PRODUCT INFORMATION

ZUMENON® TABLETS

WARNING

Oestrogens and progestogens should not be used for the prevention of cardiovascular disease or dementia.

The Women's Health Initiative (WHI) study reported increased risks of myocardial infarction, stroke, invasive breast cancer, pulmonary emboli, and deep vein thrombosis in postmenopausal women (50 to 79 years of age) during 5 years of treatment with conjugated oestrogens (0.625 mg) combined with medroxyprogesterone acetate (2.5 mg) relative to placebo (see 'Clinical Trials' and 'Precautions'). The WHI study reported increased risks of stroke and deep vein thrombosis in postmenopausal women (50 to 79 years of age) during 6.8 years of treatment with conjugated oestrogens (0.625 mg) relative to placebo (see 'Clinical Trials' and 'Precautions').

The Women's Health Initiative Memory Study (WHIMS), a sub-study of WHI, reported increased risk of developing probable dementia in postmenopausal women 65 years of age or older during 4 to 5.2 years of treatment with conjugated oestrogens, with or without medroxyprogesterone acetate, relative to placebo. It is unknown whether this finding applies to younger postmenopausal women (see 'Clinical Trials' and 'Precautions').

Other doses of conjugated oestrogens and medroxyprogesterone acetate, and other combinations and dosage forms of oestrogens and progestogens were not studied in the WHI clinical trials and, in the absence of comparable data, these risks should be assumed to be similar. Because of these risks, oestrogens with or without progestogens should be prescribed at the lowest effective doses and for the shortest duration consistent with treatment goals and risks for the individual woman.

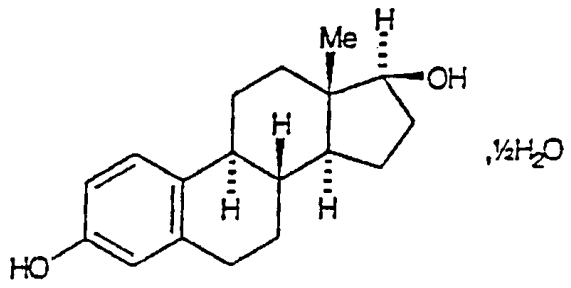
NAME OF THE MEDICINE

Non-proprietary Name

Oestradiol hemihydrate

Chemical Structure

Oestradiol Hemihydrate has the Chemical Name: Estra-1, 3, 5, (10) - triene - 3, 17β - diol; Chemical Formula: $C_{19}\ H_{24}\ O_2\ .\ ^1/_2\ H_2O$; Molecular Weight = 281.4. It has the following chemical structure:



CAS Number

50-28-2 (anhydrous)

DESCRIPTION

It is a white or almost white, crystalline powder or colourless crystals and is practically insoluble in water.

Zumenon tablets are immediate-release, film-coated tablets for oral use containing 2 mg of micronised Oestradiol (equivalent to 2.06 mg Oestradiol Hemihydrate). The tablets also contain the excipients lactose, hypromellose, maize starch, colloidal anhydrous silica, magnesium stearate. The colour used in the coating is Opadry OY-6957 Pink.

PHARMACOLOGY

Pharmacodynamics

Oestradiol is chemically and biologically identical to endogenous human oestradiol and has pharmacological actions similar to the physiological effects of the endogenous hormone. Oestradiol is the primary oestrogen and the most active of the ovarian hormones.

Zumenon restores plasma oestrogen levels and thus relieves or decreases oestrogen deficiency symptoms. It suppresses gonadotrophin secretion (FSH/LH) and improves vaginal cytology in post-menopausal women. It has a positive effect on the symptoms of the urogenital oestrogen deficiency syndrome including lower urinary tract dysfunction and atrophic vaginitis. Oestradiol is known to decrease LDL-C and increase HDL-C and triglycerides.

Pharmacokinetics

Micronised oestradiol is rapidly and efficiently absorbed from the gastrointestinal tract following oral administration. Peak plasma concentrations of oestradiol occur 4-6 hours after tablet ingestion. Thereafter elimination is slow and oestradiol levels are maintained above baseline for 24 hours. The steady state plasma level of oestradiol ranges between 70-100 pg/mL. Oestradiol has a half-life of approximately 14-16 hours. In the bloodstream more than 90% of oestradiol is bound to plasma proteins. Some oestradiol is converted to oestrone in the intestinal mucose before absorption into the portal vein. During passage through the liver a significant proportion of oestradiol is metabolised to oestrone. Oestradiol and hydroxyoestrones are also produced as well as sulfate and glucuronate conjugates. Circulating oestrone sulphate may be reconverted to oestrone and oestradiol in extrahepatic organs like the uterus. Oestrogens are excreted into the bile and undergo significant enterohepatic cycling. Biologically inactive glucuronide and sulphate conjugates are excreted in the urine (90 to 95%) and unconjugated oestrogen metabolites appear in the faeces (5 to 10%). Oestrogens are also secreted in the milk of nursing mothers.

CLINICAL TRIALS

Women's Health Initiative Studies.

The Women's Health Initiative (WHI) enrolled a total of 27,000 predominantly healthy postmenopausal women to assess the risks and benefits of either the use of oral conjugated oestrogens (CE) 0.625 mg/day alone or the use of a continuous combined regimen of conjugated oestrogens 0.625 mg/day plus medroxyprogesterone acetate 2.5 mg/day (CE+MPA) compared to placebo in the prevention of certain chronic diseases. The primary endpoint was the incidence of coronary heart disease (CHD) (nonfatal myocardial infarction and CHD death), with invasive breast cancer as the primary adverse outcome studied. A "global index" included the earliest occurrence of CHD, invasive breast cancer, stroke, pulmonary embolism (PE), endometrial cancer, colorectal cancer, hip fracture, or death due to other cause. The study did not evaluate the effects of CE alone or CE+MPA on menopausal symptoms.

The oestrogen alone substudy was stopped early because an increased risk of stroke was observed and it was deemed that no further information would be obtained regarding the risks and benefits of oestrogen alone in predetermined primary endpoints. Results of the oestrogen alone substudy, which included 10,739 women (average age of 63 years, range 50 to 79; 75.3% White, 15%Black, 6.1%Hispanic), after an average follow-up of 6.8 years are presented in Table 1.

TABLE 1. RELATIVE AND ABSOLUTE RISK SEEN IN THE OESTROGEN ALONE SUBSTUDY OF WHI[a]

Event[c]	**Relative Risk* CE alone vs Placebo at 6.8 Years (95%CI)**	**Placebo n = 5429**	**CE alone = 5310**
		Absolute Risk per 10,000 Women-years	
CHD events	0.91(0.75-1.12)	54	49
Non-fatal MI	*0.89(0.70-1.12)*	*41*	*37*
CHD death	*0.94(0.65-1.36)*	*16*	*15*
Invasive breast cancer	0.77(0.59-1.01)	33	26
Stroke	1.39(1.10-1.77)	32	44
Pulmonary embolism	1.34(0.87-2.06)	10	13
Colorectal cancer	1.08(0.75-1.55)	16	17
Hip fracture	0.61(0.41-0.91)	17	11
Death due to other causes than the events above	1.08(0.88-1.32)	50	53
Global Index[b]	1.01(0.91-1.12)	190	192
Deep vein thrombosis[c]	1.47(1.04-2.08)	15	21
Vertebral fractures[c]	0.62(0.42-0.93)	17	11
Total fractures[c]	0.70(0.63-0.79)	195	139

a: adapted from JAMA,2004;291:1701-1712

b: a subset of the events was combined in a "global index", defined as the earliest occurrence of CHD events, invasive breast cancer, stroke, pulmonary embolism, endometrial cancer, colorectal cancer, hip fracture, or death due to other causes

c: not included in Global Index

* nominal confidence intervals unadjusted for multiple looks and multiple comparisons.

For those outcomes included in the WHI "global index" that reached statistical significance, the absolute excess risk per 10,000 women-years in the group treated with CEE alone were 12 more strokes while the absolute risk reduction per 10,000 women-years was 6 fewer hip fractures. The absolute excess risk of events included in the "global index" was a nonsignificant 2 events per 10,000 women-years. There was no difference between the groups in terms of all-cause mortality. (see 'Boxed Warning' and 'Precautions').

The oestrogen plus progestogen substudy was also stopped early because, according to the predefined stopping rule, the increased risk of breast cancer and cardiovascular events exceeded the specified benefits included in the "global index". Results of the oestrogen plus progestogen substudy, which included 16,608 women (average age of 63 years, range 50 to 79; 83.9% White, 6.5% Black, 5.5% Hispanic), after an average follow-up of 5.2 Years are presented in Table 2.

TABLE 2. RELATIVE AND ABSOLUTE RISK SEEN IN THE OESTROGEN PLUS PROGESTOGEN SUBSTUDY OF WHI[a]			
Event[c]	**Relative Risk CE + MPA vs Placebo at 5.2 Years (95%CI*)**	**Placebo n = 8102**	**CE + MPA = 8506**
		Absolute Risk per 10,000 Women-years	
CHD events	1.29 (1.02-1.63)	30	37
Non-fatal MI	*1.32 (1.02-1.72)*	*23*	*30*
CHD death	*1.18 (0.70-1.97))*	*6*	*7*
Invasive breast cancer[b]	1.26 (1.00-1.59)	30	38
Stroke	1.41 (1.07-1.85)	21	29
Pulmonary embolism	2.13 (1.39-3.25)	8	16
Colorectal cancer	0.63 (0.43-0.92)	16	10
Endometrial cancer	0.83 (0.47-1.47)	6	5
Hip fracture	0.66 (0.45-0.98)	15	10
Death due to causes other than the events above	0.92 (0.74-1.14)	40	37
Global Index[c]	1.15 (1.03-1.28)	151	170
Deep vein thrombosis[d]	2.07 (1.49-2.87)	13	26
Vertebral fractures[d]	0.66 (0.44-0.98)	15	9
Other osteoporotic fractures[d]	0.77 (0.69-0.86)	170	131

a: adapted from JAMA,2002;288:321-333

b: includes metastatic and non-metastatic breast cancer with the exception of in situ breast cancer

c: a subset of the events was combined in a "global index", defined as the earliest occurrence of CHD events, invasive breast cancer, stroke, pulmonary embolism, endometrial cancer, colorectal cancer, hip fracture, or death due to other causes

d: not included in Global index

* nominal confidence intervals unadjusted for multiple looks and multiple comparisons.

For those outcomes included in the WHI "global index", the absolute excess risks per 10,000 women-years in the group treated with CE + MPA were 7 more CHD events, 8 more strokes, 8 more PEs, and 8 more invasive breast cancers, while the absolute risk reductions per 10,000 women-years were 6 fewer colorectal cancers and 5 fewer hip fractures. The absolute excess risk of events included in the "global index" was 19 per 10,000 women-years. There was no difference between the groups in terms of all-cause mortality. (see 'Boxed Warning' and 'Precautions')

Women's Health Initiative Memory Study.

The oestrogen alone Women's Health Initiative Memory Study (WHIMS), a substudy of WHI, enrolled 2,947 predominantly healthy postmenopausal women 65 years of age and older (45% were age 65 to 69 years, 36% were 70 to 74 years, and 19% were 75 years of age and older) to evaluate the effects of conjugated oestrogens (CE) 0.625 mg/day alone on the incidence of probable dementia (primary outcome) compared with placebo. After an average follow-up of 5.2 years, 28 women in the oestrogen alone group (37 per 10,000 women-

years) and 19 in the placebo group (25 per 10,000 women-years) were diagnosed with probable dementia. The relative risk of probable dementia in the oestrogen alone group was 1.49 (95% CI, 0.83 to 2.66) compared to placebo. It is unknown whether these findings apply to younger postmenopausal women. (see 'Boxed Warning' and 'Precautions', 'Dementia' and 'Use in Geriatrics').

WHIMS sub-study enrolled 4,532 predominantly healthy postmenopausal women 65 years of age and older (47% were age 65 to 69 years, 35% were 70 to 74 years, and 18% were 75 years of age and older) to evaluate the effects of CE plus MPA on the incidence of probable dementia (primary outcome) compared with placebo. After an average follow-up of 4 years, 40 women in the oestrogen/progestogen group (45 per 10,000 women-years) and 21 in the placebo group (22 per 10,000 women-years) were diagnosed with probable dementia. The relative risk of probable dementia in the hormone therapy group was 2.05 (95% CI, 1.21 to 3.48) compared to placebo. Differences between groups became apparent in the first year of treatment. It is unknown whether these findings apply to younger postmenopausal women. (see 'Boxed Warning' and 'Precautions', 'Dementia' and 'Use in Geriatrics')

INDICATIONS

Symptomatic treatment of oestrogen deficiency due to natural or surgical menopause in hysterectomised post menopausal women.

For initiation and continuation of treatment of postmenopausal symptoms, the lowest effective dose for the shortest duration should be used with the goal being short term use. (see 'Dosage and Administration' and 'Clinical Trials').

In women with intact uteri, use of opposed therapy must be considered.

CONTRAINDICATIONS

- Non-hysterectomised women without opposing progestogen.
- Known, suspected or past history of carcinoma of the breast, endometrium or other oestrogen dependent neoplasia.
- Acute or chronic liver disease or a history of liver disease where the liver function tests have failed to return to normal.
- Vaginal bleeding of unknown aetiology in women with intact uteri.
- Untreated endometrial hyperplasia.
- Previous idiopathic or current venous thromboembolism (deep venous thrombosis, pulmonary embolism), or cerebrovascular accident.
- Known thrombophilic disorders (e.g., protein C, protein S or anti-thrombin deficiency, see 'Precautions').
- Active or recurrent arterial thromboembolic disease (e.g., angina, myocardial infarction).
- Porphyria
- Known or suspected pregnancy.
- Lactation.
- Known hypersensitivity to any ingredients contained in Zumenon tablets.

PRECAUTIONS

The benefits and risks of oestrogen/progestogen therapy must always be carefully weighed including consideration of the emergence of risks as therapy continues.

Medical Examination/Follow-up

Before initiating therapy, a complete medical and family history should be taken and a physical examination performed. Pre-treatment and subsequent physical examinations should include special reference to blood pressure, breasts, abdomen and pelvic organs. Mammography is advisable. Patients who are being, or have previously been treated with unopposed oestrogens should be examined with special care to exclude endometrial stimulation before commencing Zumenon therapy.

As a general rule, hormone replacement therapy (HRT) should not be prescribed for longer than one year without another physical examination including gynaecological examination being performed. Women on HRT should have regular breast examination and regular mammography (every 1-2 years). In all cases of undiagnosed, persistent or recurring abnormal vaginal bleeding, adequate diagnostic measures, including endometrial sampling, should be undertaken to rule out malignancy. The benefits and risks of HRT should be carefully considered. HRT should be dosed at the lowest effective dose to relieve symptoms and for the shortest duration for control of symptoms.

If oestradiol is administered in women with an intact uterus it has to be opposed by a progestogen. The contraindications and precautions relating to combined HRT should be regarded carefully. A careful appraisal of the risks and benefits should be undertaken over time in women treated with hormone replacement therapy. HRT should be dosed at the lowest effective dose to relieve symptoms and for the shortest duration for control of symptoms.

Patients in the peri-menopausal phase should be advised to use non-hormonal contraceptive methods.

Cardiovascular disorders

Oestrogen and oestrogen/progestogen therapy has been associated with an increased risk of cardiovascular events such as myocardial infarction and stroke, as well as venous thrombosis and pulmonary embolism (venous thromboembolism or VTE). Should any of these occur or be suspected, oestrogen/progestogen therapy should be discontinued immediately.

Risk factors for arterial vascular disease (e.g., hypertension, diabetes mellitus, tobacco use, hypercholesterolaemia, and obesity) and/or venous thromboembolism (e.g., personal history or family history of VTE, obesity, and systemic lupus erythematosus) should be managed appropriately.

Coronary heart disease and stroke

In the oestrogen alone substudy of the Women's Health Initiative (WHI) study, an increased risk of stroke was observed in women receiving conjugated estrogens (CE) 0.625 mg per day compared to women receiving placebo (44 vs 32 per 10,000 women-years). The increase in risk was observed in year one and persisted. (see 'Clinical Trials'). 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 'Adverse Effects').

In the oestrogen plus progestogen sub-study of the Women's Health Initiative (WHI) study, an increased risk of coronary heart disease (CHD) events (defined as nonfatal myocardial infarction and CHD death) was observed in women receiving CE plus MPA (conjugated estrogens 0.625 mg/day plus medroxyprogesterone acetate 2.5 mg/day) compared to women receiving placebo (37 vs 30 per 10,000 women-years). The increase in risk was observed in year one and persisted. (see 'Clinical Trials')

In the same sub-study of WHI, an increased risk of stroke was observed in women receiving oestrogen plus progestogen compared to women receiving placebo (29 vs 21 per 10,000 women-years). The increase in risk was observed after the first year and persisted.

In postmenopausal women with documented heart disease (n = 2,763, average age 66.7 years) a controlled clinical trial of secondary prevention of cardiovascular disease (Heart and Estrogen/progestin Replacement Study; HERS) treatment with CE plus MPA demonstrated no cardiovascular benefit. During an average follow-up of 4.1 years, treatment with CE plus MPA did not reduce the overall rate of CHD events in postmenopausal women with established coronary heart disease. There were more CHD events in the oestrogen/progestogen-treated group than in the placebo group in year 1, but not during the subsequent years. Two thousand three hundred and twenty one women from the original HERS trial agreed to participate in an open label extension of HERS, HERS II. Average follow-up in HERS II was an additional 2.7 years, for a total of 6.8 years overall. Rates of CHD events were comparable among women in the oestrogen/ progestogen-treated group and the placebo group in HERS, HERS II, and overall.

Venous thromboembolism (VTE)

In the oestrogen alone substudy of the Women's Health Initiative (WHI) study, an increased risk of deep vein thrombosis was observed in women receiving CE compared to placebo (21 vs 15 per 10,000 women-years). The increase in VTE risk was observed during the first year. (see 'Clinical Trials').

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 'Contraindications').

Generally recognised risk factors for VTE include use of oestrogens, older age, major surgery, obesity (BMI > 30 kg/m^2), pregnancy/postpartum period, systemic lupus erythematosus (SLE), and cancer.

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.

In the oestrogen plus progestogen sub-study of WHI, a 2-fold greater rate of VTE, including deep venous thrombosis and pulmonary embolism, was observed in women receiving CE plus MPA compared to women receiving placebo. The rate of VTE was 34 per 10,000 women-years in the oestrogen plus progestogen-treated group compared to 16 per 10,000 women-years in the placebo group. The increase in VTE risk was observed during the first year and persisted. (see 'Clinical Trials').

If feasible, oestrogens should be discontinued at least 4 to 6 weeks before surgery of the type associated with an increased risk of thromboembolism, or during periods of prolonged immobilisation.

Malignant neoplasms

<u>Endometrial cancer</u>

The use of unopposed oestrogens in women with intact uteri has been associated with an increased risk of endometrial cancer. The reported endometrial cancer risk among unopposed oestrogens users with an intact uterus is about 2- to 12-fold greater than in non-users, and appears dependent on duration of treatment and on oestrogen dose. Most studies show no significant increased risk associated with the use of oestrogens for less than one year. The greatest risk appears associated with prolonged use, with increased risks of 15- to 24-fold for five to ten years or more, and this risk has been shown to persist for at least 8 to 15 years after oestrogen therapy is discontinued. Clinical surveillance of all women taking oestrogen/progestogen combinations is important. Adequate diagnostic measures, including endometrial sampling when indicated, should be undertaken to rule out malignancy in all cases of undiagnosed persistent or recurring abnormal vaginal bleeding. There is no evidence that the use of natural oestrogens results in a different endometrial risk profile than

synthetic oestrogens of equivalent oestrogen dose. Adding a progestogen to postmenopausal oestrogen therapy has been shown to reduce the risk of endometrial hyperplasia, which may be a precursor to endometrial cancer.

Breast cancer

The use of oestrogens and progestogens by postmenopausal women has been reported to increase the risk of breast cancer. The most important randomised clinical trial providing information about this issue is the Women's Health Initiative (WHI) trial of oestrogen plus progestogen (see 'Clinical Trials'). The results from observational studies are generally consistent with those of the WHI clinical trial. After a mean follow-up of 5.6 years, the WHI trial reported an increased risk of breast cancer in women who took oestrogen plus progestogen. Observational studies have also reported an increased risk for oestrogen/progestogen combination therapy, and a smaller increased risk for oestrogen alone therapy, after several years of use. For both findings, the excess risk increased with duration of use, and appeared to return to baseline over about five years after stopping treatment (only the observational studies have substantial data on risk after stopping). In these studies, the risk of breast cancer was greater, and became apparent earlier, with oestrogen/progestogen combination therapy as compared to oestrogen alone therapy. However, these studies have not found significant variation in the risk of breast cancer among different oestrogens or among different oestrogen/progestogen combinations, doses, or routes of administration.

In the WHI trial of oestrogen plus progestogen, 26% of the women reported prior use of oestrogen alone and/or oestrogen/progestogen combination hormone therapy. After a mean follow-up of 5.6 years during the clinical trial, the overall relative risk of invasive breast cancer was 1.24 (95% confidence interval 1.01-1.54), and the overall absolute risk was 41 vs. 33 cases per 10,000 women-years, for oestrogen plus progestogen compared with placebo. Among women who reported prior use of hormone therapy, the relative risk of invasive breast cancer was 1.86, and the absolute risk was 46 vs. 25 cases per 10,000 women-years, for oestrogen plus progestogen compared with placebo. Among women who reported no prior use of hormone therapy, the relative risk of invasive breast cancer was 1.09, and the absolute risk was 40 vs. 36 cases per 10,000 women-years for oestrogen plus progestogen compared with placebo. In the WHI trial, invasive breast cancers were larger and diagnosed at a more advanced stage in the oestrogen plus progestogen group compared with the placebo group. Metastatic disease was rare with no apparent difference between the two groups. Other prognostic factors such as histologic subtype, grade and hormone receptor status did not differ between the groups.

The observational Million Women Study in Europe reported an increased risk of mortality due to breast cancer among current users of oestrogens alone or oestrogens plus progestogens compared to never users, while the oestrogen plus progestogen sub-study of WHI showed no effect on breast cancer mortality with a mean follow-up of 5.6 years.

The use of oestrogen plus progestogen has been reported to result in an increase in abnormal mammograms requiring further evaluation. All women should receive yearly breast examinations by a healthcare provider and perform monthly breast self-examinations. In addition, mammography examinations should be scheduled based on patient age, risk factors, and prior mammogram results.

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

Dementia

In the oestrogen alone Women's Health Initiative Memory Study (WHIMS), a substudy of WHI, a population of 2,947 hysterectomised women aged 65 to 79 years was randomised to conjugated estrogens (CE) 0.625 mg/day or placebo. In the oestrogen plus progestogen

WHIMS substudy, a population of 4,532 postmenopausal women aged 65 to 79 years was randomised to CE + MPA or placebo.

In the oestrogen alone substudy , after an average follow-up of 5.2 years, 28 women in the oestrogen alone group and 19 women in the placebo group were diagnosed with probable dementia. The relative risk of probable dementia for CE alone versus placebo was 1.49 (95%CI 0.83-2.66). The absolute risk of probable dementia for CE alone versus placebo was 37 versus 25 cases per 10,000 women-years.

In the oestrogen plus progestogen substudy, after an average follow-up of 4 years, 40 women in the oestrogen plus progestogen group and 21 women in the placebo group were diagnosed with probable dementia. The relative risk of probable dementia for oestrogen plus progestogen versus placebo was 45 versus 22 cases per 10,000 women-years.

Since both substudies were conducted in women aged 65 to 79 years, it is unknown whether these findings apply to younger postmenopausal women. (see 'Boxed Warning' and 'Precautions' and 'Use in Geriatrics').

Endometrial cancer

The reported endometrial cancer risk among unopposed oestrogen users is about 2- to 12-fold greater than in nonusers, and appears dependent on duration of treatment and on oestrogen dose. Most studies show no significant increased risk associated with the use of oestrogens for less than one year. The greatest risk appears associated with prolonged use, with increased risks of 15- to 24-fold for five to ten years or more, and this risk has been shown to persist for at least 8 to 15 years after oestrogen therapy is discontinued.

<u>Addition of a progestogen when a woman has not had a hysterectomy.</u>

Studies of the addition of a progestogen for 10 or more days of a cycle of oestrogen administration, or daily with oestrogen in a continuous regimen, have reported a lowered incidence of endometrial hyperplasia than would be induced by oestrogen treatment alone. Endometrial hyperplasia may be a precursor to endometrial cancer. There are, however, possible risks that may be associated with the use of progestogens with oestrogens compared with oestrogen-alone regimens. These include a possible increased risk of breast cancer, adverse effects on lipoprotein metabolism (e.g., lowering HDL, raising LDL) and impairment of glucose tolerance. Clinical surveillance of all women taking oestrogen/progestogen combinations is important. Adequate diagnostic measures, including endometrial sampling when indicated, should be undertaken to rule out malignancy in all cases of undiagnosed persistent or recurring abnormal vaginal bleeding. There is no evidence that the use of natural oestrogens results in a different endometrial risk profile than synthetic oestrogens of equivalent oestrogen dose.

Gallbladder Disease

A 2- to 4-fold increase in the risk of gallbladder disease requiring surgery in postmenopausal women receiving oestrogens has been reported.

Hypercalcaemia

Oestrogen administration may lead to severe hypercalcaemia in patients with breast cancer and bone metastases. If hypercalcaemia occurs, use of the drug should be stopped and appropriate measures taken to reduce the serum calcium level.

Visual Abnormalities

Retinal vascular thrombosis has been reported in patients receiving oestrogens. Discontinue medication pending examination if there is sudden partial or complete loss of vision, or a sudden onset of proptosis, diplopia, or migraine. If examination reveals papilloedema or retinal vascular lesions, oestrogens should be discontinued.

Elevated blood pressure

In a small number of case reports, substantial increases in blood pressure have been attributed to idiosyncratic reactions to oestrogens. In a large, randomised, placebo-controlled clinical trial, a generalised effect of oestrogen therapy on blood pressure was not seen. Blood pressure should be monitored at regular intervals with oestrogen use.

Hypertriglyceridaemia

In patients with pre-existing hypertriglyceridaemia, oestrogen therapy may be associated with elevations of plasma triglycerides leading to pancreatitis and other complications.

Impaired liver function and past history of cholestatic jaundice

Oestrogens may be poorly metabolised in patients with impaired liver function. For patients with a history of cholestatic jaundice associated with past oestrogen use or with pregnancy, caution should be exercised and in the case of recurrence, medication should be discontinued.

Hypothyroidism

Oestrogen administration leads to increased thyroid-binding globulin (TBG) levels. Patients with normal thyroid function can compensate for the increased TBG by making more thyroid hormone, thus maintaining free T4 and T3 serum concentrations in the normal range. Patients dependent on thyroid hormone replacement therapy who are also receiving oestrogens may require increased doses of their thyroid replacement therapy. These patients should have their thyroid function monitored in order to maintain their free thyroid hormone levels in an acceptable range.

Fluid retention

Because oestrogens/progestogens may cause some degree of fluid retention, patients with conditions that might be influenced by this factor, such as cardiac or renal dysfunction, warrant careful observation when oestrogens are prescribed.

Hypocalcaemia

Oestrogens should be used with caution in individuals with severe hypocalcaemia.

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 diminished 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 ‘ADVERSE EFFECTS’).

Exacerbation of endometriosis

Endometriosis may be exacerbated with administration of oestrogen therapy. A few cases of malignant transformation of residual endometrial implants have been reported in women treated post-hysterectomy with oestrogen alone therapy. For patients known to have residual endometriosis post-hysterectomy, the addition of progesterone should be considered.

Exacerbation of other conditions

Oestrogen therapy may cause an exacerbation of asthma, diabetes mellitus, epilepsy, migraine, porphyria, systemic lupus erythematosus, and hepatic haemangiomas and should be used with caution in women with these conditions.

Zumenon is not an oral contraceptive and will not restore fertility.

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
- Hypertension
- Liver disorders (e.g., liver adenoma)
- Diabetes mellitus with or without vascular involvement
- Cholelithiasis
- Otosclerosis

Reasons for immediate withdrawal of therapy:

Therapy should be discontinued on discovery of a contraindication and in the following situations:

- Jaundice or deterioration in liver function
- Significant increase in blood pressure
- New onset of migraine-type headache, diplopia, sudden partial or complete loss of vision or a sudden onset of proptosis
- Pregnancy

It is advisable to withdraw treatment with Zumenon at least four weeks before elective surgery of the type associated with increased risk of thromboembolism or during periods of prolonged immobilisation.

When oestrogens are given to hypertensive women, supervision is necessary and blood pressure should be monitored at regular intervals.

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 in Zumenon is increased.

Oestrogens can influence carbohydrate metabolism. This has not been observed with hormone replacement therapy involving natural oestrogens.

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Use in Pregnancy

Category B1

Oestrogens are contraindicated during known or suspected pregnancy.

Use in Lactation

Zumenon should not be taken by lactating mothers. Oestrogen administration to nursing mothers has been shown to decrease the quantity and quality of milk. Detectable amounts of oestrogen have been found in breast milk receiving these compounds, but the effect on the breastfed infant has not been determined.

Use in the Elderly

Of the total number of subjects in the oestrogen plus progestogen sub-study of the Women's Health Initiative study, 44% (n = 7,320) were 65 years and over, while 6.6% (n = 1,095) were 75 years and over (see 'Clinical Trials'). There was a higher incidence of stroke and invasive breast cancer in women 75 and over compared to women less than 75 years of age. In the Women's Health Initiative Memory Study (WHIMS), an ancillary study of WHI, a population of 4,532 women aged 65 to 79 years was randomised to a continuous combined regimen of conjugated oestrogens 0.625 mg/day plus medroxyprogesterone acetate 2.5 mg/day or placebo. A population of 2,947 hysterectomised women, aged 65 to 79 years, was randomised to conjugated oestrogens (CE 0.625 mg) alone or placebo. In the planned analysis, pooling the events in women receiving CE or CE plus MPA in comparison to those in women on placebo, the overall relative risk (RR) for probable dementia was 1.76 (95% CI 1.19-2.60). In the oestrogen-alone group, after an average follow-up of 5.2 years a RR of 1.49 (95% CI 0.83-2.66) for probable dementia was observed compared to placebo. In the oestrogen-plus-progestogen group, after an average follow-up of 4 years, a RR of 2.05 (95% CI 1.21-3.48) for probable dementia was observed compared to placebo. Since this study was conducted in women aged 65 to 79 years, it is unknown whether these findings apply to younger postmenopausal women. (See 'Precautions - Dementia')

With respect to efficacy in the approved indications, there have not been sufficient numbers of geriatric patients involved in studies utilising oestrogens and progestogens to determine whether those over 65 years of age differ from younger subjects in their response to oestrogens and progestogens.

Carcinogenicity

Supraphysiological doses of oestradiol have been associated with the induction of tumours in oestrogen-dependent target organs in all rodent species tested. The relevance of these findings with respect to humans has not been established.

Unopposed oestrogen therapy by women with intact uteri is associated with an increase in endometrial carcinoma, particularly with prolonged use. Adjunctive progestogen use for a minimum of ten days reduces the risk of endometrial hyperplasia. Endometrial hyperplasia (atypical or adenomatous) often precedes endometrial cancer.

There has been concern about the possible risk of breast cancer in oestrogen-treated women. Although many studies have failed to disclose an increased incidence of breast cancer, some have shown a small increase upon prolonged therapy (e.g. 10 years or longer). It is not known whether concurrent progestogen use influences the risk of breast cancer although recent studies suggest no reduction of the risk when progestogens are added to oestrogens. Epidemiological surveys have disclosed no increase in breast cancer mortality among oestrogen-treated women.

Women who are on long-term therapy or have breast nodules or fibrocystic disease should have regular breast examinations and should be instructed in self breast examination. Regular mammographic investigations should be conducted where considered appropriate. There is a need for caution when prescribing oestrogens in women who have a history of, or known, breast nodules or fibrocystic disease. Breast status should be closely monitored, supported by regular mammography.

Interactions with other Medicines

The concomitant use of drugs known to induce drug metabolising enzymes, specifically cytochrome P450 enzymes 2B6, 3A4, 3A5, 3A7, such as anticonvulsants (e.g. Phenobarbital, carbamazepine, phenytoin) and anti-infectives (e.g., rifampicin, rifabutin, nevirapine, efavirenz) and may increase the metabolism of oestrogen resulting in decreased oestrogenic activity.

Ritonavir and nelfinavir, although known as strong inhibitors, by contrast exhibit inducing properties when used concomitantly with steroid hormones.

Herbal preparations containing St. John's Wort (Hypericum perforatum) may induce the metabolism of oestrogens.

Oestrogens might interfere with the metabolism of other drugs:

Oestrogens may inhibit CYP450 drug metabolizing enzymes via competitive inhibition. This is in particular to be considered for substances with a narrow therapeutic index, such as

- Tacrolimus and cyclosporine A
- Fentanyl
- Theophylline

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 necessary and a dosage decrease of tacrolimus, fentanyl, cyclosporine A and theophylline may be necessary.

Zumenon does not cause drowsiness.

Effects on Ability to Drive and Use Machines

Zumenon has no or negligible influence on the ability to drive and use machines.

ADVERSE EFFECTS

Side effects, if they occur, are more common in the first months of treatment: breast tenderness and breakthrough bleeding may occur. Nausea, headache and oedema may occur but symptoms are normally transient. Skin reactions have also been reported. For the most serious adverse reactions associated with hormone replacement therapy see 'Precautions'.

Treatment emergent adverse reactions with Zumenon:

Very common (>10%)	Gastrointestinal	abdominal pain, nausea
	Reproductive, female	breast pain, dysmenorrhoea
	Body as a whole, general	headache
Common (1-10%)	Body as a whole, general	oedema, weight change
	Reproductive, female	intermittent bleeding/spotting
Uncommon (0.1-1%)	Reproductive, female	ovarian cyst

The following adverse effects have also been reported:

<u>Infections and infestations</u>
Vaginal candidiasis

<u>Neoplasms benign, malignant and unspecified (incl. cysts and polyps)</u>
Breast cancers
Oestrogen dependent neoplasms benign and malignant, e.g. endometrial cancer, ovarian cancer.
Increase in size of leiomyoma

<u>Immune system disorders</u>
Hypersensitivity reactions, systemic lupus erythematosus.

<u>Metabolism and nutrition disorders</u>
Change in carbohydrate metabolism.
Hypertriglyceridaemia.

Psychiatric disorders
Depression, changes in libido.

Nervous system disorders
Probable dementia (see 'Precautions'), chorea, exacerbation of epilepsy, migraine, dizziness

Eye disorders
Intolerance to contact lenses, steepening of corneal curvature

Cardiac disorders
Myocardial infarction

Vascular disorders
Stroke
Arterial thromboembolism (see 'Contraindications' and 'Precautions')
Venous thromboembolism, i.e. deep leg or pelvic venous thrombosis and pulmonary embolism (see 'Contraindications' and 'Precautions')

Gastrointestinal disorders
Pancreatitis (in women with pre-existing hypertriglyceridaemia)
Gastrooesophageal reflux disease
Vomiting, abdominal cramps, bloating

Hepatobiliary disorders
Hepatic function abnormal, sometimes with jaundice, asthenia or malaise, and abdominal pain
Gall bladder disorder

Skin and subcutaneous tissue disorders
Angiooedema
Erythema multiforme, erythema nodosum, vascular purpura
Chloasma or melasma which may persist when drug is discontinued
Allergic skin reactions (e.g., rash, pruritus, urticaria)

Renal and urinary disorders
Urinary incontinence
Cystitic like symptoms

Reproductive system and breast disorders
Breakthrough bleeding, dysmenorrhea, premenstrual-like syndrome, change in cervical erosion and degree of cervical secretion. Fibrocystic breast changes, breast tenderness, breast enlargement.

Congenital, familial and genetic disorders
Aggravation of porphyria

Investigations
Increase or decrease in weight
Total thyroid hormones increased

Breast cancer

For oestrogen-only HRT, estimates of relative risk (RR) from a reanalysis of original data from 51 epidemiological studies (in which >80% of HRT use was oestrogen-only HRT) and from the epidemiological Million Women Study (MWS) are similar at 1.35 (95% CI 1.21-1.49)

and 1.30 (95% CI 1.21-1.40), respectively. The MWS reported that, compared to never users, the use of various types of oestrogen-progestogen combined HRT was associated with a higher risk of breast cancer (RR=2.00, 95% CI 1.88-2.12) than use of oestrogens alone (RR=1.30, 95% CI 1.21-1.40) or use of tibolone (RR=1.45, 95% CI 1.25-1.68). The absolute risks calculated from the MWS and the WHI trials are presented below:

The MWS has estimated, from the known average incidence of breast cancer in developed countries, that:

For women not using HRT, about 32 in every 1,000 are expected to have breast cancer diagnosed between the ages of 50 and 64 years.

For 1,000 current or recent users of HRT, the number of additional cases during the corresponding period will be

- For users of oestrogen-only replacement therapy

  Between 0 and 3 (best estimate = 1.5) for 5 years' use
  Between 3 and 7 (best estimate = 5) for 10 years' use
- For users of oestrogen plus progestogen combined HRT

  Between 5 and 7 (best estimate = 6) for 5 years' use
  Between 18 and 20 (best estimate = 19) for 10 years' use

The WHI trial estimated that after 5.6 years of follow-up of women between the ages of 50 and 79 years, an additional 8 cases of invasive breast cancer would be due to oestrogen-progestogen combined HRT (CE plus MPA) per 10,000 women years. According to calculations from the trial data, it is estimated that:

- For 1,000 women in the placebo group about 16 cases of invasive breast cancer would be diagnosed in 5 years.
- For 1,000 women who used oestrogen + progestogen combined HRT (CE plus MPA), the number of additional cases would be between 0 and 9 (best estimate = 4) for 5 years' use.

The number of additional cases of breast cancer in women who use HRT is broadly similar for women who start HRT irrespective of age at start of use (between the ages of 45-65).

Endometrial cancer

In women with an intact uterus, the risk of endometrial hyperplasia and endometrial cancer increases with increasing duration of use of unopposed oestrogens (See 'Precautions').

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 'PRECAUTIONS'). 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 50-54 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 an increased 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 'Precautions').

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 **'**Precautions**'**).

Risk of ischaemic stroke

The use of oestrogen-only and oestrogen-progestogen therapy is associated with an increased relative risk of ischaemic stroke.

This relative risk is not dependent on age or on duration of use, but as the baseline risk is strongly age-dependent, the overall risk of stroke in women who use HRT will increase with age (See **'**Precautions**'**).

DOSAGE AND ADMINISTRATION

One tablet administered orally daily without interruption. (see 'Indications' and 'Precautions' for treatment duration advice).

Treatment of hysterectomised women and postmenopausal women may be started on any convenient day. In oligomenorrhoea, treatment is to commence on day 5 of the withdrawal bleed.

In order to counteract endometrial hyperplasia, which occurs with oestrogen monotherapy, it is recommended that a progestogen be given for at least ten days per calendar month in women with intact uteri.

If a dose has been forgotten, it should be taken as soon as possible. If more than 12 hours have elapsed, treatment should be continued with the next tablet without taking the forgotten tablet.

OVERDOSAGE

Symptoms

Acute toxicity studies did not indicate a risk of acute adverse effects in case of inadvertent overdosage of oestradiol.
Nausea, vomiting, sleepiness, dizziness and withdrawal bleeding may occur in some women. There is no specific antidote and treatment should be symptomatic.

Treatment

There are no specific therapeutic recommendations for the management of overdosage. In the event of a large overdose, gastric lavage can be undertaken and further treatment should be symptomatic.

Contact the Poisons Information Centre on 131126 for management of overdose.

PRESENTATION AND STORAGE CONDITIONS

Packs of 28*, 56 and 84* tablets. Each blister platform contains 28 round, biconvex, brick red, film-coated tablets of 7 mm diameter each containing 2 mg oestradiol bearing the inscription "379" on one side.

Store below 30°C. Protect from light.

*Presentations not available in Australia.

NAME AND ADDRESS OF THE SPONSOR

BGP Products Pty Ltd

299 Lane Cove Road

Macquarie Park NSW 2113

Australia

POISON SCHEDULE OF THE MEDICINE

Schedule 4

DATE OF FIRST INCLUSION IN THE ARTG

08 Sep 2000

DATE OF MOST RECENT AMENDMENT

23rd September 2016 Version 06