1 NAME OF THE MEDICINAL PRODUCT

Totelle 1 mg /0.125 mg coated tablet.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each coated tablet contains 1.03 mg estradiol hemihydrate corresponding to 1.00 mg estradiol and 0.125 mg trimegestone.

Excipients with known effects: Lactose monohydrate and sucrose.
For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Coated tablet.

Blue, round, biconvex, coated tablet printed with “1/0.125”.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

- Hormone replacement therapy (HRT) for oestrogen deficiency symptoms in postmenopausal women more than 1 year postmenopause.
- 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. (See also section 4.4).

HRT should not be initiated or continued to prevent cardiovascular disease or dementia.

The benefits and risks of HRT must always be carefully weighed, including consideration of the emergence of risks as therapy continues (see section 4.4). Oestrogens with or without progestins should be prescribed at the lowest effective doses and for the shortest duration consistent with treatment goals and risks for the individual woman. When prescribing solely for the prevention of postmenopausal osteoporosis, therapy should only be considered for women at significant risk of osteoporosis and for whom non-oestrogen medications are not considered to be appropriate.

The experience treating women older than 65 years is limited.

4.2 Posology and method of administration

Posology

Treatment is a continuous combined regimen. One combined estradiol/ trimegestone tablet is taken daily without interruption.

For initiation and continuation of treatment of postmenopausal symptoms, the lowest effective dose for the shortest duration should be used (see also section 4.4). Patients should be re-evaluated periodically to determine if treatment for symptoms is still necessary.

In women who are not taking hormone replacement therapy or women who switch from another continuous combined hormone replacement therapy product, treatment may be started on any convenient day. In women transferring from a sequential hormone replacement therapy regimen, treatment should begin the day following completion of the prior regimen.

Renal impairment

There are no special dosage requirements in case of mild to moderate renal insufficiency. Subjects with severe renal insufficiency (creatinine clearance < 30 ml/min/1.73 m^2) have not been studied extensively; therefore, dosage recommendations cannot be given for this patient population (see section 4.4).

Hepatic impairment

Treatment is contraindicated in women with acute or chronic liver disease (see section 4.3).

Forgotten tablet

If one tablet is forgotten, it should be taken within 12 hours of when normally taken; otherwise, the tablet should be discarded, and the usual tablet should be taken the following day. If one or several tablets are forgotten, the risk of break-through bleeding or spotting is increased.

Method of administration

For oral use.

The tablets are to be swallowed whole, with water and can be taken during or between meals.

4.3 Contraindications

- Known, past or suspected breast cancer
- Known, or suspected oestrogen-dependent malignant tumour (e.g., endometrial cancer)
- Undiagnosed genital bleeding
- Untreated endometrial hyperplasia
- Previous or current venous thromboembolism (deep venous thrombosis, pulmonary embolism)
- Known thrombophilic disorders (e.g. protein C, protein S, or antithrombin deficiency, 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

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 Totelle 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 and in the following situations:

- Jaundice or deterioration in 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 breakthrough 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 an increased risk of breast cancer in women taking combined oestrogen-progestagen and possibly also oestrogen-only HRT, that is dependent on the duration of taking HRT.

- The randomized placebo-controlled trial the (Women's Health Initiative study (WHI), and epidemiological studies are consistent in finding an increased risk of breast cancer in women taking combined oestrogen-progestagen for HRT that becomes apparent after about 3 years (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.

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 the 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. 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 HRT may add to this risk. HRT is therefore contraindicated in these patients (see section 4.3)

Generally recognised risk factors for VTE include, use of oestrogens, older age, major surgery, prolonged immobilisation, obesity (BMI > 30 kg/m2), pregnancy/postpartum period, systemic lupus

erythematosus (SLE), and cancer. There is no consensus about the possible role of varicose veins in VTE.

As in all postoperative patients, prophylactic measures need be considered to prevent VTE following surgery. If prolonged immobilisation is to follow elective surgery temporarily stopping 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.

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 (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 combined oestrogen-progestagen or oestrogen-only HRT.

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.

Ischaemic stroke

Combined oestrogen-progestagen and oestrogen-only therapy 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).

Should a stroke occur or be suspected, oestrogens should be discontinued immediately.

Other conditions

Oestrogens may cause fluid retention, and therefore patients with cardiac or renal dysfunction should be carefully observed.

Women with pre-existing hypertriglyceridemia should be followed closely during oestrogen replacement or hormone replacement therapy, since rare cases of large increases of plasma triglycerides leading to pancreatitis have been reported with oestrogen therapy in this condition.

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-I-antitrypsin, ceruloplasmin).

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

Exogenous oestrogens may induce or exacerbate symptoms of angioedema, particularly in patients with hereditary angioedema.

Oestrogen therapy should be used with caution in women with hypoparathyroidism, as oestrogen-induced hypocalcemia may occur.

This medicinal product contains lactose and sucrose. Patients with rare hereditary problems of galactose intolerance, fructose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

The metabolism of oestrogens and progestagens may be increased by concomitant use of substances known to induce drug-metabolising enzymes, specifically cytochrome P450 enzymes, such as anticonvulsants, anti-infectives, dexamethasone and herbal preparations containing St John´s Wort (*Hypericum perforatum*). Strong CYP3A4 inducers such as phenobarbital, phenytoin, carbamazepine, rifampicin and dexamethasone may reduce plasma concentrations of 17ß-estradiol.

Ritonavir and nelfinavir, although known as strong inhibitors, by contrast exhibit inducing properties when used concomitantly with steroid hormones. Clinically, an increased metabolism of oestrogens and progestagens may lead to decreased effect and changes in the uterine bleeding profile.

CYP3A4 inhibitors such as cimetidine, erythromycin and ketoconazole may increase plasma concentrations of 17ß-estradiol and may result in increased risk of side effects.

In vitro studies have shown that trimegestone may inhibit cytochrome P450 2C19 (CYP2C19). The clinical relevance is not known; however trimegestone may moderately increase the plasma concentrations of drugs metabolised via CYP2C19 such as citalopram, imipramine, and diazepam. Similar *in vitro* studies with cytochrome P450 3A4 (CYP3A4), which is partially responsible for trimegestone metabolism, have demonstrated a low potential for an interaction.

Patients receiving concomitant telaprevir should be monitored for signs of oestrogen deficiency.

4.6 Fertility, pregnancy and lactation

Pregnancy
Totelle is not indicated during pregnancy.

If pregnancy occurs during medication with Totelle, treatment should be withdrawn immediately. For trimegestone no clinical data on exposed pregnancies are available. Studies in animals have shown reproductive toxicity (see section 5.3). The potential risk for humans is unknown. The results of most epidemiological studies to date relevant to inadvertent foetal exposure to combinations of oestrogens with other progestagens indicate no teratogenic or foetotoxic effect.

Breast-feeding
Totelle is not indicated during lactation.

4.7 Effects on ability to drive and use machines

Not relevant.

4.8 Undesirable effects

The adverse reactions listed in the table are based on post-marketing spontaneous (reporting rate), clinical trials and class-effects. Breast pain is a very common adverse event reported in ≥10% of patients.

These frequencies are based on conjugated equine oestrogens plus medroxyprogesterone acetate (MPA) data.

System Organ Class	**Very common ADRs (≥1/10)**	**Common ADRs (≥1/100 to <1/10)**	**Uncommon ADRs (≥1/1,000 to <1/100)**	**Rare ADRs (≥1/10,000 to <1/1,000)**	**Very Rare ADRs (<1/10,000)**
Infections and infestations	None	Vaginitis	Vaginal candidiasis	None	None
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	None	None	None	Breast cancer, Fibrocystic breast changes, Ovarian cancer, Growth potentiation of benign meningioma	Endometrial cancer, Enlargement of hepatic hemangiomas
Immune system disorders	None	None	None	Anaphylactic/ anapylactoid reactions, including urticaria and angioedema	None
Metabolism and nutrition disorders	None	None	None	Glucose intolerance	Exacerbation of porphyria, Hypocalcemia
Psychiatric disorders	None	Depression	Changes in libido, Mood disturbances, Dementia	Irritability	None
Nervous system disorders	None	None	Dizziness, Headache, Migraine, Anxiety	Stroke, Exacerbation of epilepsy	Exacerbation of chorea
Eye disorders	None	None	Intolerance to contact lenses	None	Retinal vascular thrombosis
Cardiac disorders	None	None	None	Myocardial infarction	None
Vascular disorders	None	None	Venous thrombosis, Pulmonary embolism	Superficial thrombophlebitis	None

System Organ Class	Very common ADRs (≥1/10)	Common ADRs (≥1/100 to <1/10)	Uncommon ADRs (≥1/1,000 to <1/100)	Rare ADRs (≥1/10,000 to <1/1,000)	Very Rare ADRs (<1/10,000)
Respiratory, thoracic and mediastinal disorders	None	None	None	Exacerbation of asthma	None
Gastrointestinal disorders	None	None	Nausea, Bloating, Abdominal pain	Vomiting, Pancreatitis, Ischaemic colitis	None
Hepatobiliary disorders	None	None	Gallbladder disease	None	Cholestatic jaundice
Skin and subcutaneous tissue disorders	None	None	Alopecia, Acne, Pruritus	Chloasma/ melasma, Hirsutism, Rash	Erythema multiforme, Erythema nodosum
Musculoskeletal and connective tissue disorders	None	Arthralgias, Leg cramps	None	None	None
Reproductive system and breast disorders	Breast pain	Breakthrough bleeding/ spotting, Dysmenorrhea , Breast tenderness/ enlargement/ discharge	Change in menstrual flow, Change in cervical ectropion and secretion	Galactorrhoea, Increased size of uterine leiomyomata	Endometrial hyperplasia
General disorders and administration site conditions	None	None	Oedema	None	None
Investigations	None	Changes in weight (increase or decrease), Increased triglycerides	None	None	Increase in blood pressure

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.
- Any 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).
- Results of the largest randomised placebo-controlled trial (WHI-study) and largest epidemiological study (MWS) are presented.

Million Women Study – 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**[*2]	**Risk ratio#**	**Additional cases per 1,000 HRT users over 5 years (95% CI)**
		Oestrogen only HRT	
50-65	9-12	1.2	1-2 (0-3)
		Combined oestrogen-progestagen	
50-65	9-12	1.7	6 (5-7)
#Overall risk ratio. The risk ratio is not constant but will increase with increasing duration on use. Note: Since the background incidence of breast cancer differs by EU country, the number of additional cases of breast cancer will also change proportionately. *2*Taken from baseline incidence rates in developed countries*			

US WHI studies - 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 HRT users over 5 years (95% CI)**
		CEE oestrogen-only	
50-79	21	0.8 (0.7-1.0)	-4 (-6 – 0)[*3]
		CEE+MPA oestrogen & progestagen‡	
50-79	17	1.2 (1.0 – 1.5)	+4 (0 – 9)
‡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. *3*WHI study in women with no uterus, which did not show an increase in risk of breast cancer*			

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 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

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 2000 users. In women aged 50 to 54 who are not taking HRT, about 2 women in 2000 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 & 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 plus 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 1000 women in placebo arm over 5 years**	**Risk ratio & 95% CI**	**Additional cases per 1000 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.*			

Other adverse reactions have been reported in association with oestrogen/progestagen treatment:

- Skin and subcutaneous tissue disorders: vascular purpura.

Paediatric population
Clinical studies have not been conducted in the paediatric population

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

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

occur in females. There is no specific antidote and further treatment if necessary should be symptomatic.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Progestagen and oestrogen in combination.
ATC code: G03F

Estradiol: 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.

Trimegestone: Trimegestone is a 19-norpregnane progestagen, with an *in vitro* affinity for the progesterone receptor approximately 6 times that of progesterone. Trimegestone has no significant androgenic, oestrogenic, mineralocorticoid, glucocorticoid, or antiglucocorticoid activity *in vivo*.

As oestrogens promote the growth of the endometrium, unopposed oestrogens increase the risk of endometrial hyperplasia and cancer. The addition of a progestagen reduces, but does not eliminate the oestrogen-induced risk of endometrial hyperplasia in non-hysterectomised women.

Clinical trial information:

- Relief of oestrogen-deficiency symptoms and bleeding patterns
  - Relief of menopausal symptoms was achieved during the first few weeks of treatment.
  - The incidence of amenorrhea (no bleeding or spotting) increased over time in women treated with Totelle. Amenorrhea was seen in 86% of women during months 10 –12 treatment. Break through bleeding and/or spotting appeared in 41% of the women during the first three months and in 14% of women during months 10-12 treatment.

- Prevention of osteoporosis
  - Oestrogen deficiency at menopause is associated with an increasing bone turnover and decline in bone mass.
  - The effect of oestrogens on the bone mineral density 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 show 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 the evidence for that is limited.
  - After 2 years of treatment with Totelle, the increase in lumbar spine bone mineral density (BMD) was 5.32% ± 3.63%. The percentage of women who maintained or gained BMD in the lumbar zone during treatment was 92%.
  - Totelle also had an effect on hip BMD. The increase after 2 years was 2.84% ± 3.01% at femoral neck and 2.93% ± 2.62% at total hip. The percentage of women who maintained or gained BMD in femoral neck and total hip during treatment was 82% and 89%, respectively.

5.2 Pharmacokinetic properties

Estradiol: Following oral administration of 1 mg estradiol in micronized form, rapid absorption from the gastrointestinal tract occurs. Concomitant intake of food moderately increases the extent of absorption of estradiol when administered as Totelle. Estradiol undergoes extensive first-pass metabolism in the liver and small intestine and reaches peak plasma concentrations of approximately 14 to 72 pg/ml within 4 to 8 hours after a single dose. Oestrogens are mainly excreted in urine in a biologically inactive form; they are also excreted in bile, where they are hydrolysed and reabsorbed (enterohepatic circulation). After repeated administration of 1 mg estradiol, the average plasma concentration is approximately 50 pg/ml with minimum plasma concentrations of 20 pg/ml. There were no alterations in the pharmacokinetics of estradiol when it was co-administered with trimegestone. Estradiol is highly bound to plasma proteins (98%), mainly albumin. Metabolism of estradiol occurs mainly in the liver and gut but also in target organs, and involves the formation of less active or inactive metabolites, including estrone, catecholoestrogens and several oestrogen sulfates and glucuronides.

Trimegestone: After single oral doses of 0.125 mg administered under fasting conditions to postmenopausal women, trimegestone is rapidly and completely absorbed with peak plasma concentrations of 2 to 5 ng/ml reached within 30 minutes. Food decreases the rate of absorption of trimegestone and reduces C_{max} by approximately 50% but does not affect the extent of its absorption when administered as Totelle. The absolute bioavailability after oral administration is approximately 100%. The terminal elimination half-life is approximately 17 hours (range 7 to 37 hours). The pharmacokinetics of trimegestone are dose proportional within the dose range of 0.0625 to 1 mg. After repeated once-a-day administration of 0.125 mg, steady state is reached by the third administration with average concentrations around 0.5 ng/ml and minimum plasma concentrations of 0.2 ng/ml. The pharmacokinetics of trimegestone after repeated administration can be predicted from single dose pharmacokinetics.

Trimegestone and its main metabolite trimegestone sulfate are highly bound to human plasma proteins (98%). Over the range of the concentrations reached after administration of the doses used in the clinical studies, the binding is constant and nonsaturable. The volume of distribution at steady state after intravenous administration is 1.8 l/kg.
Trimegestone is highly metabolised. The major metabolic pathway is sulfoconjugation; a minor pathway is oxidation via the CYP3A4 isoenzyme based on *in vitro* data. Trimegestone sulfate has 10 times greater plasma concentrations and a longer half-life (30 hours) than trimegestone, but less than one-tenth the progestin receptor-binding affinity of trimegestone. In plasma trimegestone sulfate is the main constituent of AUC after an oral single dose (approximately 55%). Unchanged trimegestone constitutes approximately 8% of AUC, while trimegestone glucuronide and 1- and 6-hydroxylated metabolites together constitute approximately 5% of AUC. After oral administration of radiolabeled trimegestone, 38% of the dose is excreted in urine while 54% is excreted in faeces. No unchanged trimegestone is excreted in urine.

Elderly
No differences in pharmacokinetic parameters for estradiol, trimegestone, and trimegestone sulfate were observed in elderly women (> 65 years) compared with younger postmenopausal women.

Renal impairment
In women with mild to moderate renal dysfunction (creatinine clearance > 30 ml/min/1.73 m^2) no effect on plasma concentrations of estradiol, trimegestone, and trimegestone sulfate were seen. In women with severe renal dysfunction (creatinine clearance < 30 ml/min/1.73 m^2) data are scarce but indicate an increase in plasma concentrations of estradiol and trimegestone sulfate.

Hepatic impairment
No pharmacokinetic studies have been conducted in women with liver disease.

5.3 Preclinical safety data

Estradiol:
In reproductive toxicity studies estradiol showed embryotoxic effects and induced feminisation of male foetuses. The relevance of these data for human exposure is unknown (see section 4.6).

Trimegestone:
Six (6) month toxicology studies in the rat and monkey showed no specific target organ toxicity other than effects associated with the progestomimetic action of the compound.
Embryotoxicity studies were conducted with high dosages of trimegestone alone in rats and rabbits. Histological examinations in rabbits showed a dose dependent masculinization of some female foetuses at all doses tested. This effect has been reported for other progestagens, and the relevance of this observation to humans is unknown.

Estradiol/Trimegestone:
In long-term studies in monkeys, estradiol/trimegestone induced reversible dose- and time-dependent hyperglycaemia at exposures that were approximately 6 or more times greater than those occurring in women. In specific clinical studies at the recommended dosage, no adverse effect on glucose and insulin metabolism has been seen.
Carcinogenicity studies in the mouse and rat showed only dose-related hormone-dependent neoplasms, an effect recognised for other oestrogen/progestagen combinations.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Core:
Lactose monohydrate
Macrogol 8000
Magnesium stearate
Talc

Coating:
Anhydrous calcium sulfate
Carnauba wax
Indigo carmine aluminium lake (E132)
Glycerol mono-oleates
Macrogol 20000
Microcrystalline cellulose
Pharmaceutical glaze (shellac)
Povidone
Printing ink (Black iron oxide (E172), Shellac and Propylene glycol)
Stearic acid
Sucrose
Titanium dioxide (E171)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

Do not store above 30°C.

6.5 Nature and content of container

28 tablets in blister (PVC/PE/ACLAR/Aluminium)
The package sizes are 1 x 28 tablets and 3 x 28 tablets. Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Wyeth AB
Box 1822
171 24 Solna

8 MARKETING AUTHORISATION NUMBER(S)

17675

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 2003-01-10
Date of latest renewal: 2009-11-22

10 DATE OF REVISION OF THE TEXT

2016-06-10