SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

TIBILIVE 2,5 MG tablet

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 2,5 mg of tibolone.

TIBILIVE 2,5 MG contains sugar (lactose monohydrate each tablet contains 43,15 mg and mannitol 43,15 mg).

For the full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Tablet.

White to off-white round uncoated tablets without any marking.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

TIBILIVE 2,5 MG is indicated for:

- 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

Posology

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 TIBILIVE 2,5 MG

Women experiencing a natural menopause should commence treatment with TIBILIVE 2,5 MG at least 12 months after their last natural bleed. In case of a surgical menopause, treatment with TIBILIVE 2,5 MG may commence immediately.

Any irregular/unscheduled vaginal bleeding, either on or off hormone replacement therapy (HRT), should be fully investigated to exclude malignancy before starting TIBILIVE 2,5 MG.

Method of administration

Oral use.

TIBILIVE 2,5 MG should be swallowed whole with some water or other drink, preferably at the same time each day.

4.3 Contraindications

- hypersensitivity to tibolone or to any of the ingredients of TIBILIVE 2,5 MG
- known or suspected hormone-dependent tumours
- personal and family history of breast cancer, including suspected breast cancer
- previous idiopathic or current venous thromboembolism (deep venous thrombosis, (DVT) pulmonary embolism)
- known thrombophilic disorders e.g. protein C, protein S or antithrombin deficiency, including inherited thrombophilia (see section 4.4)
- active liver disease, severe liver disease, or a history of liver disease as long as liver function tests have failed to return to normal
- patients known with inherited genetic mutations: BRCA1 and BRCA2 genes
- early menstrual periods (before the age of 12 years)
- history of non-cancerous breast diseases (atypical hyperplasia or lobular carcinoma in situ
- previous treatment using radiation therapy to the chest or breast
- previous exposure to diethylstilbestrol (DES)
- 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
- any history of thromboembolic disease e.g. angina, myocardial infarction, stroke or transient ischaemic attack (TIA)
- porphyria
- pregnancy and lactation.

4.4 Special warnings and precautions for use

TIBILIVE 2,5 MG is not intended for contraceptive use.

TIBILIVE 2,5 MG is prescribed for the treatment of postmenopausal symptoms and should only be initiated for symptoms that adversely affect quality of life.

The use of TIBILIVE 2,5 MG should be avoided until 12 months after the last natural menstrual bleed. If TIBILIVE 2,5 MG is taken sooner than this, the frequency of irregular bleeding may be increased.

In the event that signs of thromboembolic processes occur, results of liver function tests become abnormal or if cholestatic jaundice appears, treatment with TIBILIVE 2,5 MG should be discontinued.

As a result of an apparently stimulated endometrium due to some oestrogen production, vaginal bleeding may occur during TIBILIVE 2,5 MG therapy. Normally such bleeding is of short duration. Bleedings commencing after 3 months of treatment, or recurrent or of longer duration should be investigated.

When changing to TIBILIVE 2,5 MG from any other form of hormonal substitution therapy, it is always advisable to induce a withdrawal bleeding with a progestogen before starting TIBILIVE 2,5 MG.

Tibolone, as in TIBILIVE 2,5 MG has been shown to be teratogenic in experimental animals and should not be used in pre-menopausal women.

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.

Medical examination/follow-up

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

Before initiating or reinstituting HRT or tibolone, as in TIBILIVE 2,5 MG, 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 that 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 TIBILIVE 2,5 MG, in particular:

- leiomyoma (uterine fibroids) or endometriosis
- history of, or risk factors for, thromboembolic disorders (see below)
- risk factors for oestrogen dependant 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
- history of endometrial hyperplasia (see below)
- epilepsy
- asthma
- otosclerosis.

Reasons for immediate withdrawal therapy:

TIBILIVE 2,5 MG therapy should be discontinued either in the case of a contraindication being discovered, or in any of 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 in TIBILIVE 2,5 MG, 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, as in TIBILIVE 2,5 MG increases endometrial wall thickness, as measured by transvaginal ultrasound.

The endometrial cancer risk is about 5 in every 1 000 women with a uterus not using HRT or tibolone, as in TIBILIVE 2,5 MG.

Break-through bleeding and spotting may occur during the first months of treatment (see section 4.3). 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

TIBILIVE 2,5 MG contains tibolone which has combined estrogenic and progestogenic effects and therefore, on prolonged use, may increase the risk of developing breast cancer. A meta-analysis of prospective epidemiological studies from 1992 to 2018 reported a

significant increase in the risk of developing breast cancer in 55,575 women 40 – 59 years of age who used menopausal hormone therapy (MHT). The risk increased steadily with duration of use and was slightly greater for oestrogen-progestogen than oestrogen only preparations, and the risk persisted for more than 10 years after stopping the treatment. The relative risk (RR) to develop breast cancer for oestrogen-progestogen preparations was 1.60 at 1-4 years and RR=2.08 at 5-14 years, while that for oestrogen only preparations was 1.17 at 1-4 years and 1.33 at 5-14 years. There was no risk of to develop breast cancer in women who started MHT at 60 years of age.

All women on TIBILIVE 2,5 MG should receive yearly breast examinations by a healthcare provider and perform monthly breast self-examinations. Mammography evaluations should be done based on patient age, risk factors, and prior mammogram results.

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 other studies suggest that the use of combined HRTs may be associated with 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 in TIBILIVE 2,5 MG was similar to the risk associated with use of other types of HRT.

Venous thromboembolism

Oestrogen or oestrogen-progestogen HRT is associated with a 1,3-3- 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). 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 tibolone, as in TIBILIVE 2,5 MG may add to this risk. HRT is therefore contraindicated in these patients (see section 4.3).

Generally recognised risk factors for VTE include use of oestrogens, older age, major surgery, prolonged immobilisation, 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 to 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, if possible. 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 TIBILIVE 2,5 MG is contraindicated.

Women already on anticoagulant treatment require careful consideration of the benefit-risk of use of HRT or TIBILIVE 2,5 MG.

If VTE develops after initiating therapy, TIBILIVE 2,5 MG 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 woman 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 in TIBILIVE 2,5 MG.

Ischaemic stroke

TIBILIVE 2,5 MG increases the risk of stroke from the first year of treatment (see section 4.8). The baseline risk of stroke is strongly age-dependent and so the effect of TIBILIVE 2,5 MG 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 TIBILIVE 2,5 MG will increase with age.
- 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 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 50-59 years and 11 per 1,000 women aged 60-69 years.
- For women who use tibolone, as in TIBILIVE 2,5 MG 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 reactions have been reported in association with oestrogen and oestrogen-progestogen treatment:

- Long term use of oestrogen-only or 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, as in TIBILIVE 2,5 MG, 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 (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 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, as in TIBILIVE 2,5 MG 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.

Other conditions

Treatment with tibolone, as in TIBILIVE 2,5 MG 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 TIBILIVE 2,5 MG results in a very minor decrease of thyroid binding globulin (TBG) and total T4. Levels of total T3 are unaltered. TIBILIVE 2,5 MG decreases the level of sex-hormone-binding globulin (SHBG), whereas the levels of corticoid binding globulin (CBG) and circulating cortisol are unaffected.

HRT does not improve cognitive function. There is some evidence of increased risk of probable dementia in women who start using continuous combined or oestrogen-only HRT after the age of 65.

TIBILIVE 2,5 MG contains lactose monohydrate. Patients with the rare hereditary conditions of galactose intolerance e.g. galactosaemia, total lactose deficiency or glucose-galactose malabsorption should not take TIBILIVE 2,5 MG.

4.5 Interaction with other medicines and other forms of interaction

No examples of interaction between tibolone, as in TIBILIVE 2,5 MG and other medicines have been reported in clinical practice. However, the following potential interactions should be considered on a theoretical basis:

Since tibolone may increase blood fibrinolytic activity (lower fibrinogen levels; higher ATIII, plasminogen and fibrinolytic activity values), it may enhance the effect of anticoagulants. This effect has been demonstrated with warfarin.

Caution should therefore be exercised during the simultaneous use of TIBILIVE 2,5 MG and anticoagulants, especially when starting or stopping concurrent TIBILIVE 2,5 MG 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, medicine interactions with other CYP3A4 substrates might be expected.

CYP3A4 enzyme-inducing medicines such as barbiturates, carbamazepine, hydantoins and rifampicin may enhance the metabolism of tibolone, as in TIBILIVE 2,5 MG, and thus decrease 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.

4.6 Fertility, pregnancy and lactation

Pregnancy

TIBILIVE 2,5 MG is contraindicated during pregnancy. If pregnancy occurs during medication with TIBILIVE 2,5 MG, treatment should be withdrawn immediately.
Studies in animals have shown reproductive toxicity. The potential risk for humans is unknown.

Breastfeeding

TIBILIVE 2,5 MG is contraindicated during breastfeeding.

Fertility

In animal studies, tibolone, as in TIBILIVE 2,5 MG, had anti-fertility activities by virtue of its hormonal properties.

4.7 Effects on ability to drive and use machines

TIBILIVE 2,5 MG is not known to have any effects on alertness and concentration.

4.8 Undesirable effects

This section describes undesirable effects, which were registered in 21 placebo-controlled studies and during post-marketing surveillance.

Tabulated summary of adverse reactions

System Organ Class	Frequency	Side effects
Metabolism and nutrition disorders	Less frequent	Oedema
Psychiatric disorders	Frequency unknown	Depression
Nervous system disorders	Frequency unknown	Dizziness, headache, migraine
Eye disorders	Frequency unknown	Visual disturbances, blurred vision
Gastrointestinal disorders	Frequent Less frequent	Lower abdominal pain Gastrointestinal upset*, abdominal discomfort*
Hepato-biliary disorders	Frequency unknown	Changes in liver function parameters
Skin and subcutaneous tissue disorders	Frequent Less frequent Frequency unknown	Abnormal hair growth Acne, pruritis Rash, seborrheic dermatosis

Musculoskeletal, connective tissue and bone disorders	Frequency unknown	Arthralgia, myalgia
Reproductive system and breast disorders	Frequent	Vaginal discharge, endometrial wall thickening, postmenopausal haemorrhage, breast tenderness, genital pruritus, vaginal candidiasis, vaginal haemorrhage, pelvic pain, cervical dysplasia, genital discharge, vulvovaginitis
	Less frequent	Breast discomfort, fungal infection, vaginal mycosis, nipple pain
Investigations	Frequent	Weight increase, abnormal cervical smear*
	Less frequent	Amnesia

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

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 online service for adverse drug reaction reporting by following the link: https://www.sahpra.org.za/Publications/Index/8. An email can be sent directly to the company, pharmacovigilance@pharmadynamics.co.za to ensure safety of the product.

4.9 OVERDOSE

Signs and symptoms:

In cases of acute overdose nausea, vomiting and vaginal bleeding in females may occur.

Management of overdose:

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

Mechanism of action

Tibolone stabilises the hypothalamic-pituitary system after failure of 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 estrogenic, progestogenic and weak androgenic activities of the medicine.

Tibolone has a moderate gonadotrophin suppressing effect in post-menopausal woman.

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 woman.

5.2 Pharmacokinetic properties

Absorption:

Following oral administration, 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. The consumption of foods has no significant effects on the extent of absorption.

Biotransformation:

Tibolone is metabolised in the liver and converted to metabolites. 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.

Elimination:

Excretion of tibolone is mainly in the form of conjugated (mostly sulphated) metabolites, which are excreted mainly in the faeces and to a lesser extent in the urine.

Pharmacokinetics in special patient groups

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Ascorbyl palmitate

Lactose monohydrate

Magnesium stearate

Mannitol

Potato starch

6.2 Incompatibilities

Not applicable

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Store at or below 30 °C.

Store in the original package in order to protect from light and moisture.

6.5 Nature and contents of container

TIBILIVE 2,5 MG tablets are packed in PVC/Aluminium foil, blisters of 10 tablets, then placed in an outer carton. Each carton contains 30, 90 or 180 tablets.

6.6 Special precautions for disposal

No special requirements.

7. HOLDER OF THE CERTIFICATE OF REGISTRATION

Pharma Dynamics (Pty) Ltd

1st Floor, Grapevine House, Steenberg Office Park

Silverwood Close

Westlake, Cape Town

7945, South Africa

8. REGISTRATION NUMBER

Tibilive 2,5 mg: A52/21.13/0078

Tibolone 2,5 mg Dyna: A52/21.13/0079

9. DATE OF FIRST AUTHORISATION

April 2022

10. DATE OF REVISION OF THE TEXT

09 December 2022