PROFESSIONAL INFORMATION LEAFLET: TIBOLONE ACTOR

SCHEDULING STATUS S4

1. NAME OF THE MEDICINE

TIBOLONE ACTOR Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 2,5 mg tibolone.

Excipient with known effect:

Each tablet contains 74,80 mg lactose (as monohydrate).

For the full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

White to whitish round tablets

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

- Symptomatic treatment of hot flushes and associated sweating resulting from natural or surgical menopause.
- Prevention of post-menopausal osteoporosis.
- Improvement of bone-mineral density in patients with established post-menopausal osteoporosis.

4.2 Posology and method of administration

The dosage is 1 tablet per day. 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.

Improvement of symptoms generally occurs within a few weeks, but optimal results are obtained when therapy is continued for at least 3 months.

Starting TIBOLONE ACTOR:

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

Any irregular/unscheduled vaginal bleeding, either on or off HRT, for which there is no obvious cause, should be investigated before starting TIBOLONE ACTOR.

Method of administration:

For oral use.

Tablets should be swallowed whole with some water or other drink, preferably at the same time each day.

4.3 Contraindications

- TIBOLONE ACTOR is contraindicated in patients with a known hypersensitivity to tibolone or to any excipient listed under section 6.1.
- Pregnancy and lactation.
- Known or suspected hormone-dependent tumours.
- Known, past or suspected breast cancer - TIBOLONE ACTOR increased the risk of breast cancer recurrence in a placebo-controlled trial.
- Known or suspected oestrogen-dependent malignant tumours (e.g., endometrial cancer).
- Vaginal bleeding of unknown etiology.
- Untreated endometrial hyperplasia.
- Cardiovascular or cerebrovascular disorders e.g., thrombophlebitis, thromboembolic processes or a history of these conditions.
- Previous idiopathic or current venous thromboembolism (deep venous thrombosis, pulmonary embolism).
- Known thrombophilic disorders e.g., protein C, protein S or antithrombin deficiency (see section

4.4").

- Any history of thromboembolic disease [e.g., angina, myocardial infarction, stroke or transient ischaemic attack (TIA)].
- Severe liver disease or a history of liver disease as long as liver function tests have failed to return to normal.
- Porphyria.

4.4 Special warnings and precautions for use

TIBOLONE ACTOR is not intended for contraceptive use.

The use of TIBOLONE ACTOR should be avoided until 12 months after the last natural menstrual bleed. If TIBOLONE ACTOR is taken sooner than this, the frequency of irregular bleeding may be increased.

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 (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.

Treatment should be discontinued if signs of thromboembolic processes occur, if results of liver function tests become abnormal or if cholestatic jaundice appears.

Vaginal bleeding may occur during TIBOLONE ACTOR therapy, because of an apparently stimulated endometrium due to some oestrogen production. Normally such bleeding is of short duration.

Bleedings commencing after 3 months of treatment, or recurrent or of longer duration should be investigated.

In women changing from another form of hormonal substitution therapy to TIBOLONE ACTOR therapy, it is always advisable to induce a withdrawal bleeding with a progestogen before starting TIBOLONE ACTOR.

Tibolone has been shown to be teratogenic in experimental animals, and should not be used in pre-menopausal women.

Periodic examinations must be done for endometrial hyperplasia, as well as possible signs of virilisation.

The risks of stroke, breast cancer and endometrial cancer (women with an intact uterus) 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.

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 ACTOR, in particular:

- leiomyoma (uterine fibroids) or endometriosis
- a history of, or risk factors for, thromboembolic disorders (see below)
- risk factors for oestrogen 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

Endometrial hyperplasia and cancer:

The available data from randomised controlled trials are conflicting, however, observational studies have consistently shown that women who are prescribed tibolone as contained in TIBOLONE ACTOR in normal clinical practice are at an increased risk of having endometrial cancer diagnosed. In these studies, risk 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 (see section 5.1). Women should be advised to report any breakthrough 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

The endometrial cancer risk is about 5 in every 1 000 women with a uterus not using HRT or TIBOLONE ACTOR.

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. In this study, a diagnosis of 0,8 additional cases of endometrial cancer in every 1 000 women who used tibolone as in TIBOLONE ACTOR for one year in this study were made.

Breast cancer:

Evidence with respect to breast cancer risk in association with TIBOLONE ACTOR is inconclusive. One study 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. These results could not be confirmed in a study using the General Practice Research Database (GPRD).

Breast cancer risk:

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

Any increased risk in users of oestrogen-only and tibolone as in TIBOLONE ACTOR therapy is substantially lower than that seen in users of oestrogen-progestogen combinations.

The level of risk is dependent on the duration of use.

Ovarian cancer:

Ovarian cancer is much rarer than breast cancer. Long-term (at least 5 to 10 years) use of oestrogen-only HRT products has been associated with a slightly increased risk of ovarian cancer (see section 4.8). Some studies suggest that the long-term use of combined HRTs may confer a similar, or slightly smaller risk (see section 4.8). In one study it was shown that the relative risk for ovarian cancer with use of tibolone as contained in TIBOLONE ACTOR was similar to the risk associated with use of other types of HRT.

Venous thromboembolism:

Oestrogen or oestrogen-progestogen HRT is associated with a 1,3 to 3 fold risk of developing venous thromboembolism 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). In an epidemiological study using a UK database, the risk of VTE in association with tibolone as contained in TIBOLONE ACTOR was lower than the risk associated with conventional HRT, but only a small proportion of women were current users of TIBOLONE ACTOR and a small increase in risk compared with non-use cannot be excluded.

Generally recognised risk factors for VTE include use of oestrogens, older age, 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 post-operative patients, scrupulous attention should be given to prophylactic measures that need to be considered to prevent VTE following surgery. If prolonged immobilisation is to follow elective surgery, temporarily stopping HRT or TIBOLONE ACTOR 4 to 6 weeks earlier is recommended. Treatment should not be restarted until the woman is completely mobilised.

Patients with a history of VTE or known thrombophilic states have an increased risk of VTE. HRT may add to this risk. HRT is therefore contraindicated in these patients (see section 4.3).
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 ACTOR is contraindicated.

Women already on anticoagulant treatment require careful consideration of the benefit-risk of use of HRT or TIBOLONE ACTOR.
If VTE develops after initiating therapy, the medicine 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 randomised controlled trials of protection against myocardial infarction in women with or without existing CAD who received combined oestrogen-progestogen or oestrogen-only HRT. In an epidemiological study using the GPRD no evidence was found of protection against myocardial infarction in post-menopausal women who received tibolone as contained in TIBOLONE ACTOR.

Tibolone as contained in TIBOLONE ACTOR 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 ACTOR is greater with older age.

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 ACTOR will increase with age.

A 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 compared with placebo. 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 1 000 women aged 50 to 59 years and 11 per 1 000 women aged 60 to 69 years.

For women who use tibolone as in TIBOLONE ACTOR for 5 years, the number of additional cases would be expected to be about 4 per 1 000 users aged 50 to 59 years, and 13 per 1 000 users aged 60 to 69 years.

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

- Long term use of oestrogen-only and combined oestrogen-progestogen HRT has been associated with an increased risk of ovarian cancer. In one study 5 years of HRT resulted in 1 extra case per 2 500 users. This study showed that the relative risk for ovarian cancer with TIBOLONE ACTOR was similar to the risk with other types of HRT.
- HRT is associated with a 1, 3 to 3-fold increased relative risk of developing venous thromboembolism i.e., deep vein thrombosis and 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 increased in users of combined oestrogen-progestogen HRT over the age of 60. There is no evidence to suggest that the risk of myocardial infarction with TIBOLONE ACTOR is different to the risk with other HRT.
- Gall bladder disease.
- Skin and subcutaneous disorders: Chloasma, erythema multiforme, erythema nodosum, vascular purpura.
- 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 were also reduced. The decrease in total cholesterol and VLDL-C levels was not dose-dependent. Levels of LDL-C were unchanged. The clinical implication of these findings is not yet known.
- Oestrogens 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 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.
- 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.
- Probable dementia over the age of 65.

Lactose:

TIBOLONE ACTOR contains lactose monohydrate. Patients with rare hereditary problems of galactose intolerance e.g., galactosaemia, total lactase deficiency or glucose-galactose malabsorption should not take TIBOLONE ACTOR.

4.5 Interaction with other medicines and other forms of interaction

No examples of interaction between tibolone as in TIBOLONE ACTOR and other medicines have been reported in clinical practice. However, the following potential interactions should be considered on a theoretical basis:

- Enzyme-inducing compounds such as barbiturates, carbamazepine, hydantoins and rifampicin may enhance the metabolism of TIBOLONE ACTOR and thus decrease its therapeutic effect.
- Since tibolone as in TIBOLONE ACTOR may increase blood fibrinolytic activity (lower fibrinogen levels; higher ATIII, plasminogen and fibrinolytic activity values), it may enhance the effect of anticoagulants. Therefore, the simultaneous use of TIBOLONE ACTOR and warfarin should be monitored, especially when starting or stopping concurrent TIBOLONE ACTOR treatment, and the warfarin dose should be appropriately 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, medicine interactions with other CYP3A4 substrates might be expected.

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.

4.6 Fertility, pregnancy and lactation

Pregnancy:

TIBOLONE ACTOR is contraindicated during pregnancy (see section 4.3). If pregnancy occurs during medication with TIBOLONE ACTOR, treatment should be withdrawn immediately.

Breastfeeding:

TIBOLONE ACTOR is contraindicated during breastfeeding (see section 4.3).

Fertility:

In animal studies, tibolone had anti-fertility activities by virtue of its hormonal properties.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Table 1: Tabulated summary of adverse reactions

The following undesirable effects have been reported.

System Organ Class	**TIBOLONE ACTOR Tablets Side Effects**
Metabolism and nutrition disorders:	
Frequent:	Weight increase
Gastrointestinal disorders:	
Frequent:	Lower abdominal pain
Skin and subcutaneous tissue disorders:	
Frequent:	Abnormal hair growth
Less frequent:	Acne
Reproductive system and breast disorders:	
Frequent:	Vaginal discharge Endometrial wall thickening, post-menopausal haemorrhage, breast tenderness, genital pruritus, vaginitis candidiasis, vaginal haemorrhage, pelvic pain, cervical dysplasia, genital discharge, vulvovaginitis
Less frequent:	Breast discomfort, fungal infection, vaginal mycosis, nipple pain

Investigations:	
Frequent:	Abnormal Cervical smear*
Less frequent:	Amnesia
* The majority consisted of benign changes. Cervix pathology (cervical carcinoma) was not increased with tibolone compared to placebo.	

In post-marketing experience, the following additional undesirable effects have been reported with frequency unknown:

System Organ Class	**TIBOLONE ACTOR Tablets Side Effects**
Metabolism and nutrition disorders:	Oedema
Psychiatric disorders:	Depression
Nervous system disorders:	Dizziness, headache, migraine
Eye disorders:	Visual disturbances (including blurred vision)
Gastrointestinal disorders:	Gastrointestinal upset
Skin and subcutaneous tissue disorders:	Rash, pruritus, seborrheic dermatosis
Musculoskeletal, connective tissue and bone disorders:	Arthralgia or myalgia
Investigations:	Changes in liver function parameters

Reporting of suspected adverse reactions:

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare providers are asked to report any suspected adverse reactions to SAHPRA via the “6.04 Adverse Drug Reaction Reporting Form”, found online under SAHPRA’s publications: https://www.sahpra.org.za/Publications/Index/8.

In addition, suspected adverse reactions can be reported to Actor Pharma (Pty) Ltd via email: pharmacovigilance@ actorpharma.co.za or telephonically on 011 312 3812.

4.9 Overdose

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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacological classification:

A 21.13 Others.

Pharmacotherapeutic group: urogenital system (including sex hormones), ATC code: G03CX01.

Tibolone stabilises the hypothalamic-pituitary system after failure of the ovarian function in the climacteric, which leads to the occurrence of vasomotor complaints as a result of the involvement of the thermoregulatory centre in the hypothalamus. The therapeutic central effect of Tibolone is due to the combined oestrogenic, progestogenic and weak androgenic activities of the drug.

Tibolone has a moderate gonadotrophin suppressing effect in post-menopausal women. The peripheral effect of Tibolone is the combination of hormonal activities which exerts a balanced effect and does not stimulate the endometrium in post-menopausal women.

5.2 Pharmacokinetic properties

Absorption & Distribution:

Tibolone is rapidly and extensively absorbed, appearing in the blood within 30 minutes of oral administration with peak levels between 1,5 and 4 hours.

Metabolism & Elimination:

Tibolone is metabolised in the liver and converted to metabolites which are excreted mainly in the faeces and to a lesser extent in the urine. Some metabolites may contribute to the biological effects of the medicine. The elimination half-life of tibolone and active metabolites is less than 2 days, justifying once a day administration.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate

Potato starch

Ascorbyl palmitate

Magnesium stearate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Store at or below 25 °C in the original package.

6.5 Nature and contents of container

PVC-PVDC/Aluminium blisters enclosed in a carton.

Pack sizes:

1 x 28 film-coated tablets (1 blister strip per carton; 28 tablets per blister strip)

3 x 28 film-coated tablets (3 blister strips per carton; 28 tablets per blister strip)

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirement.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Actor Pharma (Pty) Ltd[1]

Royal Palm Business Estate

Unit 7, 646 Washington Street

Halfway House, Midrand, 1685

8. REGISTRATION NUMBER

48/21.13/0297

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

04 August 2022

10. DATE OF REVISION OF THE TEXT

Not applicable

[1] Company Registration number.: 2008/008787/07

FEM/PI/01/05.2021