease (e.g. angina, myocardial infarction);
- Acute liver disease or a history of liver disease as long as liver function tests have failed to return to normal
- Hypersensitivity to the active substances or to any of the excipients listed in section 6.1.
- Porphyria.
- Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.4 Special warnings and precautions for use

For the treatment of postmenopausal symptoms, HRT 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 HRT should only be continued as long as the benefit outweighs the risk.

Evidence regarding the risks associated with HRT in the treatment of premature menopause is limited. Due to the low level of absolute risk in younger women, however, the balance of benefits and risks for these women may be more favourable than in older women.

Medical examination/follow-up

Before initiating or reinstituting HRT, 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 Tridestra, 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
- Angioedema (hereditary and acquired).

Reasons for immediate withdrawal of therapy

Therapy should be discontinued in case a contra-indication is discovered and in the following situations:

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

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 the duration of treatment and oestrogen dose (see Section 4.8). After stopping treatment risk may remain elevated for at least 10 years.

- The addition of a progestagen cyclically for at least 12 days per month/28 day cycle or continuous combined oestrogen-progestagen therapy in non-hysterectomised women prevents the excess risk associated with oestrogen-only HRT.
- Break-through bleeding and spotting may occur during the first months of treatment. If break-through bleeding or spotting appears after some time of therapy, or continues after treatment has been discontinued, the reason should be investigated, which may include endometrial biopsy to excluded endometrial malignancy.

Breast cancer

The overall evidence shows an increased risk of breast cancer in women taking combined oestrogen-progestagen or oestrogen-only HRT, that is dependent on the duration of taking HRT.

Combined oestrogen-progestagen therapy

- The randomised placebo-controlled trial, the Women's Health Initiative study (WHI) and a meta-analysis of prospective epidemiological studies including the Million Women Study (MWS), are consistent in reporting findings of an increased risk of breast cancer in women taking combined oestrogen-progestagen for HRT that becomes apparent after about 3 (1-4) years (see Section 4.8).

Oestrogen-only therapy

- The WHI trial found no increase in the risk of breast cancer in hysterectomised women using oestrogen-only HRT. Observational studies have mostly reported a small increase in risk of having breast cancer diagnosed that is lower than that found in users of oestrogen-progestagen combinations (see section 4.8).

In the MWS, the relative risk of breast cancer with conjugated equine estrogens (CEE) or estradiol (E2) was greater when a progestagen was added, either sequentially or continuously, and regardless of type of progestagen. There was no evidence of a difference in risk between the different routes of administration.

In the WHI study, the continuous combined conjugated equine estrogen and medroxyprogesterone acetate (CEE + MPA) product used was associated with breast cancers that were slightly larger in size and more frequently had local lymph node metastases compared to placebo.

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.

HRT, especially oestrogen-progestagen combined treatment, increases the density of mammographic images which may adversely affect the radiological detection of breast cancer.

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 or combined oestrogen-progestagen 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).

Venous thromboembolism

- HRT is associated with a 1.3-3 fold risk of developing venous thromboembolism (VTE), i.e. deep vein thrombosis or pulmonary embolism. One randomised controlled trial and epidemiological studies found a two- to threefold higher risk for users compared with non-users, For non-users it is estimated that the number of cases of VTE that will occur over a 5 year period is about 3 per 1 000 women aged 50-59 years and 8 per 1 000 women aged between 60-69 years. It is estimated that in healthy women who use HRT for 5 years, the number of additional cases of VTE over a 5 year period will be between 2 and 6 (best estimate = 4) per 1 000 women aged 50-59 years and between 5 and 15 (best estimate = 9) per 1 000 women aged 60-69 years. The occurrence of such an event is more likely in the first year of HRT than later (see Section 4.8).
- Patients with a history of VTE or known thrombophilic states have an increased risk of VTE and HRT may add to this risk. HRT is therefore contraindicated in these patients (see section 4.3). Personal or strong family history of thromboembolism or recurrent spontaneous abortion should be investigated in order to exclude a thrombophilic predisposition. Until a thorough evaluation of thrombophilic factors has been made or anticoagulant treatment initiated, use of HRT in such patients should be viewed as contraindicated. Those women already on anticoagulant treatment require careful consideration of the benefit-risk of use of HRT.
- Generally recognised risk factors for VTE include, use of oestrogen, older age, major surgery, prolonged immobilization, a personal history or family history, 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 HRT 4 to 6 weeks earlier is recommended. Treatment should not be restarted until the woman is completely mobilised.
- 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) HRT is contraindicated.
- Women already on chronic anticoagulant treatment require careful consideration of the benefit-risk of use of HRT.
- The risk of VTE may be temporarily increased with prolonged immobilisation, major trauma or major surgery. As in all postoperative patients, scrupulous attention should be given to prophylactic measures to prevent VTE following surgery. Where prolonged immobilisation is liable to follow elective surgery, particularly abdominal or orthopaedic surgery to the lower limbs, consideration should be given to temporarily stopping HRT 4 to 6 weeks earlier, if possible. Treatment should not be restarted until the woman is completely mobilised.
- If VTE develops after initiating therapy, the drug should be discontinued. Patients should be told to contact their doctors immediately when they are aware of a potential thromboembolic symptom (eg, 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 combined oestrogen-

progestagen or oestrogen-only HRT. Two large clinical trials (WHI and HERS i.e. Heart and Estrogen/progestin Replacement Study) showed a possible increased risk of cardiovascular morbidity in the first year of use and no overall benefit. For other HRT products there are only limited data from randomised controlled trials examining effects in cardiovascular morbidity and mortality. Therefore, it is uncertain whether these findings also extend to other HRT products.

Combined oestrogen-progestagen therapy
The relative risk of CAD during use of combined oestrogen+progestagen HRT is slightly increased. As the baseline absolute risk of CAD is strongly dependent on age, the number of extra cases of CAD due to oestrogen+progestagen use is very low in healthy women close to menopause, but will rise with more advanced age.

Oestrogen-only
Randomised controlled data found no increased risk of CAD in hysterectomised women using oestrogen-only therapy.

Ischaemic stroke

- Combined oestrogen-progestagen and oestrogen-only therapies are 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 HRT will increase with age (see section 4.8). One large randomised clinical trial (WHI-trial) found, as a secondary outcome, an increased risk of ischaemic stroke in healthy women during treatment with continuous combined conjugated estrogens and MPA. For women who do not use HRT, it is estimated that the number of cases of stroke that will occur over a 5 year period is about 3 per 1 000 women aged 50-59 years and 11 per 1 000 women aged 60-69 years. It is estimated that for women who use conjugated estrogens and MPA for 5 years, the number of additional cases will be between 0 and 3 (best estimate = 1) per 1 000 users aged 50-59 years and between 1 and 9 (best estimate = 4) per 1 000 users aged 60-69 years. It is unknown whether the increased risk also extends to other HRT products.

Other conditions

- Oestrogens may cause fluid retention and, therefore, patients with cardiac or renal dysfunction should be carefully observed. Patients with terminal renal insufficiency should be closely observed, since it is expected that the level of circulating active ingredients of Tridestra is increased.
- Women with pre-existing hypertriglyceridaemia should be followed closely during oestrogen replacement or HRT, since rare cases of large increases of plasma triglycerides leading to pancreatitis have been reported with oestrogen therapy in this condition.
- Exogenous oestrogens may induce or exacerbate symptoms of hereditary and acquired angioedema.
- 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 radio-immunoassay) 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).
- Chloasma may occasionally occur, especially in women with a history of chloasma gravidarum. Women with a tendency to chloasma should minimise exposure to the sun or ultraviolet radiation whilst taking HRT.

- HRT use does not improve cognitive function. There is some evidence from the WHI trial of increased risk of probable dementia in women who start using continuous combined or oestrogen-only HRT after the age of 65. It is unknown whether the findings apply to younger post-menopausal women or other HRT products.

ALT Elevations

During clinical trials with patients treated for hepatitis C virus (HCV) infections with the combination regimen ombitasvir/paritaprevir/ritonavir with and without dasabuvir, ALT elevations greater than 5 times the upper limit of normal (ULN) were significantly more frequent in women using ethinylestradiol-containing medicinal products such as CHCs. Additionally, also in patients treated with glecaprevir/pibrentasvir, ALT elevations were observed in women using ethinylestradiol-containing medications such as CHCs. Women using medicinal products containing oestrogens other than ethinylestradiol, such as estradiol, had a rate of ALT elevation similar to those not receiving any oestrogens; however, due to the limited number of women taking these other oestrogens, caution is warranted for co-administration with the combination drug regimen ombitasvir/paritaprevir/ritonavir with or without dasabuvir and also the regimen glecaprevir/pibrentasvir. See section 4.5.

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

4.5 Interaction with other medicinal products and other forms of interaction

The metabolism of oestrogens and progestogens may be increased by concomitant use of substances known to induce drug-metabolising enzymes, specifically cytochrome P450 enzymes, such as anticonvulsants (e.g. phenobarbital, phenytoin, carbamazepine) and 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.

When co-administered with sex hormones, many combinations of HIV protease inhibitors and non-nucleoside reverse transcriptase inhibitors including combinations with HCV inhibitors, can increase or decrease plasma concentrations of oestrogen. The net effect of these changes may be clinically relevant in some cases.

Therefore, the prescribing information of concomitant medications including HIV/HCV antivirals should be consulted to identify potential interactions and any related recommendations.

Herbal preparations containing St John's wort (*Hypericum perforatum*) may induce the metabolism of oestrogens and progestogens.

Clinically, an increased metabolism of estrogens and progestogens 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.

Pharmacodynamic Interactions
During clinical trials with the HCV combination drug regimen ombitasvir/paritaprevir/ritonavir with and without dasabuvir, ALT elevations greater than 5 times the upper limit of normal (ULN) were significantly more frequent in women using ethinylestradiol-containing medicinal products such as CHCs. Women using medicinal products containing oestrogens other than ethinylestradiol, such as estradiol, had a rate of ALT elevation similar to those not receiving any oestrogens; however, due to the limited number of women taking these other oestrogens, caution is warranted for co-administration with the combination drug regimen ombitasvir/paritaprevir/ritonavir with or without dasabuvir and also the regimen with glecaprevir/pibrentasvir (see section 4.4).

4.6 Fertility, pregnancy and lactation

Pregnancy
Tridestra is not indicated during pregnancy. If pregnancy occurs during medication with Tridestra treatment should be withdrawn immediately.

Clinically, data on a limited number of exposed pregnancies indicate no adverse effects of medroxyprogesterone acetate on the foetus.

The results of most epidemiological studies to date relevant to inadvertent foetal exposure to combinations of oestrogens and progestogen indicate no teratogenic or foetotoxic effect.

Breast-feeding
Tridestra is not indicated during lactation.

4.7 Effects on ability to drive and use machines

No effects on ability to drive and use machines have been observed

4.8 Undesirable effects

Adverse drug reactions occur most commonly in the first months of the treatment. They are usually mild and subside with continued treatment.

The most common adverse effect is breakthrough bleeding and spotting appearing in 22% of patients. The overall percentage of treated patients experiencing at least 1 adverse reaction is 47%.

Undesirable effects according to system organ class associated with HRT treatment are presented in the table below.

Organ system class	**Common ADRs, ≥1/100 <1/10**	**Uncommon ADRs, ≥1/1 000 <1/100**	**Rare ADRs, ≥1/10 000 <1/1 000**	**Adverse events reported post marketing with frequency not known (cannot be estimated**

				from the available data)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)		Benign breast neoplasm, benign endometrial neoplasm		Uterine fibroids
Immune system disorders		Hypersensitivity reaction		Exacerbation of angioedema (hereditary and acquired)
Metabolism and nutrition disorders	Oedema, weight increase, weight decrease	Increased appetite, hypercholesterolemia[1]		
Psychiatric disorders	Depression, nervousness, lethargy	Anxiety, insomnia, apathy, emotional lability, impaired concentration, changes in mood or libido, euphoria[1], agitation[1]		
Nervous system disorders	Headache, dizziness	Migraine, paraesthesia, tremor[1]		
Eye disorders		Visual impairment, dry eye[1]	Contact lense intolerance	
Cardiac disorders		Palpitations		
Vascular disorders	Hot flushes	Hypertension[1], superficial phlebitis[1], purpura[1]	Venous thromboembolism (i.e. deep leg or pelvic venous thrombosis and pulmonary embolism)[2]	Cerebral ischaemic events
Respiratory, thoracic and mediastinal disorders		Dyspnoea[1], rhinitis[1]		
Gastrointestinal disorders	Nausea, vomiting, stomach cramps, flatulence	Constipation dyspepsia[1], diarrhoea[1], rectal disorder[1]		Abdominal pain, bloating (abdominal distension)
Hepatobiliary disorders			Alterations in liver function and biliary flow	Cholestatic jaundice
Skin and subcutaneous		Acne, alopecia, dry skin, nail disorder[1],	Rash	Eczema

tissue disorders		skin nodule[1], hirsutism[1] erythema nodosum, urticaria		
Musculoskeletal and connective tissue disorders		Joint disorders, muscle cramps		
Renal and urinary disorders		Increased urinary frequency/urgency, urinary incontinence[1], cystitis[1], urine discoloration[1], haematuria[1]		
Reproductive system and breast disorders	Breast pain/tension, unscheduled vaginal bleeding or spotting, vaginal discharge, disorder of vulva/vagina, menstrual disorder	Breast enlargement, breast tenderness, endometrial hyperplasia, uterine disorder[1]	Dysmenorrhea, pre-menstrual like syndrome	
General disorders and administration site conditions	Increased sweating	Fatigue, abnormal laboratory test[1], asthenia[1], fever[1], flu syndrome[1], malaise[1]		

1) have been reported in single cases in clinical trials. Given the small study population (n = 611) it cannot be determined based on these results if the events are uncommon or rare
2) see sections 4.3 and 4.4

Other adverse reactions have been reported in association with estrogen-progestagen treatment:

- Myocardial infarction
- Gall bladder disease
- Skin and subcutaneous disorders: chloasma, erythema multiforme
- Pancreatitis (see section 4.4)
- Probable dementia over the age of 65 (see section 4.4)

Breast cancer risk

- An up to 2-fold increased risk of having breast cancer diagnosed is reported in women taking combined oestrogen-progestagen therapy for more than 5 years.
- The increased risk in users of oestrogen-only therapy is substantially lower than that seen in users of oestrogen-progestagen combinations.
- The level of risk is dependent on the duration of use (see section 4.4).
- Absolute risk estimations based on results of the largest randomised placebo-controlled trial (WHI-study) and the largest meta-analysis of prospective epidemiological studies are presented.

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 HRT			
50	13.3	1.2	2.7
Combined oestrogen-progestagen			
50	13.3	1.6	8.0
Note: Since the background incidence of breast cancer differs by EU country, the number of additional cases of breast cancer will also change proportionately.			

**Taken from baseline incidence rates in England in 2015 in women with BMI 27 (kg/m^2)*

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 HRT			
50	26.6	1.3	7.1
Combined oestrogen-progestagen			
50	26.6	1.8	20.8
Note: Since the background incidence of breast cancer differs by EU country, the number of additional cases of breast cancer will also change proportionately.			

**Taken from baseline incidence rates in England in 2015 in women with BMI 27 (kg/m^2)*

US WHI studies - additional risk of breast cancer after 5 years' use

Age range (yrs)	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 (95%CI)
		CEE oestrogen-only	
50-79	21	0.8 (0.7 – 1.0)	-4 (-6 – 0)*
		CEE+MPA oestrogen & progestagen‡	
50-79	17	1.2 (1.0 – 1.5)	+4 (0 - 9)

* WHI study in women with no uterus, which did not show an increase in risk of breast cancer.
‡When the analysis was restricted to women who had not used HRT prior to the study there was no increased risk apparent during the first 5 years of treatment: after 5 years the risk was higher than in non-users.

Endometrial cancer

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 between 5 and 55 extra cases diagnosed in every 1 000 women between the ages of 50 and 65.

Adding a progestagen to oestrogen-only therapy for at least 12 days per cycle can prevent this increased risk. In the Million Women Study the use of five years of combined (sequential or continuous) HRT did not increase risk of endometrial cancer (RR of 1.0 (0.8-1.2)).

Ovarian cancer risk
Use of oestrogen-only or combined oestrogen-progestagen 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
HRT is associated with a 1.3-3-fold increased relative risk of developing venous thromboembolism (VTE), i.e. deep vein thrombosis or pulmonary embolism. The occurrence of such an event is more likely in the first year of using HT (see section 4.4). Results of the WHI studies are presented:

WHI Studies - Additional risk of VTE over 5 years' use

Age range (years)	Incidence per 1 000 women in placebo arm over 5 years	Risk ratio and 95%CI	Additional cases per 1 000 HRT users
*Oral oestrogen-only*4*			
50-59	7	1.2 (0.6-2.4)	1 (-3 – 10)
Oral combined oestrogen-progestagen			
50-59	4	2.3 (1.2 – 4.3)	5 (1 – 13)

4 *Study in women with no uterus

Risk of coronary artery disease
- The risk of coronary artery disease is slightly increased in users of combined oestrogen-progestagen HRT over the age of 60 (see section 4.4).

Risk of ischaemic stroke
- The use of oestrogen-only and oestrogen + progestagen therapy is associated with an up to 1.5 fold increased relative risk of ischaemic stroke. The risk of haemorrhagic stroke is not increased during use of HRT.

- 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 HRT will increase with age, see section 4.4.

WHI studies combined - Additional risk of ischaemic stroke*5 over 5 years' use

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

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

- The adverse event table is to be followed by ADRs, (usually class-effects), common to all HRT products.

Other adverse reactions have been reported in association with oestrogen/progestagen treatment:
- Estrogen-dependent neoplasms benign and malignant, e.g. endometrial cancer.
- Venous thromboembolism, i.e. deep leg or pelvic venous thrombosis and pulmonary embolism, is more frequent among HRT users than among non-users. For further information see sections 4.3. Contraindications and 4.4. Special warnings and precautions for use.
- Myocardial infarction and stroke.
- Gall bladder disease.
- Skin and subcutaneous disorders: chloasma, erythema multiforme, erythema nodosum, vascular purpura.
- Probable dementia over the age of 65 (see section 4.4)

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 Yellow Card Scheme at: www.mhra.gov.uk/yellowcard.

4.9 Overdose

Overdosage of oestrogen may cause nausea, headache and withdrawal bleeding. Serious ill effects have not been reported following acute ingestion of large doses of oestrogens and progestogens in contraceptive formulations by young children. When needed, therapy is symptomatic.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Progestogens and Estrogens in Combination
ATC code: G03FB 06

- **Estradiol / Estradiol valerate**: the active ingredient, synthetic 17β-estradiol, is chemically and biologically identical to endogenous human estradiol. It substitutes for the loss of oestrogen production in menopausal women, and alleviates menopausal symptoms. Oestrogens prevent bone loss following menopause or ovariectomy.
- **Progestagen**: Medroxyprogesterone acetate (MPA) is a synthetic derivative of natural progesterone, a 17-α-hydroxy-6-methylprogesterone acetate. It has a similar effect to progesterone with slight androgenic activity. As oestrogens promote the growth of the endometrium, unopposed oestrogens increase the risk of endometrial hyperplasia and cancer. The addition of a progestagen greatly reduces the oestrogen-induced risk of endometrial hyperplasia in non-hysterectomised women.

- **Relief of oestrogen-deficiency symptoms and bleeding patterns**
  - Relief of menopausal symptoms was achieved during the first few weeks of treatment.
  - Tridestra causes a withdrawal bleed at the end of a 3 monthly cycle

- Regular withdrawal bleeding occurred in 77% of women with a mean duration of 5 days. Withdrawal bleeding usually started 2-3 days after the last tablet is taken of the 14 days of the oestrogen/progestagen phase (2 mg E_2V + 20 mg MPA). Break through bleeding and/or spotting appeared in 15% of the women during the first three months of therapy and in 27% during months 10-12 of treatment. Amenorrhoea (no bleeding or spotting) occurred in 0% of the cycles during the first year of treatment (for cyclic or sequential products).

- **Prevention of osteoporosis**
  - Oestrogen deficiency at menopause is associated with an increasing bone turnover and decline in bone mass.
  - The effect of oestrogens on bone mineral density (BMD) is dose dependent. Protection appears to be effective for as long as treatment is continued. After discontinuation of HRT, bone mass is lost at a rate similar to that in untreated women.
  - Evidence from the WHI trial and meta-analysed trials shows that current use of HRT, alone or in combination with a progestagen – given to predominantly healthy women – reduces the risk of hip, vertebral and other osteoporotic fractures. HRT may also prevent fractures in women with low bone density and/or established osteoporosis, but evidence for that is limited.
  - After 1 year of treatment with Tridestra, the increase in lumbar spine bone mineral density (BMD) was 3.3 □ 3.6 % (mean □ SD). The percentage of women who maintained or gained BMD in lumbar zone during treatment was 72.7%. After 2 years of treatment with Tridestra, the increase in BMD was 5.9 □ 3.0 % (mean □ SD). The percentage of women who maintained or gained BMD in lumber zone during treatment was 95.2%.
  - Tridestra also had an effect on hip BMD. The increase after 1 year was 2.3% □ 3.4% (mean □ SD) at the femoral neck. The percentage of women who maintained or gained BMD in the hip zone during treatment was 72.7%. The increase after 2 years was 0.6% □ 3.6% (mean □ SD) at femoral neck. The percentage of women who maintained or gained BMD in the hip zone during treatment was 52.4%.

5.2 Pharmacokinetic properties

Maximum plasma levels (C_{max}) of estradiol (about 250 pmol/l) are reached in about 5-7 hours. The trough concentration (C_{min}) of estradiol was about 142 pmol/l and the average concentration ($C_{average}$) about 185 pmol/l. In circulation, natural oestrogens are bound to sex hormone binding globulin and albumin. Free estradiol is metabolised in the liver and partly converted to less active oestrogens like estrone.

Maximum plasma levels (C_{max}) of estrone (about 1790 pmol/l) are reached in 5–7 hours after intake of the tablet. C_{min} of estrone was about 864 pmol/l, $C_{average}$ about 1160 pmol/l. Estrone is subjected to an enterohepatic cycle and its half-life is 15–20 hours. The majority of oestrogens are excreted via kidneys as conjugates (sulfates or glucuronides).

MPA is well absorbed from the gastrointestinal tract and rapidly distributed from circulation to extravascular tissues. After the intake of the Tridestra combination tablet, the maximum plasma level (C_{max}) of MPA (about 5 μg/L) is reached in about 2 hours. $C_{average}$ (after a single dose) was about 1.3 μg/L. The elimination half-life is 40-50 hours. MPA is metabolised in the liver and excreted as glucuronides both in urine and bile. The extent of absorption from the combination tablet is comparable to MPA given alone.

5.3. Preclinical Safety Data

Data from animal toxicity studies with estrodial and medroxyprogesterone acetate have shown expected oestrogenic and gestagenic effects, and do not reveal any particular risk for humans in the therapeutic dose-range..

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tridestra tablet (white):
Lactose
Maize starch
Gelatine
Purified water
Magnesium stearate
Talc

Tridestra tablet (light blue, sometimes spotted):
Lactose
Maize starch
Gelatine
Purified water
Magnesium stearate
Indigo carmine (E132)

Tridestra tablet (yellow):
Lactose
Maize starch
Gelatine
Purified water
Magnesium stearate
Yellow iron oxide (E172)

6.2. Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Store at room temperature (15-25 ^{o}C)
Store in a dry place

6.5. Nature and Contents of Container

A PVC/PVDC/AL thermofoiled blister pack.

Quantity: 91

6.6 Special precautions for disposal

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

7. MARKETING AUTHORISATION HOLDER

Orion Corporation
Orionintie 1
FIN-02200 Espoo
Finland

8. MARKETING AUTHORISATION NUMBER

PL 27925/0014

9. DATE OF FIRST AUTHORISATION/RENEWAL OF AUTHORISATION

11/01/2006

10 DATE OF REVISION OF THE TEXT

28/07/2023