New Zealand Datasheet

1. PRODUCT NAME
Ethinyloestradiol tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Ethinyloestradiol 10mcg.
For excipients see 6.1.

3. PHARMACEUTICAL FORM
Round white biconvex unscored tablets.

4. CLINICAL PARTICULARS
4.1 Therapeutic indications
Postmenopausal symptoms due to oestrogen deficiency including prevention of postmenopausal osteoporosis. In women with an intact uterus the addition of a progestogen is essential.

Treatment of metastatic breast cancer in postmenopausal women.

Treatment of prostatic cancer.

4.2 Dose and method of administration
This will depend on the particular indication used, but treatment should be undertaken with as low a dose as possible and for as short a period as is necessary.

Post menopausal symptoms due to oestrogen deficiency including prevention of postmenopausal osteoporosis: the usual dose range is 0.01-0.05mg daily, usually on a cyclical basis (e.g. 3 weeks on and 1 week off).

For women without a uterus, who did not have endometriosis diagnosed, it is not recommended to add a progestogen.

In women with an intact uterus (or in endometriosis when endometrial foci may be present despite hysterectomy), where a progestogen is necessary, it should be added for at least 12–14 days every month/28 day cycle to reduce the risk to the endometrium.
The benefits of the lower risk of hyperplasia and endometrial cancer due to adding progestogen should be weighed against the increased risk of breast cancer (see Warnings and Precautions, and Adverse Effects).

Therapy with ethinyloestradiol tablets may start at any time in women with established amenorrhoea or who are experiencing long intervals between spontaneous menses. In women who are menstruating, it is advised that therapy starts on the first day of bleeding. As ethinyloestradiol tablets are usually taken on a cyclical basis direct switching from other oestrogen-only HRT preparations taken cyclically is possible.

Treatment of prostatic cancer: 1-2mg daily.

4.3 Contraindications
- Pregnancy.
- Active or recent (e.g. within the last year) arterial thromboembolic disease (e.g. angina, myocardial infarction, stroke)

- Current or previous idiopathic venous thromboembolism (deep venous thrombosis, pulmonary embolism)
- Known, past or suspected breast cancer or other known or suspected oestrogen-dependent tumours (e.g. endometrial cancer).
- Untreated endometrial hyperplasia, uterine fibromyomata.
- Undiagnosed vaginal bleeding
- Acute liver disease or a history of liver disease as long as liver function tests have failed to return to normal
- Porphyria.

Ethinyloestradiol tablets are contraindicated for use with the Hepatitis C combination druq reqimen ombitasvir/paritaprevir/ritonavir and dasabuvir with or without ribavirin (see Warnings and Precautions).

4.4 Special warnings and precautions for use

For the treatment of postmenopausal symptoms, HRT should only be initiated for symptoms that adversely affect quality of life. In all cases, a careful appraisal of the risks and benefits should be undertaken at least annually and HRT should only be continued as long as benefit outweighs the risk.

Medical examination/follow-up

Before initiating or reinstituting HRT, a complete personal and family medical history should be taken. Physical (including pelvic and breast) examination should be guided by this and by the contraindications and warnings for use. During treatment, periodic check-ups are recommended of a frequency and nature adapted to the individual woman. Women should be advised what changes in their breasts should be reported to their doctor or nurse (see 'Breast cancer' below). Investigation, including mammography, should be carried out in accordance with currently accepted screening practices, modified to the clinical needs of the individual.

Conditions which need supervision

If any of the following conditions are present, have occurred previously, and/or have been aggravated during pregnancy or previous hormone treatment, the patient should be closely supervised. It should be taken into account that these conditions may recur or be aggravated during treatment with ethinyloestradiol tablets, in particular:

- Risk factors for oestrogen dependent tumours e.g. 1st degree heredity for breast cancer
- Leimyoma (uterine fibroids) or endometriosis
- A history of, or risk factors for, thromboembolic disorders (see below)
- Hypertension
- Liver disorders (e.g. liver adenoma)
- Diabetes Mellitus with or without vascular involvement
- Cholelithiasis
- Otosclerosis
- Asthma
- Migraine or (severe) headache and epilepsy
- Systemic Lupus erythematosis
- Hyperplasia of the endometrium (see below)

Reasons for immediate withdrawal of therapy

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

Endometrial hyperplasia

The risk of endometrial hyperplasia and carcinoma is increased when oestrogens are administered alone for prolonged periods (see Adverse Effects). The addition of a progestogen for at least 12 days of the cycle in non-hysterectomised women greatly reduces this risk.

The reduction in risk to the endometrium should be weighed against the increase in the risk of breast cancer of added progestogen (see 'Breast cancer' below and Adverse Effects).

Break-through bleeding and spotting may occur during the first months of treatment. If break-through bleeding or spotting appears after some time on therapy, or continues after treatment has been discontinued, the reason should be investigated, which may include endometrial biopsy to exclude endometrial malignancy.

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

Breast cancer

A randomised placebo-controlled trial, the Women's Health Initiative study (WHI) and epidemiological studies, including the Million Women Study (MWS), have reported an increased risk of breast cancer in women taking oestrogens, oestrogen-progestogen combinations or tibolone for HRT for several years (see Adverse Effects). For all HRT, an excess risk becomes apparent within a few years of use and increases with duration of intake but returns to baseline within a few (at most five) years after stopping treatment.

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

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

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

Ovarian cancer

Long-term (at least 5 to 10 years) use of oestrogen-only HRT products in hysterectomised women has been associated with an increased risk of ovarian cancer in some epidemiological studies. It is uncertain whether long-term use of combined HRT confers a different risk than oestrogen-only products.

Venous thromboembolism

HRT is associated with a higher relative risk of developing venous thromboembolism (VTE), i.e. deep vein thrombosis or pulmonary embolism. One randomised controlled trial and epidemiological studies found a two- to three fold higher risk for users compared with non-users. For non-users, it is estimated that the number of cases of VTE that will occur over a 5 year period is about 3 per 1000 women aged 50–59 years and 8 per 1000 women aged

between 60–69 years. It is estimated that in healthy women who use HRT for 5 years, the number of additional cases of VTE over a 5 year period will be between 2 and 6 (best estimate = 4) per 1000 women aged 50–59 years and between 5 and 15 (best estimate = 9) per 1000 women aged 60–69 years. The occurrence of such an event is more likely in the first year of HRT than later.

Generally recognised risk factors for VTE include a personal history or family history, severe obesity (BMI > 30 kg/m^2) and systemic lupus erythematosus (SLE). There is no consensus about the possible role of varicose veins in VTE.

Patients with a history of VTE or known thrombophilic states have an increased risk of VTE. HRT may add further to this risk. Personal or strong family history of recurrent thromboembolism or recurrent spontaneous abortion should be investigated in order to exclude a thrombophilic predisposition. Until a thorough evaluation of thrombophilic factors has been made or anticoagulant treatment initiated, use of HRT in such patients should be viewed as contraindicated. Those women already on anticoagulant treatment require careful consideration of the benefit-risk of use of HRT.

The risk of VTE may be temporarily increased with prolonged immobilization, major trauma or major surgery. As in all postoperative patients, scrupulous attention should be given to prophylactic measures to prevent VTE following surgery. Where prolonged immobilisation is liable to follow elective surgery, particularly abdominal or orthopaedic surgery to the lower limbs, consideration should be given to temporarily stopping HRT 4 to 6 weeks earlier, if possible. Treatment should not be restarted until the woman is completely mobilised.

If VTE develops after initiating therapy, the drug should be discontinued. Patients should be told to contact their doctors immediately when they are aware of a potential thromboembolic symptom (e.g. painful swelling of a leg, sudden pain in the chest, dyspnoea).

Stroke

One large randomised clinical trial (WHI-trial) found, as a secondary outcome, an increased risk of ischaemic stroke in healthy women during treatment with continuous combined continuous oestrogens and medroxyprogesterone acetate (MPA). For women who do not use HRT, it is estimated that the number of cases of stroke that will occur over a 5 year period is about 3 per 1000 women aged 50–59 years and 11 per 1000 women aged 60–69 years. It is estimated that for women who use conjugated oestrogens and MPA for 5 years, the number of additional cases will be between 0 and 3 (best estimate = 1) per 1000 users aged 50–59 years and between 1 and 9 (best estimate = 4) per 1000 users aged 60–69 years. It is unknown whether the increased risk also extends to other HRT products.

Coronary artery disease (CAD)

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

Hepatitis C

During clinical trials with the combination drug regimen ombitasvir/paritaprevir/ritonavir and dasabuvir with and without ribavirin, transient. asymptomatic elevations of alanine transaminase (ALT) greater than 5 times the upper limit of normal (ULN) were significantly more frequent in women using ethinyloestradiol-containing medications such as combined oral contraceptives, contraceptive patches, or contraceptive vaginal rings.

Ethinyloestradiol tablets must be discontinued 2 weeks prior to starting therapy with the combination drug regimen ombitasvir/paritaprevir/ritonavir and dasabuvir with and without ribavirin. Ethinyloestradiol tablets can be restarted approximately 2 weeks following completion of treatment with the combination drug regimen.

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 ethinyloestradiol tablets is increased.

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

Oestrogens increase thyroid binding globulin (TBG), leading to increased circulating total thyroid hormone, as measured by protein-bound iodine (PBI), T4 levels (by column or by radio-immunoassay) or T3 levels (by radio-immunoassay). T3 resin uptake is decreased, reflecting the elevated TBG. Free T4 and free T3 concentrations are unaltered. Other binding proteins may be elevated in serum, i.e. corticoid binding globulin (CBG), sex-hormone-binding globulin (SHBG) leading to increased circulating corticosteroids and sex steroids, respectively. Free or biological active hormone concentrations are unchanged. Other plasma proteins may be increased (angiotensinogen/renin substrate, alpha-I-antitrypsin, ceruloplasmin).

There is no conclusive evidence for improvement of cognitive function. There is some evidence from the WHI trial of increased risk of probable dementia in women who start using continuous combined CEE and MPA after the age of 65. It is unknown whether the findings apply to younger post-menopausal women or other HRT products.

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

4.5 Interaction with other medicinal products and other forms of interaction

The metabolism of oestrogens may be increased by concomitant use of substances known to induce drug metabolising enzymes, specifically cytochrome P450 enzymes, such as anti-convulsants (e.g. phenobarbital, phenytoin, carbamazepine), anti-infectives (e.g. rifampicin, rifabutin, nevirapine, efavirenz) and modafinil.

Ritonavir and nelfinavir, although known as strong inhibitors, by contrast exhibit inducing properties when used concomitantly with steroid hormones. Herbal preparations containing St Johns Wort (Hypericum Perforatum) may induce the metabolism of oestrogens.

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

Ethinyloestradiol doses greater than 50 micrograms per day may cause imipramine toxicity in patients on concomitant therapy.

Through its effects on the coagulation system, ethinyloestradiol may reduce the effects of anticoagulants such as warfarin.

The doses of insulin or hypoglycaemic medicines may need to be adjusted due to the mild diabetogenic effect of ethinyloestradiol.

Ethinyloestradiol may inhibit the metabolism of theophylline and reduce its clearance.

Ethinyloestradiol has been shown to decrease serum concentrations of lamotrigine when the two medicines are co-administered.

4.6 Fertility, pregnancy and lactation

Ethinyloestradiol tablets are not indicated during pregnancy. If pregnancy occurs during medication with ethinyloestradiol tablets, treatment should be withdrawn immediately. The results of most epidemiological studies to date relevant to inadvertent foetal exposure to oestrogens indicate no teratogenic or fetotoxic effects.

Ethinyloestradiol tablets are not indicated during lactation.

4.7 Effects on ability to drive and use machines

None stated

4.8 Undesirable effects

Breast cancer

According to evidence from a large number of epidemiological studies and one randomised placebo-controlled trial, the Women's Health Initiative (WHI), the overall risk of breast cancer increases with increasing duration of HRT use in current or recent HRT users.

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.

For *oestrogen plus progestogen* combined HRT, several epidemiological studies have reported an overall higher risk for breast cancer than with oestrogens alone.

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 WHI trial reported a risk estimate of 1.24 (95% CI 1.01–1.54) after 5.6 years of use of oestrogen-progestogen combined HRT (CEE + MPA) in all users compared with placebo.

The absolute risks calculated from the MWS and the WHI trial 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 1000 are expected to have breast cancer diagnosed between the ages of 50 and 64 years.
- For 1000 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 (CEE + MPA) per 10,000 women years.

According to calculations from the trial data, it is estimated that:
- For 1000 women in the placebo group, about 16 cases of invasive breast cancer would be diagnosed in 5 years.
- For 1000 women who used oestrogen + progestogen combined HRT (CEE + 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) (see Warnings and Precautions).

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. According to the data from epidemiological studies, the best estimate of the risk of endometrial cancer is that for women not using HRT, about 5 in every 1000 are expected to have endometrial cancer diagnosed between the ages of 50 and 65. Depending on the duration of treatment and oestrogen dose, the reported increase in endometrial cancer risk among unopposed oestrogen users varies from 2- to 12-fold greater compared with non-users. Adding a progestogen to oestrogen-only therapy greatly reduces this increased risk.

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

Genito-urinary tract: Endometrial neoplasia, endometrial cancer, intermenstrual bleeding, increase in the size of uterine fibromyomata, endometrial proliferation or aggravation of endometriosis, excessive production of cervical mucus.

Breast: Tenderness, pain, enlargement, secretion.

Gastrointestinal tract: Nausea, vomiting, cholelithiasis, cholestatic jaundice.

Cardiovascular system: Hypertension, thrombosis, thrombophlebitis, thromboembolism, myocardial infarction, stroke.

Venous thromboembolism, i.e. deep leg or pelvic venous thrombosis and pulmonary embolism, is more frequent among hormone replacement therapy users than among non-users. For further information, see Contraindications and Warnings and Precautions sections.

Skin: Erythema nodosum, erythema multiforme, vascular purpura, rash, chloasma.

Eyes: Corneal discomfort if contact lenses are used.

CNS: Headache, migraines, mood changes (elation or depression), probable dementia (see Warnings and Precautions).

Metabolic: Sodium and water retention, reduced glucose tolerance and change in bodyweight, hypercalcaemia.

In Men: Feminisation, gynaecomastia, testicular atrophy, and impotence.

4.9 Overdose
Acute overdose of ethinyloestradiol may cause nausea and vomiting and may result in withdrawal bleeding in females.

5. PHARMACOLOGICAL PROPERTIES
5.1 Pharmacodynamic properties
Pharmacotherapeutic group: Natural and semisynthetic estrogens, plain
ATC code: G03CA

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

Oestrogen deficiency at menopause is associated with an increasing bone turnover and decline in bone mass. The effect of oestrogens on the bone mineral density is dose-dependent. Protection appears to be effective for as long as treatment is continued.
After discontinuation of HRT, bone mass is lost at a rate similar to that in untreated women.

Evidence from the WHI trial and meta-analysed trials shows that current use of HRT, alone or in combination with a progestogen — given to predominantly healthy women — reduces the risk of hip, vertebral, and other osteoporotic fractures. HRT may also prevent fractures in women with low bone density and/or established osteoporosis, but the evidence for that is limited.

The main therapeutic use of exogenous oestrogens is replacement in deficiency states.

5.2 Pharmacokinetic properties
Ethinyloestradiol is rapidly and completely absorbed from the gut but it undergoes some first pass metabolism in the gut wall.

Ethinyloestradiol is rapidly distributed throughout most body tissues with the largest concentration found in adipose tissue. It distributes into breast milk in low concentrations. More than 80% of ethinyloestradiol in serum is conjugated as the sulphate and almost all the conjugated form is bound to albumin.

Ethinyloestradiol is metabolised in the liver. Hydroxylation appears to be the main metabolic pathway. 60% of a dose is excreted in the urine and 40% in the faeces. About 30% is excreted in the urine and bile as the glucuronide or sulphate conjugate.
The rate of metabolism of ethinyloestradiol is affected by several factors, including enzyme-inducing agents, antibiotics and cigarette smoking.

After oral administration, an initial peak occurs in plasma at 2 to 3 hours, with a secondary peak at about 12 hours after dosing; the second peak is interpreted as evidence for extensive enterohepatic circulation of ethinyloestradiol.

The elimination half-life of ethinyloestradiol ranges from 5 to 16 hours.

5.3 Pre-clinical safety data
None stated

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Acacia (Gum Powder)
Alginic acid
Magnesium stearate
Potato starch
Lactose monohydrate

6.2 Incompatibilities

None stated

6.3 Shelf-life

60 months

6.4 Special precautions for storage

Store below 25ºC.

6.5 Nature and contents of container

10mcg: 100 tablets.

6.6 Special precautions for disposal and other handling

Not applicable

7. MEDICINE SCHEDULE

Prescription Medicine

8. SPONSOR

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9. DATE OF FIRST APPROVAL

First authorisation: 31 December 19699

10. DATE OF REVISION OF THE TEXT

14 November 2016

SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
Section 4.3:	Addition of: Ethinyloestradiol tablets are contraindicated for use with the Hepatitis C combination druq reqimen ombitasvir/paritaprevir/ritonavir and dasabuvir with or without ribavirin (see Warnings and Precautions).
Section 4.4:	Addition of: <u>Hepatitis C</u> During clinical trials with the combination drug regimen ombitasvir/paritaprevir/ritonavir and dasabuvir with and without ribavirin, transient. asymptomatic elevations of alanine transaminase (ALT) greater than 5 times the upper limit of normal (ULN) were significantly more frequent in women using ethinyloestradiol-containing medications such as combined oral contraceptives, contraceptive patches, or contraceptive vaginal rings. Ethinyloestradiol tablets must be discontinued 2 weeks prior to starting therapy with the combination drug regimen ombitasvir/paritaprevir/ritonavir and dasabuvir with and without ribavirin. Ethinyloestradiol tablets can be restarted approximately 2 weeks following completion of treatment with the combination drug regimen.