AUSTRALIAN PRODUCT INFORMATION

ZUMENON®

estradiol hemihydrate tablets

WARNING

Estrogens 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 estrogens (0.625 mg) combined with medroxyprogesterone acetate (2.5 mg) relative to placebo (see Section 5.1 PHARMACODYNAMIC PROPERTIES - CLINICAL TRIALS and Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE). 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 estrogens (0.625 mg) relative to placebo (see Section 5.1 PHARMACODYNAMIC PROPERTIES - CLINICAL TRIALS and Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

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 estrogens, with or without medroxyprogesterone acetate, relative to placebo. It is unknown whether this finding applies to younger postmenopausal women (see Section 5.1 PHARMACODYNAMIC PROPERTIES - CLINICAL TRIALS and Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Other doses of conjugated estrogens and medroxyprogesterone acetate, and other combinations and dosage forms of estrogens 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, estrogens 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.

1 NAME OF THE MEDICINE

Estradiol hemihydrate

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

ZUMENON tablets are immediate-release, film-coated tablets for oral use containing 2 mg of micronised estradiol (equivalent to 2.06 mg estradiol hemihydrate).

Excipients with known effect: sugars as lactose.

For the full list of excipients, see Section 6.1 LIST OF EXCIPIENTS.

3 PHARMACEUTICAL FORM

Round, biconvex, brick red, film-coated tablets of 7 mm diameter each containing 2 mg estradiol bearing the inscription "379" on one side.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Symptomatic treatment of estrogen 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 Section 4.2 DOSE AND METHOD OF ADMINISTRATION and Section 5.1 PHARMACODYNAMIC PROPERTIES - CLINICAL TRIALS).

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

4.2 DOSE AND METHOD OF ADMINISTRATION

One tablet administered orally daily without interruption (see Section 4.1 THERAPEUTIC INDICATIONS and Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE 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 estrogen 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.

4.3 CONTRAINDICATIONS

- Non-hysterectomised women without opposing progestogen.
- Known, suspected or past history of carcinoma of the breast, endometrium or other estrogen 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 Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).
- 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.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

The benefits and risks of estrogen/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. Women should be advised that changes in their breasts should be reported to their doctor or nurse (see 'Breast Cancer' below). Mammography is advisable. Patients who are being, or have previously been treated with unopposed estrogens 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 estradiol 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

Estrogen and estrogen/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, estrogen/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 estrogen 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 Section 5.1 PHARMACODYNAMIC PROPERTIES - 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 Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)).

In the estrogen 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 Section 5.1 PHARMACODYNAMIC PROPERTIES - CLINICAL TRIALS).

In the same sub-study of WHI, an increased risk of stroke was observed in women receiving estrogen 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 estrogen/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 estrogen/ progestogen treated group and the placebo group in HERS, HERS II, and overall.

Venous thromboembolism (VTE)

In the estrogen 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 Section 5.1 PHARMACODYNAMIC PROPERTIES - 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 Section 4.3 CONTRAINDICATIONS).

Generally recognised risk factors for VTE include use of estrogens, 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.

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).

In the estrogen 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 estrogen 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 Section 5.1 PHARMACODYNAMIC PROPERTIES - CLINICAL TRIALS).

If feasible, estrogens 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.

Endometrial cancer

The use of unopposed estrogens in women with intact uteri has been associated with an increased risk of endometrial cancer. The reported endometrial cancer risk among unopposed estrogens 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 estrogen dose. Most studies show no significant increased risk associated with the use of estrogens 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 estrogen therapy is discontinued. Clinical surveillance of all women taking estrogen/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 estrogens results in a different endometrial risk profile than synthetic estrogens of equivalent estrogen dose. Adding a progestogen to postmenopausal estrogen therapy has been shown to reduce the risk of endometrial hyperplasia, which may be a precursor to endometrial cancer.

Addition of a progestogen when a woman has not had a hysterectomy

Studies of the addition of a progestogen for 10 or more days of a cycle of estrogen administration, or daily with estrogen in a continuous regimen, have reported a lowered incidence of endometrial hyperplasia than would be induced by estrogen 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 estrogens compared with estrogen-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 estrogen/progestogen combinations is important. Breakthrough 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. 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 estrogens results in a different endometrial risk profile than synthetic estrogens of equivalent estrogen dose.

Breast cancer

The use of estrogen-only HRT and combined estrogen-progestogen by women has been shown to increase the risk of breast cancer, that is dependent on the duration of taking HRT.

Combined estrogen-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 estrogen-progestogen for HRT that becomes apparent after about 3 (1-4) years (see Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)).

Estrogen-only therapy:

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

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

The observational Million Women Study in Europe reported an increased risk of mortality due to breast cancer among current users of estrogens alone or estrogens plus progestogens compared to never users, while the estrogen 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 estrogen 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 estrogen-progestogen combined treatment, increases the density of mammographic images which may adversely affect the radiological detection of breast cancer.

Dementia

HRT use does not improve cognitive function. In the estrogen 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 estrogen 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 estrogen alone substudy, after an average follow-up of 5.2 years, 28 women in the estrogen 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 estrogen plus progestogen substudy, after an average follow-up of 4 years, 40 women in the estrogen plus progestogen group and 21 women in the placebo group were diagnosed with probable dementia. The relative risk of probable dementia for estrogen 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, Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE and - Use in the Elderly).

Gallbladder Disease

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

Hypercalcaemia

Estrogen 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 estrogens. 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, estrogens 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 estrogens. In a large, randomised, placebo-controlled clinical trial, a generalised effect of estrogen therapy on blood pressure was not seen. Blood pressure should be monitored at regular intervals with estrogen use.

Hypertriglyceridaemia

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

Impaired liver function and past history of cholestatic jaundice

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

Hypothyroidism

Estrogen 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 estrogens 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 estrogens/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 estrogens are prescribed.

Hypocalcaemia

Estrogens 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 estrogen-only or combined estrogen-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 Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)).

Exacerbation of endometriosis

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

Exacerbation of other conditions

Estrogen 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
- Risk factors for thromboembolic disorders (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE - Venous thromboembolism (VTE))
- Risk factors for estrogen dependent tumours, e.g. 1st degree heredity for breast cancer
- Hypertension
- Liver disorders (e.g. liver adenoma)
- Diabetes mellitus with or without vascular involvement
- Cholelithiasis
- Migraine or (severe) headache
- Systemic lupus erythematosus.
- A history of endometrial hyperplasia (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE – Endometrial cancer)
- Epilepsy
- Asthma
- 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 estrogens are given to hypertensive women, supervision is necessary and blood pressure should be monitored at regular intervals.

Other conditions

Estrogens 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.

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

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

Exogenous estrogens may induce or exacerbate symptoms of hereditary and acquired angioedema.

ALT elevations

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

Use in the Elderly

Of the total number of subjects in the estrogen 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 estrogens 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 estrogens (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 estrogen-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 estrogen-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 Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE - Dementia).

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

Paediatric Use

No data available.

Effects on Laboratory Tests

No data available.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

No interaction studies have been performed.

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 (phenobarbitone), carbamazepine, phenytoin) and anti-infectives (e.g. rifampicin, rifabutin, nevirapine, efavirenz) may increase the metabolism of estrogen resulting in decreased estrogenic 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 estrogens.

Other interactions

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

Estrogens might interfere with the metabolism of other drugs:

Estrogens 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 ciclosporin
- 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, ciclosporin and theophylline may be necessary.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on Fertility

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

Use in Pregnancy

Category B1

Estrogens are contraindicated during known or suspected pregnancy.

Use in Lactation

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

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

ZUMENON does not cause drowsiness. ZUMENON has no or negligible influence on the ability to drive and use machines. However, adverse effects of ZUMENON include dizziness and visual disturbances which could

affect the ability to drive or use machines (see Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)).

4.8 ADVERSE EFFECTS (UNDESIRABLE 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 Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Table 1. Treatment emergent adverse reactions with ZUMENON

MedDRA system organ class	Very Common >1/10	Common ≥1/100 to <1/10	Uncommon ≥1/1,000 to<1/100	Rare ≥1/10,000 to <1/1,000
Infections and infestations			vaginal candidiasis	
Immune system disorders			hypersensitivity reactions	
Metabolism and nutritional disorders		weight change		
Psychiatric disorders			depression	changes in libido, anxiety
Nervous system disorders	headache		dizziness	migraine
Eye disorders			visual disturbances	Contact lens intolerance
Cardiac disorders			palpitations	
Gastrointestinal disorder	abdominal pain, nausea		dyspepsia	bloating, vomiting
Hepatobiliary disorders			gall bladder disorders	
Skin and subcutaneous tissue disorders		rash, pruritus,	erythema nodosum, urticaria	hirsutism, acne
Musculoskeletal and connective tissue disorders				muscle cramps
Reproductive system and breast disorders	breast pain, dysmenorrheoa	metrorrhagia, intermittent bleeding/spotting	ovarian cyst, breast tenderness	vaginal discharge, premenstrual-like syndrome, breast enlargement
General disorders		oedema		fatigue

The following adverse effects have also been reported (frequency unknown):

<u>Neoplasms benign, malignant and unspecified (incl. cysts and polyps)</u>

Breast cancers

Estrogen dependent neoplasms benign and malignant, e.g. endometrial cancer, ovarian cancer

Increase in size of leiomyoma

<u>Immune system disorders</u>

systemic lupus erythematosus

Metabolism and nutrition disorders

Change in carbohydrate metabolism

Hypertriglyceridaemia

Nervous system disorders

Probable dementia (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE), chorea, exacerbation of epilepsy

Eye disorders

steepening of corneal curvature

Cardiac disorders

Myocardial infarction

Vascular disorders

Stroke

Arterial thromboembolism, i.e. angina and myocardial infarction (see Section 4.3 CONTRAINDICATIONS and Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE)

Venous thromboembolism, i.e. deep leg or pelvic venous thrombosis and pulmonary embolism (see Section 4.3 CONTRAINDICATIONS and Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE)

Gastrointestinal disorders

Pancreatitis (in women with pre-existing hypertriglyceridaemia)

Gastro-oesophageal reflux disease

abdominal cramps

Hepatobiliary disorders

Hepatic function abnormal, sometimes with jaundice, asthenia or malaise

Skin and subcutaneous tissue disorders

Angioedema

Erythema multiforme, 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

Cystitis-like symptoms

Reproductive system and breast disorders

Breakthrough bleeding, change in cervical erosion and degree of cervical secretion.

Fibrocystic breast changes

Congenital, familial and genetic disorders

Aggravation of porphyria

Investigations

Increase or decrease in weight

Total thyroid hormones increased

Breast cancer

For estrogen-only HRT, estimates of relative risk (RR) from a reanalysis of original data from 51 epidemiological studies (in which >80% of HRT use was estrogen-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 increased risk in users of estrogen-only therapy is lower than that seen in users of estrogen-progestogen combinations. The MWS reported that, compared to never users, the use of various types of estrogen-progestogen combined HRT was associated with a higher risk of breast cancer (RR=2.00, 95% CI 1.88-2.12) than use of estrogens 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 risk estimations based on the results of the largest meta-analysis of prospective epidemiological studies, and the WHI trials are presented below.

Table 2. Estimated additional risk of breast cancer after 5 years' use in women with BMI 27 (kg/m^2) - from the largest meta-analysis of prospective epidemiological studies

Age at start HRT (years)	Incidence per 1000 never-users of HRT over a 5 year period (50-54 years)*	Risk ratio	Additional cases per 1000 HRT users after 5 years
		Estrogen only HRT	
50	13.3	1.2	2.7
		Combined estrogen/progestogen	
50	13.3	1.6	8.0
*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 country, the number of additional cases of breast cancer will also change proportionately.			

Table 3. Estimated additional risk of breast cancer after 10 years' use in women with BMI 27 (kg/m^2) - from the largest meta-analysis of prospective epidemiological studies

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
		Estrogen only HRT	
50	26.6	1.3	7.1
		Combined estrogen/progestogen	
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 country, the number of additional cases of breast cancer will also change proportionately.			

Table 4. Additional risk of breast cancer after 5 years' use - from the WHI trial

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 estrogen-only	
50-79	21	0.8 (0.7 – 1.0)	-4 (-6 – 0)*
		CEE+MPA estrogen & progestogen‡	
50-79	17	1.2 (1.0 – 1.5)	+4 (0 – 9)
* WHI study in women with no uterus, which did not show an increase in risk of breast cancer ‡ When the analysis was restricted to women who had not used HRT prior to the study there was no increased risk apparent during the first 5 years of treatment: after 5 years the risk was higher than in non-users.			

Endometrial cancer

In women with an intact uterus, the risk of endometrial hyperplasia and endometrial cancer increases with increasing duration of use of unopposed estrogens (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE.

Ovarian cancer risk

Use of estrogen-only or combined estrogen-progestogen HRT has been associated with a slightly increased risk of having ovarian cancer diagnosed (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE). 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 Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Risk of coronary artery disease

The risk of coronary artery disease is slightly increased in users of combined estrogen-progestogen HRT over the age of 60 (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Risk of ischaemic stroke

The use of estrogen-only and estrogen-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 Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Reporting Suspected Adverse Effects

Reporting suspected adverse reactions after registration 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 at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

Symptoms

Acute toxicity studies did not indicate a risk of acute adverse effects in case of inadvertent overdosage of estradiol.

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.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of Action

Estradiol is chemically and biologically identical to endogenous human estradiol and has pharmacological actions similar to the physiological effects of the endogenous hormone. Estradiol is the primary estrogen and the most active of the ovarian hormones.

ZUMENON restores plasma estrogen levels and thus relieves or decreases estrogen 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 estrogen deficiency syndrome including lower urinary tract dysfunction and atrophic vaginitis. Estradiol is known to decrease LDL-C and increase HDL-C and triglycerides.

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 estrogens (CE) 0.625 mg/day alone or the use of a continuous combined regimen of conjugated estrogens 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 estrogen 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 estrogen alone in predetermined primary endpoints. Results of the estrogen 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 5.

Table 5. Relative and absolute risk seen in the estrogen 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 Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

The estrogen plus progestogen substudy was also stopped early because, accordingto 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 estrogen 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 6.

Table 6. Relative and absolute risk seen in the estrogen 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 Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Women's Health Initiative Memory Study.

The estrogen 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 estrogens (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 estrogen 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 estrogen 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 Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE – Dementia and Use in the Elderly).

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 estrogen/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 Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE - Dementia and Use in the Elderly).

5.2 PHARMACOKINETIC PROPERTIES

Absorption

Micronised estradiol is rapidly and efficiently absorbed from the gastrointestinal tract following oral administration. Peak plasma concentrations of estradiol occur 4-6 hours after tablet ingestion. Thereafter elimination is slow and estradiol levels are maintained above baseline for 24 hours. The steady state plasma level of estradiol ranges between 70-100 pg/mL. Estradiol has a half-life of approximately 14-16 hours.

Distribution

In the bloodstream more than 90% of estradiol is bound to plasma proteins.

Metabolism

Some estradiol is converted to estrone in the intestinal mucose before absorption into the portal vein. During passage through the liver a significant proportion of estradiol is metabolised to estrone. Estradiol and

hydroxyestrones are also produced as well as sulfate and glucuronate conjugates. Circulating estrone sulphate may be reconverted to estrone and estradiol in extrahepatic organs like the uterus.

Excretion

Estrogens 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 estrogen metabolites appear in the faeces (5 to 10%). Estrogens are also secreted in the milk of nursing mothers.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

No data available.

Carcinogenicity

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

Unopposed estrogen 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 estrogen-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 estrogens. Epidemiological surveys have disclosed no increase in breast cancer mortality among estrogen-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 estrogens in women who have a history of, or known, breast nodules or fibrocystic disease. Breast status should be closely monitored, supported by regular mammography.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Lactose monohydrate, hypromellose, maize starch, colloidal anhydrous silica, magnesium stearate. The colour used in the coating is Opadry complete film coating system OY-6957 Pink (ARTG PI No: 4158).

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 30°C.

6.5 NATURE AND CONTENTS OF CONTAINER

ZUMENON 2 mg tablets are available in PVC/aluminium blister packs containing 7, 28, 56 or 84 tablets.

Some pack sizes may not be marketed.

Australian Register of Therapeutic Goods (ARTG)

AUST R 75888 – ZUMENON estradiol (as hemihydrate) 2mg tablet blister pack

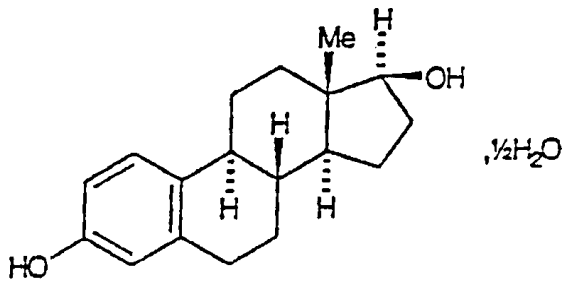
6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking it to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical Structure

Estradiol 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:



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

CAS Number

Estradiol hemihydrate: 35380-71-3

7 MEDICINE SCHEDULE (POISONS STANDARD)

S4 (Prescription Only Medicine)

8 SPONSOR

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Phone: 1800 274 276

9 DATE OF FIRST APPROVAL

08/09/2000

10 DATE OF REVISION

14/11/2022

Summary Table of Changes

Section Changed	Summary of New Information
4.4	Amendment of angioedema and liver enzyme elevation in concomitant use with HCV - medications
4.5	Liver enzyme elevation when used concomitantly with HCV – medications.

ZUMENON® is a Viatris company trade mark

ZUMENON_pi\Nov22/00 (CCDS 25-Feb-2022)