SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

TIBOLONE ADCO 2,5 mg tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 2,5 mg tibolone.

Contains mannitol: 43,2 mg per tablet.

Excipient with known effect

Contains sugar: 43,2 mg lactose monohydrate per tablet.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablets.

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

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

TIBOLONE ADCO 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, orally.

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 ADCO

Women experiencing a natural menopause should commence treatment with TIBOLONE ADCO at least 12 months after their last natural bleed.

In case of a surgical menopause, treatment with TIBOLONE ADCO may commence immediately.

Any irregular/unscheduled vaginal bleeding, either on or off hormone replacement therapy (HRT), for which there is no obvious cause, should be investigated before starting TIBOLONE ADCO.

Paediatric population

There is no relevant use of TIBOLONE ADCO in the paediatric population.

Method of administration

TIBOLONE ADCO 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 excipients listed in section 6.1.
- Pregnancy and lactation (see section 4.6).
- Known or suspected hormone-dependent tumours.
- Known history (personal and/or family) or suspected breast cancer. TIBOLONE ADCO 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 aetiology.
- Untreated endometrial hyperplasia.
- Cardiovascular or cerebrovascular disorders e.g. thrombophlebitis, thromboembolic processes or a history of these conditions.
- Previous or current venous thromboembolism (deep venous thrombosis, pulmonary embolism).
- Inherited thrombophilia.

- Known thrombophilic disorders (e.g., protein C, protein S, or antithrombin deficiency, see section 4.4).
- Any history of arterial thromboembolic disease (e.g. angina, myocardial infarction, stroke or transient ischaemic attack [TIA]).
- Acute liver disease, or a history of liver disease for as long as liver function tests have failed to return to normal.
- Patients known with inherited genetic mutations: BRCA1 and BRCA 2 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).
- Porphyria.

4.4 Special warnings and precautions for use

TIBOLONE ADCO is not intended for contraceptive use. For the treatment of postmenopausal symptoms, TIBOLONE ADCO should only be initiated for symptoms that adversely affect quality of life.

The use of TIBOLONE ADCO should be avoided until 12 months after the last natural menstrual bleed. If TIBOLONE ADCO is taken sooner than this, the frequency of irregular bleeding may be increased. 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 ADCO therapy, because of an apparently stimulated endometrium due to some estrogen 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 woman changing from another form of hormonal substitution therapy to TIBOLONE ADCO, it is always advisable to induce a withdrawal bleeding with a progestogen before starting TIBOLONE ADCO.

Tibolone as in TIBOLONE ADCO 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, in women with an intact uterus, endometrial cancer (see below and section 4.8) 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 ADCO in the treatment of premature menopause is limited.

Medical examination/follow-up

Before initiating or reinstituting HRT or tibolone, as in TIBOLONE ADCO, 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.

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 ADCO, in particular:

- Leiomyoma (uterine fibroids) or endometriosis.
- Risk factors for thromboembolic disorders (see below).
- Risk factors for oestrogen-dependent tumours, 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 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 carcinoma

The available data from randomised controlled trials are conflicting; however, observational studies have consistently shown that women who are prescribed tibolone, as in TIBOLONE ADCO in normal clinical practice are at an increased risk of having endometrial cancer diagnosed (see also section 4.8). In these studies, risk increased with increasing duration of use. Tibolone, as in TIBOLONE ADCO 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.

Breakthrough 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 3 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

A 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 3 years of use and increased with duration of intake (see 'Breast cancer risk' below). After stopping treatment, the excess risk will decrease with time and the time needed to return to baseline depends on the duration of prior HRT use. When HRT was taken for more than 5 years, the risk may persist for 10 years or more.

No data for persistence of risk after stopping are available for tibolone as in TIBOLONE ADCO, but a similar pattern cannot be ruled out.

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 therapy is substantially lower than that seen in users of oestrogen-progestogen combinations. The level of risk is dependent on the duration of use.

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 TIBOLONE ADCO should receive yearly breast examinations by a health care 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. Epidemiological evidence from a large meta-analysis suggests a slightly increased risk in women taking oestrogen-only or combined oestrogen-progestogen HRT, which becomes apparent within 5 years of use and diminishes over time after stopping.

Some other studies suggest that the use of combined HRTs may be associated with a similar, or slightly smaller risk (see section 4.8). 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

Oestrogen or oestrogen-progestogen HRT is associated with a 1,3- to 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 in TIBOLONE ADCO 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.

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 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.

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 is contraindicated.

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

If VTE develops after initiating therapy, TIBOLONE ADCO 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 postmenopausal women who received tibolone as in TIBOLONE ADCO.

Ischaemic stroke

Tibolone increases the risk of ischaemic 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 TIBOLONE ADCO is greater with older age.

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 as in TIBOLONE ADCO 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 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 TIBOLONE ADCO for 5 years, the number of additional cases would be expected to be about 4 per 1 000 users aged 50 – 59 years and 13 per 1 000 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 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 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.

Other conditions

Treatment with tibolone as in TIBOLONE ADCO resulted 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 hypertriglyceridemia 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 ADCO results in a very minor decrease of thyroid binding globulin (TBG) and total T4. Levels of total T3 are unaltered. TIBOLONE ADCO decreases the level of sex hormone-binding globulin (SHBG), whereas the levels of corticosteroid-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.

TIBOLONE ADCO contains lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take TIBOLONE ADCO.

4.5 Interaction with other medicines and other forms of interaction

Since tibolone 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 TIBOLONE ADCO and anticoagulants, especially when starting or stopping concurrent TIBOLONE ADCO treatment. If necessary, the dose of warfarin should be adjusted.

There is limited information regarding pharmacokinetic interactions with TIBOLONE ADCO. An *in vivo* study showed that simultaneous treatment with tibolone, as in TIBOLONE ADCO, 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.

Medicines that induce CYP3A4 activity such as barbiturates, carbamazepine, hydantoins and rifampicin may enhance the metabolism of TIBOLONE ADCO 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.

4.6 Fertility, pregnancy and lactation

Pregnancy

TIBOLONE ADCO is contraindicated during pregnancy (see section 4.3). If pregnancy occurs during medication with TIBOLONE ADCO, treatment should be withdrawn immediately. For TIBOLONE ADCO no clinical data on exposed pregnancies are available. Studies in animals have shown reproductive toxicity.

Breastfeeding

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

Fertility

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

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Undesirable effects reported from clinical trials and during post-marketing surveilance.

System organ class	**Frequent**	**Less frequent**	**Frequency unknown**
Metabolism and nutrition disorders		Oedema	
Psychiatric disorders			Depression
Nervous system disorders			Dizziness headache, migraine
Eye disorders			Visual disturbances (including blurred vision)
Gastrointestinal disorders	Lower abdominal pain	Abdominal discomfort	
Hepato-biliary disorders			Changes in liver function parameters
Skin and subcutaneous tissue disorders	Abnormal hair growth	Acne, pruritis	Rash, seborrheic dermatosis
Musculoskeletal and connective tissue disorders			Effects on the musculoskeletal system such as arthralgia or myalgia
Reproductive system and breast disorders	Vaginal discharge, endometrial wall thickening, postmenopausal haemorrhage, breast tenderness, genital pruritus,	Breast discomfort, fungal infection, vaginal mycosis, nipple pain	

	vaginal candidiasis, vaginal haemorrhage, pelvic pain, cervical dysplasia, genital discharge, vulvovaginitis		
Investigations	Weight increase, abnormal cervical smear*	Amnesia	
* The majority consisted of benign changes. Cervix pathology (cervical carcinoma) was not increased with tibolone as in TIBOLONE ADCO compared to placebo.			

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of TIBOLONE ADCO is important. It allows continued monitoring of the benefit/risk balance of TIBOLONE ADCO. Health care providers are asked to report any suspected adverse reactions via the "**6.04 Adverse Drug Reaction Reporting Form**", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8.

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

Category and class: 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 lead 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 gonadotropin 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 women.

Following oral administration, tibolone is rapidly metabolised into three compounds, which all contribute to the pharmacodynamic profile of TIBOLONE ADCO. Two of the metabolites (3α-OH-tibolone and 3β-OH-tibolone) have oestrogenic-like activities, whereas the third metabolite (Δ4-isomer of tibolone) has progestogenic and androgenic-like activities.

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

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

Elimination

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

Other special populations

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

36 months

6.4 Special precautions for storage

- Store at or below 25 °C. Store in the original package in order to protect from light, moisture and heat.
- Keep blister strip in outer carton until required for use.

6.5 Nature and contents of container

Tablets are presented in blister strips of PVC/aluminium foil.

One blister strip containing 28 tablets is packed into an outer carton.

6.6 Special precautions for disposal

Not applicable

7. HOLDER OF CERTIFICATE OF REGISTRATION

Adcock Ingram Limited

1 New Road,

Erand Gardens,

Midrand,1685

Customer Care: 0860 ADCOCK/ 232625

8. REGISTRATION NUMBER

52/21.13/0510.509

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

13 September 2022

10. DATE OF REVISION OF THE TEXT

17 March 2023

adcock ingram

PI 28067894 05/2023