PACKAGE INSERT TEMPLATE FOR TIBOLONE TABLET 2.5MG

Brand or Product Name
[Product name] Tablet 2.5mg

Name and Strength of Active Substance(s)

Tibolone …..2.5mg

Product Description
[Visual description of the appearance of the product (eg colour, markings etc)
eg White, circular flat beveled edge film-coated tablets marked '2.5' on one side

Pharmacodynamics
Tibolone is a synthetic steroidal agent (C-19 nortestosterone derivative) possessing estrogenic, progestogenic, and androgenic activity. Tibolone inhibits ovulation, blocks gonadotropin secretion, prevents bone loss following ovariectomy, and restores sex drive after castration in animal models.

The mechanism of tibolone in alleviating menopausal symptoms may be related to increased secretion of plasma beta-endorphin and beta-lipoprotein. Circulating levels of both of these peptides are normally lower in postmenopausal as opposed to fertile women, and increases in their plasma concentrations induced by tibolone have correlated with alleviation of hot flushes and other menopausal symptoms. Tibolone appears at least as effective as conjugated estrogens in restoring circulating beta-endorphin and beta-lipoprotein levels in postmenopausal subjects.

Benefits of tibolone in reducing bone resorption in postmenopausal women may be secondary to reduced urinary calcium excretion via an increase in renal tubular reabsorption of calcium; this would result in increases in serum calcium levels and decreased parathyroid hormone secretion.

Pharmacokinetics

Tibolone is rapidly and extensively absorbed after oral doses and quickly metabolised into three active metabolites, two of which have mainly oestrogenic activity while the third, like the parent compound, has progestogenic and androgenic activity. Peak concentrations of tibolone and its metabolites occur after about 1 to 1.5 hours, and the two main metabolites have an elimination

half-life of about 7 hours. Metabolites are excreted in the bile and eliminated in the faeces. About 30% of a dose is excreted in the urine.

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

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

Indication

• Treatment of complaints resulting from the natural or artificial menopause. Women above 60 years of age should only start with tibolone treatment when they are intolerant of, or contraindicated for, other medicinal products approved for the treatment of estrogen deficiency symptoms.

• Prevention of osteoporosis in postmenopausal women at high risk of future fractures who are intolerant of, or contraindicated for, other medicinal products approved for the prevention of osteoporosis.

Recommended Dosage

The dosage is one tablet per day. No dose adjustment is necessary for the elderly. The tablets should be swallowed with some water or other drink, preferably at the same time every day.

For initiation and continuation of treatment of postmenopausal symptoms, the lowest effective dose for the shortest duration should be used.
A separate progestogen should not be added with tibolone treatment.

Starting tibolone

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

Any irregular/unscheduled vaginal bleeding, either on or off HRT, should be investigated to exclude malignancy before starting tibolone.

Switching from a sequential or continuous combined HRT preparation

If changing from a sequential HRT preparation, treatment with tibolone should start the day following completion of the prior regimen. If changing from a continuous-combined HRT preparation, treatment can start at any time.

Missed dose

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.

Mode of Administration
Oral

Contraindications
• Known, past or suspected breast cancer
• Pregnancy and lactation
• Known or suspected estrogen-dependent malignant tumors (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

Warnings and Precautions

Tibolone is not intended for contraceptive use.

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

The risks of stroke, breast cancer and, in women with an intact uterus, endometrial cancer 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 tibolone 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.

Use of tibolone within 12 months of a natural menopause is not recommended because irregular vaginal bleeding is likely. Breakthrough bleeding and spotting may occur in the first few months of therapy, but should be investigated if it persists beyond 6 months, starts after that time, or continues after tibolone has been stopped. Missing a dose may increase the likelihood of bleeding and spotting.

Medical examination/follow-up

Before initiating or reinstituting HRT or tibolone, 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. 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 tibolone, in particular:

- Leiomyoma (uterine fibroids) or endometriosis
- Risk factors for thromboembolic disorders
- Risk factors for estrogen dependent tumors, 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 erythematosis

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- A history of endometrial hyperplasia
- Epilepsy
- Asthma
- Otosclerosis
- Dyslipidaemia
- Disorders that may be exacerbated by fluid retention such as cardiac or renal dysfunction

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
- Signs of thromboembolism

*Consideration should be given to stopping tibolone 4 to 6 weeks before elective surgery when prolonged immobilisation after surgery is likely.

Effects on the ability to drive and use machines
Tibolone is not known to have any effects on alertness and concentration.

Interactions with Other Medicaments

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.
Compounds that induce liver enzymes, such as phenytoin, carbamazepine, and rifampicin, might theoretically enhance the metabolism of tibolone and thus reduce its activity.

Concomitant tibolone treatment with warfarin led to enhanced warfarin-induced anticoagulation. When tibolone is initiated or discontinued in patients on warfarin therapy, monitoring of coagulation parameters, especially prothrombin time, is recommended. Warfarin doses should be adjusted accordingly.

Women already on anticoagulant treatment require careful consideration of the benefit-risk of use of HRT or tibolone.

Concomitant use of St. John's wort and tibolone may result in severe liver damage. If treatment with both agents is unavoidable, monitor closely for symptoms of hepatotoxicity.

Herbal preparations containing St.John`s wort (Hypericum Perforatum) may induce the metabolism of oestrogens and progestagens via CYP3A4. Clinically, an increased metabolism of oestrogens and progestagens may lead to decreased effect and changes in the uterine bleeding profile.

Interaction Effect with tricyclic antidepressants(amitriptyline, clomipramine, desipramine, dothiepin, doxepin, imipramine, nortriptyline)**:** attenuation of antidepressant effectiveness; tricyclic toxicity (drowsiness, hypotension, akathisia). If signs or symptoms of altered tricyclic response are noted, dose adjustment downward of either the estrogen or tricyclic component may be successful in restoring effectiveness or resolving toxicity. However, drug withdrawal may be required.

Statement on Usage During Pregnancy and Lactation

Pregnancy
Tibolone is contraindicated during pregnancy. If pregnancy occurs during medication with tibolone, treatment should be withdrawn immediately. There is no clinical data on exposed pregnancies available. The potential risk for humans is unknown.

Lactation
Tibolone is contraindicated during lactation.

Adverse Effects / Undesirable Effects
Irregular vaginal bleeding or spotting may occur with tibolone, mainly during the first few months of treatment; unlike cyclical, but similar to continuous, combination HRT (Hormone Replacement Therapy), tibolone does not produce regular withdrawal bleeding. Other effects on

the genital tract may include leucorrhoea, pruritus, candidiasis, and vaginitis. Other adverse effects have included breast pain, weight gain, oedema, dizziness, skin reactions, headache, migraine, visual disturbances, gastrointestinal disturbances, hypertrichosis, altered liver function, depression, and arthralgia or myalgia.

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

- Long term use of estrogen-only and combined estrogen-progestagen HRT has been associated with a slightly increased risk of ovarian cancer.
- 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
- The risk of coronary artery disease is slightly increased in users of combined estrogen-progestagen HRT over the age of 60. There is no evidence to suggest that the risk of myocardial infarction with tibolone is different to the risk with other HRT.
- Gall bladder disease
- Skin and subcutaneous disorders: chloasma, erythema multiforme, erythema nodosum, vascular purpura
- Probable dementia over the age of 65

<u>Breast cancer risk</u>

- An up to 2-fold increased risk of having breast cancer diagnosed is reported in women taking combined estrogen-progestagen 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-progestagen combinations.
- The level of risk is dependent on the duration of use

<u>Endometrial cancer risk</u>

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

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 tibolone will increase with age

Overdose and Treatment

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

Storage Conditions
[eg Store below…. °C]

Dosage Forms and Packaging Available
[Packaging type & pack size]

Name and Address of Manufacturer
[Name & full address of manufacturer]

Name and Address of Marketing Authorization Holder
[Name & full address of marketing authorization holder]

Date of Revision of Package Insert
[day/month/year]

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