AUSTRALIAN PRODUCT INFORMATION

XYVION® (tibolone) tablets

1 NAME OF THE MEDICINE

tibolone

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet containing 2.5mg of the steroid tibolone.

List of excipients with known effect: lactose.

For the full list of excipients, see **Section 6.1 List of Excipients**.

3 PHARMACEUTICAL FORM

Tablets.

XYVION (tibolone) tablets 2.5 mg are 6 mm in diameter, white, round and flat with bevelled edges, coded "MK" above "2" on one side and "Organon" and a star on the reverse side.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

- Short-term treatment of symptoms resulting from the natural or surgical menopause in postmenopausal women.
- Second line therapy for the prevention of bone mineral density loss in postmenopausal women at high risk of future osteoporotic fractures who are intolerant of, or contraindicated for, other medicinal products approved for the prevention of bone mineral density loss.

After careful selection of users, XYVION should be prescribed for the shortest duration consistent with treatment goals. Review the need for continuation of treatment after 6 months, taking into account the risk-benefit ratio for the individual user at that moment (including cardiovascular disease and breast cancer, see **Section 5.1 Pharmacodynamic Properties, Clinical trials** and **Section 4.4 Special Warnings and Precautions for Use**). XYVION should only be continued for as long as the benefit outweighs the risks.

4.2 DOSE AND METHOD OF ADMINISTRATION

Treatment of symptoms resulting from the natural or surgical menopause, more than one year after menopause:
The recommended dose is 2.5 mg once daily.

Prevention of post-menopausal bone mineral density loss:
The recommended dose is 2.5 mg once daily.

No dose adjustment is necessary for the elderly.

The tablets should be swallowed with some water or other drink, preferably at the same time of day. Improvement of symptoms generally occurs within a few weeks, but optimal results are obtained when therapy is continued for at least 3 months.

For initiation and continuation of treatment of postmenopausal symptoms, the lowest effective dose for the shortest duration (see **Section 4.4 Special Warnings and Precautions for Use**) should be used. Review the need for continuation of treatment after 6 months, taking into account the risk-benefit ratio for the individual user at that moment.

A separate progestogen should not be added with XYVION treatment.

Starting XYVION
Women experiencing a natural menopause should commence treatment with XYVION at least 12 months after their last natural bleed. In case of a surgical menopause, treatment with XYVION may commence immediately.

Any irregular/ unscheduled vaginal bleeding, either on or off HRT, should be investigated to exclude malignancy before starting XYVION (see **Section 4.3 Contraindications**).

Switching from combined or estrogen only hormone replacement therapy (HRT)
In women with a uterus who change from an estrogen-only preparation, a withdrawal bleed should be induced before starting XYVION. If changing from a sequential HRT preparation, treatment with XYVION should start after the progestogen phase has been completed. If changing from a continuous-combined HRT preparation, treatment can start at any time. If abnormal vaginal bleeding is the reason for switching from combined HRT, it is advised to investigate the cause of bleeding before starting XYVION.

Missed tablets
A missed dose should be taken as soon as remembered, unless it is more than 12 hours overdue. In the latter case, the missed dose should be skipped and the next dose should be taken at the normal time. Missing a dose may increase the likelihood of breakthrough bleeding and spotting.

Monitoring advice
As for all steroids with hormonal activity, yearly medical examination particularly of the breasts and pelvic areas is advisable. Review the need for continuation of treatment after 6 months (see **Section 4.4 Special Warnings and Precautions for Use** and **Section 4.1 Therapeutic Indications**).

The occurrence of vaginal bleeding or spotting soon after starting treatment with XYVION may be due to the residual effects of endogenous or exogenous estrogens. Bleeding commencing after three months of treatment, or recurrent or persistent bleeding should be investigated.

4.3 CONTRAINDICATIONS

- Pregnancy and lactation
- Known, past or suspected breast cancer - tibolone increased the risk of breast cancer recurrence in a placebo-controlled trial
- Known or suspected estrogen dependent malignant tumours (e.g. endometrial cancer)
- Undiagnosed genital bleeding
- Untreated endometrial hyperplasia
- Previous or current venous thromboembolism (deep venous thrombosis, pulmonary embolism)
- Known thrombophilic disorders (e.g. protein C, protein S, or antithrombin deficiency)
- Any history of arterial thromboembolic disease (e.g. angina, myocardial infarction, stroke or TIA)
- Acute liver disease or a history of liver disease as long as liver function tests have failed to return to normal
- Known hypersensitivity to the active substance or to any of the excipients
- Porphyria

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

For the treatment of postmenopausal symptoms, XYVION 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 XYVION should only be continued as long as the benefit outweighs the risk.

For all women the decision to prescribe XYVION should be based on an assessment of the individual patient's overall risks and, particularly in the over 60s, should include consideration of the risk of stroke. The risks of stroke, breast cancer and, in women with an intact uterus, endometrial cancer (see below and **Section 4.8 Adverse Effects (Undesirable Effects)**) for each woman should be carefully assessed, in the light of her individual risk factors and bearing in mind the frequency and characteristics of both cancers and stroke, in terms of their response to treatment, morbidity and mortality.

Evidence regarding the risks associated with HRT or XYVION in the treatment of premature menopause is limited. Due to the low level of absolute risk in younger women, however, the balance of benefits and risks for these women may be more favourable than in older women.

Medical examination/follow-up

- Before initiating or reinstituting HRT or XYVION, 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 precautions for use. During treatment, periodic check-ups are recommended of a frequency and nature adapted to the individual woman. Women should be advised what changes in their breasts should be reported to their doctor or nurse (see 'Breast cancer' below). Investigations, including appropriate imaging tools, e.g. mammography, should be carried out in accordance with currently accepted screening practices, modified to the clinical needs of the individual.

Conditions which need supervision

- If any of the following conditions are present, have occurred previously, and/or have been aggravated during pregnancy or previous hormone treatment, the patient should be closely supervised. It should be taken into account that these conditions may recur or be aggravated during treatment with XYVION, in particular:
    - Leiomyoma (uterine fibroids) or endometriosis
    - Risk factors for thromboembolic disorders (see below)
    - 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 below)
    - Epilepsy
    - Asthma
    - Otosclerosis

Reasons for immediate withdrawal of therapy

Therapy should be discontinued in case a contraindication is discovered and in the following situations:

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

- Pregnancy

Endometrial hyperplasia and carcinoma

- The available data from randomised controlled clinical trials are conflicting, however, observational studies have consistently shown that women who are prescribed XYVION in normal clinical practice are at an increased risk of having endometrial cancer diagnosed (see **Section 4.8 Adverse Effects (Undesirable Effects)**). In these studies the risk increases with increasing duration of use. Tibolone increases endometrial wall thickness, as measured by transvaginal ultrasound.

- Break-through bleeding and spotting may occur during the first months of treatment (see **Section 5.1 Pharmacodynamic Properties**). Women should be advised to report any break-through bleeding or spotting if it is still present after 6 months of treatment, if it starts beyond that time or if it continues after treatment has been discontinued. The woman should be referred for gynaecological investigation, which is likely to include endometrial biopsy to exclude endometrial malignancy.

Breast cancer

- Evidence with respect to breast cancer risk in association with tibolone is inconclusive. The Million Women Study (MWS) has identified a significant increase in the risk of breast cancer in association with use of the 2.5 mg dose. This risk became apparent within a few years of use and increased with duration of intake, returning to baseline within a few (at most five) years after stopping treatment. However, a study using the General Practice Research Database (GPRD), did not show an increased risk (see **Section 4.8 Adverse Effects (Undesirable Effects)**). The THEBES study provided comparisons with continuous daily doses of conjugated estrogens 0.625 mg and medroxyprogesterone acetate 2.5 mg) risk (see **Section 4.8 Adverse Effects (Undesirable Effects)**).

Ovarian cancer

- Ovarian cancer is much rarer than breast cancer. Epidemiological evidence from a large meta-analysis suggests an increased risk in women taking estrogen-only or combined estrogen-progestogen HRT, which becomes apparent within 5 years of use and diminishes over time after stopping. Some other studies, including the Women's Health Initiative (WHI) trial, suggest that use of combined HRTs may be associated with a similar risk (see **Section 4.8 Adverse Effects (Undesirable Effects)**). In the Million Women Study, it was shown that the relative risk for ovarian cancer with use of tibolone was similar to the risk associated with use of other types of HRT.

Venous thromboembolism

- Estrogen or estrogen-progestogen HRT is associated with a 1.3-3 fold risk of developing venous thromboembolism (VTE), i.e. deep vein thrombosis or pulmonary embolism. The occurrence of such an event is more likely in the first year of HRT than later (see **Section 4.8 Adverse Effects (Undesirable Effects)**). In an epidemiological study using a UK database, the risk of VTE in association with tibolone was lower than the risk associated with conventional HRT, but only a small proportion of women were current users of tibolone and a small increase in risk compared with non-use cannot be excluded.

- Patients with known thrombophilic states have an increased risk of VTE and HRT or XYVION may add to this risk. HRT is therefore contraindicated in these patients (see **Section 4.3 Contraindications**).

- Generally recognised risk factors for VTE include a personal history or family history, use of estrogens, older age, major trauma or major surgery, prolonged immobilisation, obesity (BMI > 30 kg/m^2), pregnancy/postpartum period, systemic lupus erythematosus (SLE), and cancer. There is no consensus about the possible role of varicose veins in

VTE. As in all postoperative patients, prophylactic measures need be considered to prevent VTE following surgery. If prolonged immobilisation is to follow elective surgery, temporarily stopping HRT or XYVION 4 to 6 weeks earlier is recommended. Treatment should not be restarted until the woman is completely mobilised.

- In women with no personal history of VTE but with a first degree relative with a history of thrombosis at young age, screening may be offered after careful counselling regarding its limitations (only a proportion of thrombophilic defects are identified by screening). If a thrombophilic defect is identified which segregates with thrombosis in family members or if the defect is 'severe' (e.g. antithrombin, protein S, or protein C deficiencies or a combination of defects) HRT or tibolone is contraindicated.
- Women already on anticoagulant treatment require careful consideration of the benefit-risk of use of HRT or tibolone.
- If VTE develops after initiating therapy, the drug should be discontinued. Patients should be told to contact their doctors immediately when they are aware of a potential thromboembolic symptom (e.g. painful swelling of a leg, sudden pain in the chest, dyspnoea).

Coronary artery disease (CAD)

- There is no evidence from randomized controlled trials of protection against myocardial infarction in women with or without existing CAD who received combined estrogen-progestogen or estrogen-only HRT. In an epidemiological study using the GPRD no evidence was found of protection against myocardial infarction in postmenopausal women who received tibolone.

Ischaemic stroke

- Tibolone increases the risk of ischaemic stroke from the first year of treatment (see **Section 4.8 Adverse Effects (Undesirable Effects)**). The baseline risk of stroke is strongly age-dependent and so the effect of tibolone is greater with older age.

Other conditions

- Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.
- XYVION is not intended for contraceptive use.
- Treatment with XYVION results in a dose-dependent decrease in HDL-cholesterol, total triglycerides and lipoprotein(a) levels. The decrease in total cholesterol and VLDL-C levels was not dose-dependent. Levels of LDL-C were unchanged.
- Estrogens may cause fluid retention, and therefore patients with cardiac or renal dysfunction should be carefully observed.
- Women with pre-existing hypertriglyceridaemia should be followed closely during estrogen replacement or HRT, since rare cases of large increases of plasma triglycerides leading to pancreatitis have been reported with estrogen therapy in this condition.
- Treatment with XYVION results in a very minor decrease of thyroid binding globulin (TBG) and total T4. Levels of total T3 are unaltered. XYVION decreases the level of sex-hormone-binding globulin (SHBG), whereas the levels of corticoid binding globulin (CBG) and circulating cortisol are unaffected.
- HRT use does not improve cognitive function. There is some evidence of increased risk of probable dementia in women who start using continuous combined or estrogen-only HRT after the age of 65.

Use in hepatic impairment

See **Section 4.3 Contraindications** and **Section 4.4 Special Warnings and Precautions for Use, Conditions which need supervision and Reasons for immediate withdrawal of therapy**.

Use in renal impairment

See **Section 4.4 Special Warnings and Precautions for Use, Other conditions**.

Use in the elderly

See **Section 4.2 Dose and Method of Administration**.

Paediatric use

No data available.

Effects on laboratory tests

No data available.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Since XYVION may increase blood fibrinolytic activity, it may enhance the effect of anticoagulants. This effect has been demonstrated with warfarin. Caution should therefore be exercised during the simultaneous use of XYVION and anticoagulants, especially when starting or stopping concurrent XYVION treatment. If necessary, the dose of warfarin should be adjusted.

There is limited information regarding pharmacokinetic interactions with tibolone. An *in vivo* study showed that simultaneous treatment of tibolone affects pharmacokinetics of the cytochrome P450 3A4 substrate midazolam to a moderate extent. Based on this, drug interactions with other CYP3A4 substrates might be expected.

CYP3A4 inducing compounds such as barbiturates, carbamazepine, hydantoins and rifampicin may enhance the metabolism of tibolone and thus affect its therapeutic effect.

Herbal preparations containing St. John's wort *(Hypericum perforatum)* may induce the metabolism of estrogens and progestogens via CYP3A4. Clinically, an increased metabolism of estrogens and progestogens may lead to decreased effect and changes in the uterine bleeding profile.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

No data available.

Use in pregnancy

(Category D)

XYVION is contraindicated in women of reproductive potential including the women in the perimenopausal period. If pregnancy occurs during medication with XYVION, treatment should be withdrawn immediately. For XYVION, no clinical data on exposed pregnancies are available. Studies in animals have shown that tibolone crosses the placenta in rabbits, and is teratogenic. Oral treatment of rats with tibolone during the period of organogenesis was associated with foetal microphthalmia (doses ≥ 0.7 mg/kg/day). In rabbits, a range of abnormalities were observed following oral maternal tibolone treatment (doses

≥ 0.7 mg/kg/day), including hydrocephaly, cleft palate, umbilical hernia, limb flexure and malrotation, bilateral microphthalmia and ocular opacity. A no-effect dose could not be demonstrated in either species. No evidence for teratogenic activity was observed in mice. Systemic exposure to tibolone and its metabolites in the rat study (not measured in the rabbit or mouse study) was substantially lower than the anticipated human exposure. The potential risk for humans is unknown.

Use in lactation

XYVION is contraindicated in lactating women (see **Section 4.3 Contraindications**).

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

XYVION is not known to have any effects on alertness and concentration.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

This section describes undesirable effects, which were registered in 21 placebo-controlled studies (including the LIFT study), with 4079 women receiving therapeutic doses (1.25 or 2.5 mg) of tibolone and 3476 women receiving placebo. The duration of treatment in these studies ranged from 2 months to 4.5 years. Table 1 shows the undesirable effects that occurred statistically significantly more frequently during treatment with tibolone than with placebo.

Table 1: Adverse effects of XYVION

System organ class	Common >1%,<10%	Uncommon >0.1%,<1%
Gastrointestinal disorders	Lower abdominal pain	
Skin and subcutaneous tissue disorders	Abnormal hair growth	Acne
Reproductive system and breast disorders	Vaginal discharge Endometrial wall thickening Postmenopausal haemorrhage Breast tenderness Genital pruritus Vaginal candidiasis Vaginal haemorrhage Pelvic pain Cervical dysplasia Genital discharge Vulvovaginitis	Breast discomfort Fungal infection Vaginal mycosis Nipple pain
Investigations	Weight increased Abnormal cervical smear*	

* The majority consisted of benign changes. Cervix pathology (cervical carcinoma) was not increased with tibolone compared to placebo.

In market use, other undesirable effects that have been observed include dizziness, rash, pruritus, seborrheic dermatosis, headache, migraine, visual disturbances (including blurred vision), gastrointestinal upset, depression, oedema, effects on the musculoskeletal system such as arthralgia or myalgia and changes in liver function parameters.

Breast cancer risk

- An up to 2-fold increased risk of having breast cancer diagnosed was reported in the MWS in women taking combined estrogen-progestogen therapy for more than 5 years.

- Any increased risk in users of estrogen-only and tibolone therapy is substantially lower than that seen in users of estrogen-progestogen combinations.
- The level of risk is dependent on the duration of use (see **Section 4.4 Special Warnings and Precautions for Use**).

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

- For women not using HRT or tibolone, 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 compared to never users during the corresponding period will be
    - For users of estrogen-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 estrogen-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

For women who use tibolone the number of additional cases of breast cancer is comparable with that for estrogen-only use.

A GPRD study reported that, compared with never users, the rate of breast cancer was not elevated in subjects who exclusively used unopposed estrogens (RR 0.97: 95% CI: 0.86-1.09) or tibolone (RR 0.86: 95% CI: 0.65-1.13). However, the rate was significantly increased in subjects who used combined estrogen-progestogen HRT (adjusted rate ratio [RR] 1.33: 95% CI: 1.23-1.44), and further increased with longer duration of use.

In the THEBES study, a multi-national, multicentre, randomized, double blind, parallel group, active controlled, comparative study in which 807 healthy postmenopausal women, aged 45 to 65 years, were randomised to tibolone 1.25 mg, 816 to tibolone 2.5 mg and 1,617 to continuous CE/MPA (conjugated estrogens 0.625 mg and medroxyprogesterone acetate 2.5 mg) to study various safety endpoints. Breast cancer was diagnosed more with tibolone than with CE/MPA: the tibolone 2.5 mg daily group 8 adjudicated cases, tibolone 1.25 mg daily had 2 cases and CE/MPA had 8 cases. Tibolone 2.5 mg tablet had a RR (95% CI) of 2.47 (0.88 to 7.19) compared with CE/MPA and 4.82 (1.03 to 45.21) compared with the 1.25 mg dosage form. The study cannot provide comparisons against no treatment as there was no placebo arm. The study was not specifically designed to provide these comparisons but these findings do underscore the need to observe the relevant Precautions for use.

Endometrial cancer risk
The endometrial cancer risk is about 5 in every 1000 women with a uterus not using HRT or XYVION.

In the randomised placebo controlled trial that included women who had not been screened for endometrial abnormalities at baseline, and therefore reflected clinical practice, identified the highest risk of endometrial cancer (LIFT study, mean age 68 years). In this study, no cases of endometrial cancer were diagnosed in the placebo group (n=1,773) after 2.9 years compared with 4 cases of endometrial cancer in the tibolone group (n=1,746). This corresponds to a diagnosis of 0.8 additional cases of endometrial cancer in every 1000 women who used tibolone for one year in this study (see **Section 4.4 Special Warnings and Precautions for Use**).

Risk of ischaemic stroke

- The relative risk of ischaemic stroke is not dependent on age or on duration of use, but as the baseline risk is strongly age-dependent, the overall risk of ischaemic stroke in women who use HRT or XYVION will increase with age (see **Section 4.4 Special Warnings and Precautions for Use**).
- A 2.9 year randomised controlled study has estimated a 2.2-fold increase in the risk of stroke in women (mean age 68 years) who used 1.25 mg tibolone (28/2249) compared with placebo (13/2257). The majority (80%) of strokes were ischaemic.
- The baseline risk of stroke is strongly age-dependent. Thus, the baseline incidence over a 5 year period is estimated to be 3 per 1000 women aged 50-59 years and 11 per 1000 women aged 60-69 years.
- For women who use XYVION for 5 years, the number of additional cases would be expected to be about 4 per 1000 users aged 50-59 years and 13 per 1000 users aged 60-69 years.

Other adverse effects have been reported in association with estrogen and estrogen-progestogen treatment:

Ovarian cancer

- Use of estrogen-only or combined estrogen-progestogen HRT has been associated with an 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 50-54 years taking 5 years of HRT, this results in about 1 extra case per 2000 users. In women aged 50-54 years who are not taking HRT, about 2 women in 2000 will be diagnosed with ovarian cancer over a 5 year period. In the Million Women Study, taking 5 years of tibolone resulted in 1 extra case per 2500 users (see **Section 4.4 Special Warnings and Precautions for Use)**.

Venous thromboembolism risk

- HRT is associated with a 1.3 - 3 fold increased relative risk of developing venous thromboembolism (VTE), i.e. deep vein thrombosis or pulmonary embolism. The occurrence of such an event is more likely in the first year of using HRT (see **Section 4.4 Special Warnings and Precautions for Use**). Results of the WHI studies are presented:

Table 2: WHI Studies - Additional risk of VTE over 5 years' use

Age range (years)	Incidence per 1000 women in placebo arm over 5 years	Risk ratio and 95%CI	Additional cases per 1000 HRT users
Oral estrogen-only*4			
50-59	7	1.2 (0.6-2.4)	1 (-3-10)
Oral combined estrogen-progestogen			
50-59	4	2.3 (1.2–4.3)	5 (1-13)

4 *Study in women with no uterus

Coronary artery disease risk

- 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**). There is no evidence to suggest that the risk of myocardial infarction with tibolone is different to the risk with other HRT.
- Estrogen-dependent neoplasms benign and malignant, e.g. endometrial carcinoma.

- Venous thromboembolism, i.e. deep leg or pelvic venous thrombosis and pulmonary embolism, is more frequent among HRT users than among non-users. For further information, (see **Section 4.3 Contraindications and Section 4.4 Special Warnings** and **Precautions for Use**).
- Myocardial infarction
- Gall bladder disease
- Skin and subcutaneous disorders: chloasma, erythema multiforme, erythema nodosum, vascular purpura
- Probable dementia over the age of 65 (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

The acute toxicity of tibolone in animals is very low. Therefore, toxic symptoms are not expected to occur if several tablets are taken simultaneously. In cases of acute overdose, nausea, vomiting, and withdrawal bleeding in females may develop. No specific antidote is known. Symptomatic treatment can be given if necessary.

For information on the management of overdose, contact the Poisons Information Centre on 131126 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

ATC code: G03CX01

After oral administration tibolone is rapidly metabolised into three compounds which all contribute to the pharmacological effects of XYVION. Two of these metabolites (the 3αOH and 3βOH metabolite) have predominantly estrogenic activity, a third metabolite (Δ^4-isomer of tibolone) and the parent compound have predominantly progestogenic and androgenic activities.

XYVION substitutes for the loss of estrogen production in postmenopausal women and alleviates menopausal symptoms. XYVION prevents bone loss following menopause or ovariectomy.

XYVION has various tissue-specific effects. It has estrogenic effects on the vagina, on bone and on the thermoregulatory centres in the brain (hot flushes). Based on *in vitro* data, XYVION inhibits the sulphatase enzyme in cultured breast cancer cells thereby reducing the levels of active estrogens produced in those cells. Due to local conversion to the Δ^4-isomer, the endometrial findings have been mainly atrophic or in some cases weakly proliferative, which can, in themselves, be considered normal endometrial states. Therefore, if vaginal bleeding occurs, this usually results from an atrophic endometrium. XYVION also has androgenic effects on certain metabolic and haematological parameters such as a decrease in plasma high density lipoprotein cholesterol, triglycerides and lipoprotein(a), and may increase blood

fibrinolytic activity. XYVION improves vaginal dryness and vaginal atrophy. There are indications that XYVION has effects on mood and libido.

Effects on the endometrium and bleeding patterns

- There have been reports of endometrial hyperplasia and endometrial cancer in patients treated with XYVION (see **Section 4.4 Special Warnings and Precautions for Use** and **Section 4.8 Adverse Effects (Undesirable Effects)**).
- Amenorrhoea has been reported in 88% of women using XYVION 2.5 mg after 12 months of treatment. Breakthrough bleeding and/or spotting has been reported in 32.6% of women during the first 3 months of treatment, and in 11.6% of women after 11-12 months of use.

Effects on the breast

In clinical studies, mammographic density is not statistically significantly increased in women treated with XYVION 2.5 mg daily compared to placebo but a trend to higher mammographic density was noted for XYVION 2.5 mg daily.

Clinical trials

Relief of estrogen deficiency symptoms

Two pivotal, multicentre, randomized, double-blind studies assessed the effects of tibolone on climacteric complaints. One of these studies was a placebo-controlled study and assessed the effects on hot flushes and sweats in groups of about 150 subjects after a 12-week treatment with various doses of tibolone and placebo. The 2.5 mg dose appeared to be the optimal dose for relieving hot flushes, sweats and other climacteric complaints. The other study was an active controlled study that compared the effects of a 48-week treatment of 2.5 mg tibolone with that of a continuous combined estradiol/norethisterone acetate combination in groups of about 220 post-menopausal subjects. Tibolone significantly relieved the climacteric symptoms (hot flushes, sweats, vaginal dryness and rating scores on well-being); the effects appeared to be similar to that of the continuous combined HT-preparation. The efficacy of tibolone on the climacteric symptoms was confirmed in three Organon-sponsored studies and in published studies. In addition to the positive effects on climacteric complaints, tibolone also has an effect on mood and libido.

Prevention of osteoporosis

In two identical pivotal, multicentre, randomised, double-blind, placebo-controlled studies four doses of tibolone or placebo were given for 2 years to groups of about 75 women per dose and per study to assess the efficacy for preventing post-menopausal bone mineral density loss, safety and acceptability. In these studies, the bone mineral density measured with DEXA was significantly increased at all sites (spine, femoral neck, trochanter and Ward's, and distal radius) with the 2.5 mg dose compared to the placebo-groups. The results on BMD were confirmed by the results on the biochemical markers of bone turnover, showing that tibolone reduces the markers for bone resorption to a greater extent than the markers for bone formation. The efficacy of tibolone on bone was confirmed in 11 Organon sponsored studies and many other studies published in literature.

In the LIFT study, tibolone reduced the number of women (mean age 68 years) with new vertebral fractures compared to placebo during the 3 years of treatment (ITT: tibolone to placebo odds ratio 0.57; 95% CI [0.42,0.78]). Because this study used only tibolone 1.25 mg daily versus placebo, its contribution to the risk: benefit profile of tibolone 2.5 mg daily in the prevention of osteoporosis is unknown.

5.2 PHARMACOKINETIC PROPERTIES

Absorption

Following oral administration tibolone is rapidly and extensively absorbed.

The consumption of food has no significant effects on the extent of absorption.

Distribution and metabolism

Due to rapid metabolism, the plasma levels of tibolone are very low. The plasma levels of the Δ^4-isomer of tibolone are also very low. Therefore some of the pharmacokinetic parameters could not be determined.

Peak plasma levels of the 3α-OH and the 3β-OH metabolites are higher but accumulation does not occur.

Table 3: Pharmacokinetic parameters of XYVION (2.5 mg)

	Tibolone		3α-OH metabolite		3β-OH metabolite		Δ4-isomer	
	SD	MD	SD	MD	SD	MD	SD	MD
C_{max} (ng/ml)	1.37	1.72	14.23	14.15	3.43	3.75	0.47	0.43
$C_{average}$	--	--	--	1.88	--	--	--	--
T_{max} (h)	1.08	1.19	1.21	1.15	1.37	1.35	1.64	1.65
$T_{1/2}$ (h)	--	--	5.78	7.71	5.87	--	--	--
C_{min} (ng/ml)	--	--	--	0.23	--	--	--	--
AUC_{0-24} (ng/ml.h)	--	--	53.23	44.73	16.23	9.20	--	--

SD = single dose; MD = multiple dose

Excretion

Excretion of tibolone is mainly in the form of conjugated (mostly sulfated) metabolites. Part of the administered compound is excreted in the urine, but most is eliminated via the faeces.

The pharmacokinetic parameters for tibolone and its metabolites were found to be independent of renal function.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

Tibolone did not show any evidence of genotoxicity in assays for gene mutations, chromosomal damage and DNA damage.

Carcinogenicity

Tibolone treatment, similar to treatment with other sex hormones, in rodent studies demonstrated an association with the development of a range of tumours in long-term oral carcinogenicity studies. These included pituitary adenomas, mammary carcinomas and fibroadenomas, hepatic adenomas, uterine carcinoma, stromal polyps and stromal sarcoma, and carcinomas of the urinary bladder and testes.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

XYVION tablets 2.5 mg contain potato starch, magnesium stearate, ascorbyl palmitate and lactose monohydrate.

6.2 INCOMPATIBILITIES

No incompatibilities have been found.

6.3 SHELF LIFE

The shelf life for XYVION tablets 2.5 mg is 2 years. The tablets should not be used after the expiry date on the package.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 25°C, protected from light and moisture.

6.5 NATURE AND CONTENTS OF CONTAINER

XYVION tablets 2.5 mg are packed in push-through strips of clear polyvinyl chloride film and aluminium foil containing a heat seal coating on the side in contact with the tablets and white on the other side.

The following packages are available: 1 or 3* push-through strips with 28 white tablets each containing 2.5 mg tibolone.

*Not currently marketed in Australia

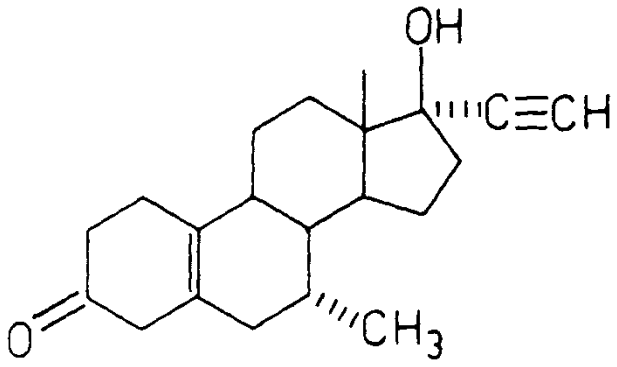
6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

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

6.7 PHYSICOCHEMICAL PROPERTIES

Tibolone exists as white to almost white crystals or crystalline powder. Tibolone is related to and derived from naturally occurring steroids. It is optically pure and has the D-configuration. It is practically insoluble in water, aqueous acid or alkali at 20°C.

Chemical structure



Molecular formula $C_{21}H_{28}O_2$
Molecular mass 312.45

Chemical name:
(7α, 17α) - 17 - hydroxy-7-methyl-19-norpregn-5 (10)-en-20-yn-3-one.

Other name:
17α-ethynyl-17-hydroxy-7α-methyl-5(10)-estren-3-one.

CAS number

5630-53-5

7 MEDICINE SCHEDULE (POISONS STANDARD)

Prescription Only Medicine (Schedule 4)

8 SPONSOR

Organon Pharma Pty Ltd
Building A, 26 Talavera Road
Macquarie Park NSW 2113

9 DATE OF FIRST APPROVAL

14 August 2008

10 DATE OF REVISION

21 December 2020

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
8	Amend sponsor details due to transfer of sponsorship

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