Tibol®
(Tibolone)

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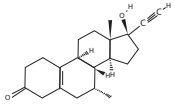
QUALITATIVE AND QUANTITATIVE COMPOSITION
Each tablet contains:
Tibolone (BP)..... 2.5 mg

DESCRIPTION
Tibol (Tibolone) is a synthetic anabolic steroid with estrogenic, androgenic and progestogenic activities. Tibolone is a 19-nortestosterone derivative and is related structurally to other 19-nortestosterone progestins.It is the 7α-methyl derivative of noretynodrel.



CLINICAL INFORMATION
Indications
• Treatment of estrogen deficiency symptoms in postmenopausal women, more than one year after menopause.
• 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.
For all women the decision to prescribe Tibol (Tibolone) 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.

Dosage and Administration
The dosage is one tablet per 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 Tibol (Tibolone) treatment.
Starting Tibol (Tibolone)
Women experiencing a natural menopause should commence treatment with Tibol (Tibolone) at least 12 months after their last natural bleed. In case of a surgical menopause, treatment with Tibol (Tibolone) may commence immediately.
Any irregular/unscheduled vaginal bleeding, either on or off HRT, should be investigated to exclude malignancy before starting Tibol (Tibolone).
Switching from a sequential or continuous combined HRT preparation
If changing from a sequential HRT preparation, treatment with Tibol (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.
Dosage Adjustment
Pediatrics
There is no relevant use of Tibol (Tibolone) in the paediatric population.
Elderly
No dose adjustment is necessary for the elderly.
Administration Requirements
The tablets should be swallowed with some water or other drink, preferably at the same time every day.

Contraindications
• Pregnancy and lactation
• Known, past or suspected breast cancer 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
• Porphyria

Warnings and Precautions
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 (below) 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.
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. first 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
- A history of endometrial hyperplasia
- 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

Endometrial hyperplasia and carcinoma

• Data suggests that women who are prescribed Tibolone in normal clinical practice are at an increased risk of having endometrial cancer diagnosed. Risk may be increased 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. 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 gynecological 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. Data suggests a significant increase in the risk of breast cancer in association with use of the 2.5mg dose. This risk may become 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

Ovarian cancer

• Ovarian cancer is much rarer than breast cancer. Long-term (at least 5-10 years) use of estrogen-only HRT products may be associated with a slightly increased risk of ovarian cancer. Data suggest that the long-term use of combined HRTs may confer a similar or slightly smaller risk. Data suggests that the relative risk for ovarian cancer with use of Tibolone is 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. Data suggests that the risk of VTE in association with Tibolone is lower than the risk associated with conventional HRT, but only a small proportion of women are 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 Tibolone may add to this risk. HRT is therefore contraindicated in these patients.

• Generally recognized risk factors for VTE include use of estrogens, older age, major surgery, prolonged immobilization, obesity (BMI > 30 kg/m2), 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 Tibolone 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, dyspnea).

Coronary artery disease (CAD)

There is no evidence of protection against myocardial infarction in women with or without existing CAD who received combined estrogen-progestogen or estrogen-only HRT.

Ischaemic stroke

• Tibolone increases the risk of ischaemic stroke from the first year of treatment. 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.

• Tibolone is not intended for contraceptive use.

• Treatment with Tibolone results in a marked dose-dependent decrease in HDL cholesterol (from -16.7% with a 1.25 mg dose to -21.8% for the 2.5 mg dose after 2 years). Total triglycerides and lipoprotein(a) levels are also known to be reduced. The decrease in total cholesterol and VLDL-C levels is not dose-dependent. Levels of LDL-C are unchanged. The clinical implication of these findings is not yet known.

• Estrogens may cause fluid retention, and therefore patients with cardiac or renal dysfunction should be carefully observed.

• Women with pre-existing hypertriglyceridemia should be followed closely during estrogen replacement or HRT, since rare cases of large increases of plasma triglycerides leading to pancreatitis are known to occur with estrogen therapy in this condition.

• Treatment with Tibolone results in a very minor decrease of thyroid binding globulin (TBG) and total T4. Levels of total T3 are unaltered. Tibolone 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.

Interactions

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

• There is limited information regarding pharmacokinetic interactions with Tibolone. Data indicates 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 oestrogens and progestogens via CYP3A4. Clinically, an increased metabolism of oestrogens and progestogens may lead to decreased effect and changes in the uterine bleeding profile.

Pregnancy and Breastfeeding

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

Effects on ability to drive and use machines

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

Adverse Reactions

System organ class	Common	Uncommon	Rare
Metabolism and nutrition disorders		Oedema	
Gastrointestinal disorders	Lower abdominal pain		
Skin and subcutaneous tissue disorders	Abnormal hair growth	Acne	Pruritus
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 increase Abnormal cervical smear		

Other adverse reactions that may be observed include: dizziness, rash, seborrheic dermatosis, headache, migraine, visual disturbances (including blurred vision), depression, effects on the musculoskeletal system such as arthralgia or myalgia and changes in liver function parameters.

Breast cancer

An up to 2-fold increased risk of having breast cancer diagnosed may be observed in women taking combined oestrogen-progestogen therapy for more than 5 years.

Any increased risk in users of oestrogen-only and Tibolone therapies is substantially lower than in users of

oestrogen-progestogen combinations. The level of risk is dependent on the duration of use.

Endometrial cancer risk

Postmenopausal women with a uterus

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

Ovarian cancer

Use of estrogen-only or combined estrogen-progestogen HRT may be associated with a slightly increased risk of having ovarian cancer diagnosed.

Risk of venous thromboembolism

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.

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. There is no evidence to suggest that the risk of myocardial infarction with Tibolone is different to the risk with other HRT.

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.

• The use of estrogen-only and estrogen + progestogen therapy is associated with an up to 1.5 fold increased relative risk of ischaemic stroke. The risk of haemorrhagic stroke is not increased during use of HRT.

Other adverse reactions that may be associated with estrogen/progestogen treatment:

• Gall bladder disease

• Skin and subcutaneous disorders: chloasma, erythema multiforme, erythema nodosum, vascular purpura

• Probable dementia over the age of 65

Overdose

The acute toxicity of Tibolone 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.

PHARMACOLOGICAL PROPERTIES

Pharmacotherapeutic group: ATC code: G03CX01, other estrogens

Pharmacodynamic properties

Following oral administration, Tibolone is rapidly metabolized into three compounds, which all contribute to the pharmacodynamic profile of Tibolone. Two of the metabolites (3α-OH-Tibolone and 3β-OH-Tibolone) have estrogenic-like activities, whereas the third metabolite (Δ 4-isomer of Tibolone) has progestogenic and androgenic-like activities.

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

Pharmacokinetic properties

Absorption and biotransformation

Following oral administration, Tibolone is rapidly and extensively absorbed. Due to rapid metabolism, the plasma levels of Tibolone are very low. The plasma levels of the Δ4-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 3 β-OH metabolites are higher but accumulation does not occur.

Elimination

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 feces.

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

The pharmacokinetic parameters for Tibolone and its metabolites are found to be independent of renal function.

PHARMACEUTICAL INFORMATION

Shelf life

2 years

Special Precautions for Storage

ہدایات:

- Store below 25°C. ۲۵ ڈگری سینٹی گریڈ سے کم درجہ حرارت پر رکھیں۔
- Protect from light and moisture. دوا کو روشنی اور نمی سے بچائیں۔
- Keep out of the reach of children. بچوں کی پہنچ سے دور رکھیں۔

To be sold on the prescription of a registered medical practitioner only. صرف مستند ڈاکٹر کے نسخے پر فروخت کریں۔

Nature and contents of container

Tibol (Tibolone) 2.5 mg tablets are available in a blister pack of 28's (1 x 28's).

MANUFACTURED BY

OBS Pakistan (Pvt.) Ltd.

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MANUFACTURED FOR

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