SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Zumenon® 2mg Film-coated Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 2 mg estradiol (as hemihydrate)

Excipient with known effect: each tablet contains 118.2 mg lactose monohydrate.

For the full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Brick-red, round, biconvex, film-coated tablets imprinted with '379' on one side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Hormone replacement therapy (HRT) for oestrogen deficiency symptoms in postmenopausal women at least 6 months since last menses.

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)

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

4.2 Posology and method of administration

Posology

One tablet to be taken orally

Zumenon is an oestrogen only continuous HRT for women with or without a uterus. In women with a uterus, a progestogen should be added to Zumenon for 12-14 days each month to reduce the risk to the endometrium. Unless there is a previous

diagnosis of endometriosis, it is not recommended to add a progestogen in hysterectomised women.

For initiation and continuation of treatment of postmenopausal symptoms, the lowest effective dose for the shortest duration (see also section 4.4) should be used.
In general, treatment should start with Zumenon 1mg. Depending on the clinical response, the dosage can afterwards be adjusted to individual need. If the complaints linked to oestrogen deficiency are not ameliorated the dosage can be increased by using Zumenon 2mg.

Starting Zumenon
In women who are not taking hormone replacement therapy and who are amenorrhoeic, are hysterectomised, or women who switch from a continuous combined hormone replacement therapy, treatment may be started on any convenient day. In women transferring from a cyclic or continuous sequential HRT regimen, treatment should begin the day following completion of the prior regimen. If the patient has regular menstruation periods, treatment is started on day one of bleeding

Administration
The dosage is one tablet per day. Zumenon should be taken continuously without a break between packs. Zumenon can be taken with or without food.

If a dose has been forgotten, it should be taken as soon as possible. When more than 12 hours have elapsed, it is recommended to continue with the next dose without taking the forgotten tablet. In the case of a missed or delayed dose the likelihood of breakthrough bleeding or spotting may be increased.

Paediatric population:
There is no relevant indication for the use of Zumenon in the paediatric population.

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 or current venous thromboembolism (deep vein 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;
Known hypersensitivity to the active substance or to any of the excipients;
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 Zumenon, in particular:

- Leiomyoma (uterine fibroids) or endometriosis
- A history of, or 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 cases where a contra-indication 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 progestogen cyclically for at least 12 days per month/28 day cycle or continuous combined oestrogen-progestogen therapy in non-hysterectomised women prevents the excess risk associated with oestrogen-only HRT.

For oral doses of estradiol >2 mg the endometrial safety of added progestogens has not been demonstrated.

Break-through bleeding and spotting may occur during the first few months of 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.

Unopposed oestrogen stimulation may lead to premalignant or malignant transformation in the residual foci of endometriosis. Therefore, the addition of progestogens to oestrogen replacement therapy should be considered in women who have undergone hysterectomy because of endometriosis, if they are known to have residual endometriosis.

Breast cancer

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

Combined oestrogen-progestogen therapy

- The randomised placebo-controlled trial the (Women's Health Initiative study (WHI), and a meta-analysis of prospective epidemiological studies are consistent in finding an increased risk of breast cancer in women taking combined oestrogen-progestogen 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 substantially lower than that found in users of oestrogen-progestogen combinations (see section 4.8).

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

HRT, especially oestrogen-progestogen 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-progestogen 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-progestogen or oestrogen-only HRT.

Combined oestrogen-progestogen therapy
The relative risk of CAD during use of combined oestrogen+progestogen 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+progestogen 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-progestogen 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).

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.
- Exogenous estrogens 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).
- 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.
- Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.
- Women who may be at risk of pregnancy should be advised to adhere to non-hormonal contraceptive methods.

ALT elevations

During clinical trials with patients treated for hepatitis C virus (HCV) infections with the combination regimen ombitasvir/paritaprevir/ritonavir and dasabuvir with and without ribavirin, 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 or sofosbuvir/velpatasvir/voxilaprevir, 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, and ombitasvir/paritaprevir/ritonavir and dasabuvir with or without ribavirin 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 following combination drug regimens: ombitasvir/paritaprevir/ritonavir and dasabuvir with or without ribavirin, glecaprevir/pibrentasvir or sofosbuvir/velpatasvir/voxilaprevir. See section 4.5.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed.

The efficacy of oestrogens might be impaired:

- The metabolism of oestrogens may be increased by concomitant use of substances known to induce drug-metabolising enzymes, specifically cytochrome P450 enzymes, 2B6, 3A4, 3A5, 3A7, such as anticonvulsants (eg. phenobarbital, phenytoin, carbamezepine) and anti-infectives (e.g. rifampicin, rifabutin, nevirapine, efavirenz).

- Ritonavir and nelfinavir, although known as strong inhibitors of CYP450 3A4, A5, A7, by contrast exhibit inducing properties when used concomitantly with steroid hormones.
- Herbal preparations containing St John's wort (Hypericum perforatum) may induce the metabolism of oestrogens and progestogens via the CYP450 3A4 pathway.

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

Oestrogens might interfere with the metabolism of other drugs:
Oestrogens per se may inhibit CYP450 drug-metabolising enzymes via competitive inhibition. This is in particular to be considered for substrates with a narrow therapeutic index, such as •
tacrolimus and cyclosporine A (CYP450 3A4, 3A3)
• fentanyl (CYP450 3A4)
• theophylline (CYP450 1A2).

Clinically this may lead to a plasma increase of the affected substances up to toxic levels. Thus, careful drug monitoring for an extended period of time might be indicated and a dosage decrease of tacrolimus, fentanyl, cyclosporin A, and theophylline may be necessary.

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 and dasabuvir with or without ribavirin, 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 with glecaprevir/pibrentasvir or sofosbuvir/velpatasvir/voxilaprevir, 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, and ombitasvir/paritaprevir/ritonavir and dasabuvir with or without ribavirin 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 following combination drug regimens: ombitasvir/paritaprevir/ritonavir and dasabuvir with or without ribavirin, glecaprevir/pibrentasvir or sofosbuvir/velpatasvir/voxilaprevir (see section 4.4).

4.6 Fertility, pregnancy and lactation

Pregnancy
Zumenon is not indicated during pregnancy. If pregnancy occurs during medication with Zumenon, treatment should be withdrawn immediately.
The results of most epidemiological studies to date relevant to inadvertant foetal exposure to oestrogens indicate no teratogenic or foetotoxic effects.

Lactation:
Zumenon is not indicated during lactation.

4.7 Effects on ability to drive and use machines

Zumenon does not affect the ability to drive and use machines.

4.8 Undesirable effects

Serious undesirable effects associated with the use of hormone replacement therapy are also mentioned in section 4.4 'Special warnings and precautions for use'.

The table below reports undesirable effects, that have been reported in users of hormone replacement therapy (HRT) by MedDRA system organ classes (MedDRA SOCs).

MedDRA system organ class	**Common >1/100, <1/10**	**Uncommon >1/1,000, <1/100**	**Rare >1/10,000, <1/1,000**	**Very rare <1/10,000 incl. isolated reports**
Infections and manifestations		Vaginal candidiasis		
Immune system disorders		Hypersensitivity		
Metabolism and nutrition disorders	Weight increased, Weight decreased			
Blood and the lymphatic system disorders				Haemolytic anaemia
Psychiatric disorders		Nervousness, Depressed mood	Anxiety, libido decreased, libido increased	
Nervous system disorders	Headache,	Dizziness	Migraine	
Eye disorders		Visual disturbances	Intolerance to contact lenses	
Cardiac disorders		Palpitations		
Vascular disorders		Hypertension, Peripheral vascular disease, Varicose vein, Venous thromboembolism		
Gastrointestinal disorders	Nausea, Abdominal pain	Dyspepsia	Bloating, Vomiting	
Hepatobiliary disorders		Gall bladder disorder		
Skin and subcutaneous tissue disorders	Rash, Pruritus	Urticaria Erythema nodosum,	Hirsutism, Acne	
Musculoskeletal	Leg cramps	Back pain	Muscle cramps	

and connective tissue disorders				
Reproductive system and breast disorders	Metrorrhagia, Uterine/vaginal bleeding including spotting, Pelvic pain	Change in cervical secretion, Menorrhagia, Breast pain/tenderness,	Breast enlargement, Premenstrual-like symptoms, Vaginal discharge, Dysmenorrhoea,	
General disorders and administration site reactions	Asthenia	Peripheral oedema, Oedema	Fatigue	

Other adverse reactions have been reported in association with estradiol treatment (frequency unknown):

Neoplasms benign, malignant and unspecified (incl. cysts and polyps)
Breast cancer[a]
Oestrogen dependent neoplasms benign and malignant, e.g. endometrial cancer[b], ovarian cancer[c]
Increase in size of leiomyoma

Nervous system disorders
Probable dementia over the age of 65 (see section 4.4)
Chorea
Exacerbation of epilepsy

Vascular disorders
Stroke[f]
Arterial thromboembolism, i.e. angina[e] and myocardial infarction[e]. For further information see sections 4.3 and 4.4.
Venous thromboembolism[d], i.e. deep leg or pelvic venous thrombosis and pulmonary embolism. For further information see sections 4.3 and 4.4.

Gastrointestinal disorders
Pancreatitis (in women with pre-existing hypertriglyceridaemia)
Gastroesophageal reflux disease

Hepatobiliary disorders
Hepatic function abnormal, sometimes with jaundice

Skin and subcutaneous tissue disorders
Angioedema, chloasma, erythema multiforme, vascular purpura.

Renal and urinary disorders
Urinary incontinence

Reproductive system and breast disorders
Fibrocystic breast disease

a. Breast cancer risk

• An up to 2-fold increased risk of having breast cancer diagnosed is reported in women taking combined oestrogen-progestogen therapy for more than 5 years.
• The increased risk in users of oestrogen-only therapy is lower than that seen in users of oestrogen-progestogen 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 or 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 1000 never-users of HRT over a 5 year period (50-54 years)[*1]	Risk ratio	Additional cases per 1000 HRT users after 5 years
Oestrogen only HRT			
50	13.3	1.2	2.7
Combined oestrogen-progestogen			
50	13.3	1.6	8.0
[*1]*Taken from baseline incidence rates in England in 2015 in women with BMI 27 (kg/m^2)*			
Note: Since the background incidence of breast cancer differs by EU country, the number of additional cases of breast cancer will also change proportionately.			

Estimated additional risk of breast cancer after 10 years' use in women with BMI 27 (kg/m2)

Age at start HRT (years)	Incidence per 1000 never-users of HRT over a 10 year period (50-59 years) *	Risk ratio	Additional cases per 1000 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
*Taken from baseline incidence rates in England in 2015 in women with BMI 27 (kg/m^2) Note: Since the background incidence of breast cancer differs by EU country, the number of additional cases of breast cancer will also change proportionately.			

US WHI studies - additional risk of breast cancer after 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 (95%CI)
CEE oestrogen-only			
50-79	21	0.8 (0.7 – 1.0)	-4 (-6 – 0)[*2]
CEE+MPA oestrogen & progestogen‡			
50-79	17	1.2 (1.0 – 1.5)	+4 (0 – 9)
[*2]*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.			

b. Endometrial cancer risk

Postmenopausal women with a uterus
The endometrial cancer risk is about 5 in every 1000 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 1000 women between the ages of 50 and 65.

Adding a progestogen 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)).

c. Ovarian cancer risk

Use of oestrogen-only or combined oestrogen-progestogen 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.

d. 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 1000 women in placebo arm over 5 years	Risk ratio and 95%CI	Additional cases per 1000 HRT users
Oral oestrogen-only[*3]			
50-59	7	1.2 (0.6-2.4)	1 (-3 – 10)
Oral combined oestrogen-progestogen			
50-59	4	2.3 (1.2 – 4.3)	5 (1 - 13)
[*3] *Study in women with no uterus*			

e. Risk of coronary artery disease

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

f. Risk of ischaemic stroke

• The use of oestrogen-only and oestrogen + progestogen 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[*4] over 5 years' use

Age range (years)	Incidence per 1000 women in placebo arm over 5 years	Risk ratio and 95%CI	Additional cases per 1000 HRT users
50-59	8	1.3 (1.1-1.6)	3 (1–5)
[*4] *no differentiation was made between ischaemic and haemorrhagic stroke.*			

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 directly via the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

Nausea, vomiting, sleepiness, dizziness and withdrawal bleeding may occur in some women. There is no specific antidote and treatment should be symptomatic. Aforementioned information is also applicable for overdosing in children.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Natural and semisynthetic oestrogens, plain.
ATC code: G03CA03.

Oestradiol
The active ingredient, synthetic 17β-oestradiol, is chemically and biologically identical to endogenous human oestradiol. It substitutes for the loss of oestrogen production in menopausal women, and alleviates menopausal symptoms. Oestrogens prevent bone loss following menopause or ovariectomy.

Combined therapy with progestogens is also recommended in hysterectomised women with a history of endometriosis as cancer development in extra-uterine endometriotic implants in women on oestrogen-only therapy has been reported (see section 4.4 Special warnings and precautions).

Clinical trial information
- Relief of oestrogen-deficiency symptoms and bleeding patterns

- Relief of menopausal symptoms was achieved during the first few weeks of treatment.
- Hot flushes have been shown to be significantly reduced with 1 mg and 2 mg 17 beta estradiol at 4 weeks.
- Regular withdrawal bleeding in women treated with Zumenon 1mg daily for 28 days and Dydrogesterone 10mg daily for the last 12-14 days of a 28 day cycle, occurred in approximately 75-80% of women with a mean duration of 5 days. Withdrawal bleeding usually started on the day of the last pill of the progestogen phase. Break-through bleeding and/or spotting occurred in approximately 10% of the women; amenorrhoea occurred in 21-25% of the women for months 10 to 12 of treatment.
- In women treated with Zumenon 2mg daily for 28 days and Dydrogesterone 10mg daily for the last 12-14 days of a 28 day cycle, approximately 90% of women had regular withdrawal bleeding. The start day and duration of bleeding, and the number of women with intermittent bleeding was the same as with Zumenon 1mg, amenorrhoea (no bleeding or spotting) occurred in 7-11% of the women for months 10 to 12 of 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 shows that current use of HRT, alone or in combination with a progestogen – 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 two years of treatment with Zumenon 2mg, the increase in lumbar spine bone mineral density (BMD) was 6.7% ± 3.9% (mean ± SD). The percentage of women who maintained or gained BMD in lumbar zone during treatment was 94.5%.
  - Zumenon 2mg also had an effect on hip BMD. The increase after two years of treatment with 2mg oestradiol was 2.6% ± 5.0% (mean ± SD) at femoral neck, 4.6% ± 5.0% (mean ± SD) at trochanter and 4.1%±7.4% (mean ± SD) at Wards triangle. The percentage of women who maintained or gained BMD in the 3 hip areas after treatment with 2mg oestradiol was 71-88%.
  - After 18 months treatment spinal trabecular bone density increased (annual increases of 2.5% in the women taking 2.0 mg micronized 17 betaestradiol).

5.2 Pharmacokinetic properties

Estradiol, estra-1,3,5(10)-triene-3,17ß-diol is identical to human ovarian estradiol.

Absorption

Absorption of estradiol is dependent on the particle size: micronized estradiol is rapidly absorbed from the gastrointestinal tract with arithmetic mean Tmax values at steady-state of 5.8 hours.

The following table provides the arithmetic mean steady state pharmacokinetic parameters of estradiol (E2), estrone (E1) and estrone sulphate (E1S) for 2 mg dose of micronized estradiol. Data is presented as arithmetic mean (standard deviation).

Estradiol 2 mg				
Parameters	E2	E1	Parameters	E1S*
C_{max} (pg/mL)	89 (16)	591 (178)	C_{max} (ng/mL)	25.9 (16.4)
C_{min} (pg/mL)	35.0 (13.4)	208 (102)	C_{min} (ng/mL)	5.7 (5.9)
C_{av} (pg/mL)	62.9 (15.6)	392 (142)	C_{av} (ng/mL)	13.1 (9.4)
AUC_{0-24} (pg.h/mL)	1486 (374)	9275 (3389)	AUC_{0-24} (ng.h/mL)	307.3 (224.1)

* E1S: data is taken from oral dosing of estradiol 2 mg + dydrogesterone 20 mg (no clinically relevant effects of dydrogesterone on estradiol kinetics are reported).

Distribution

Oestrogens can be found either unbound or bound. About 98- 99% of the estradiol dose binds to plasma proteins, from which about 30-52% to albumin and about 46-69% to the sex hormonebinding globulin (SHBG).

Biotransformation

Following oral administration, estradiol is extensively metabolised. The major unconjugated and conjugated metabolites are estrone and estrone sulphate. These metabolites can contribute to the oestrogen activity, either directly or after conversion to estradiol. Estrone sulphate may undergo enterohepatic circulation.

Elimination

In urine, the major compounds are the glucuronides of estrone and estradiol. The elimination half-life of estradiol and its main metabolites is between 10-16 h.

Oestrogens are secreted in the milk of nursing mothers.

Linearity/non-linearity

The mean estradiol exposure at steady-state after oral daily dosing of 2 mg micronized estradiol is approximately 2-fold greater than that after daily dosing of 1 mg micronized estradiol. Based on the elimination half-life of the micronized estradiol, it can be estimated that estradiol concentrations reach steady-state approximately within one week following oral daily administration

5.3 Preclinical safety data

There are no preclinical safety data of relevance to the prescriber in the target population that are additional to those already included in other sections of the Summary of Product Characteristics.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:

Lactose

Hypromellose

Maize starch

Colloidal anhydrous silica

Magnesium stearate

Film coat:

Hypromellose

Talc

Macrogol 400

Titanium dioxide E171

Iron oxide red E172

Iron oxide black E172

Iron oxide yellow E172

6.2 Incompatibilities

Not applicable

6.3 Shelf life

3 years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

The tablets are packed in blister strips of 28. The blister strips are made of PVC film with covering Aluminium foil. Each carton contains 84 tablets.

6.6 Special precautions for disposal

Medicines no longer required should not be disposed of via wastewater or household waste. Any unused product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

- Mylan Products Ltd.
  20 Station Close
  Potters Bar
  Herts
  EN6 1TL
  United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL 46302/0053

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

23/03/2006

10 DATE OF REVISION OF THE TEXT

17/04/2025