PROFESSIONAL INFORMATION

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

TANILIVE 100 mg VAGINAL CAPSULES soft gelatin capsules

TANILIVE 200 mg VAGINAL CAPSULES soft gelatin capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each soft gelatin capsule contains progesterone 100 mg.

Each soft gelatin capsule contains progesterone 200 mg.

Ingredients with known effect: Soy Lecithin.

TANILIVE VAGINAL CAPSULES are sugar free.

For the full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Soft gelatin capsule.

TANILIVE 100 mg VAGINAL CAPSULES are ovoid soft gelatin capsules off-white coloured, approximately 12 mm long and 8 mm wide.

TANILIVE 200 mg VAGINAL CAPSULES are ovoid soft gelatin capsules off-white coloured, approximately 16 mm long and 9,6 mm wide.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

PROFESSIONAL INFORMATION

Vaginal route:

- progesterone support during ovarian insufficiency or complete ovarian failure in women lacking ovarian function (oocyte donation)
- supplementation of the luteal phase during *in-vitro* fertilization (IVF) cycles
- supplementation of the luteal phase during spontaneous or induced cycles, in cases of sub-fertility or primary or secondary infertility, particularly due to dysovulation
- in cases of threatened miscarriage or prevention of recurrent miscarriage due to luteal phase deficiency, until week 12 of pregnancy.

For all other indications of progesterone, the vaginal route represents an alternative to the oral route in cases of:

- side effects caused by progesterone (drowsiness following absorption via the oral route).

4.2 Posology and method of administration

It is important to adhere strictly to the recommended dosages for all therapeutic indications. The dosage must not exceed 200 mg per dose, regardless of the indication and route of administration (oral or vaginal).

Vaginal route:

Progesterone replacement therapy in cases of ovarian insufficiency or complete ovarian failure in women lacking ovaries (oocyte donation).

The therapeutic regimen (in addition to appropriate estrogen therapy) is as follows:

- 100 mg TANILIVE VAGINAL CAPSULES per day on days 13 and 14 of the transfer cycle,

then

- 200 mg of TANILIVE VAGINAL CAPSULES per day on days 15 and 25 of the transfer cycle, split over one or two doses per day, then
- from day 26 of the cycle, and in cases of an incipient pregnancy, the dose may be increased up to a maximum of 600 mg per day, split over three doses.

This dosage should be adhered to until day 60, or until week 12 of pregnancy at the latest.

- **Supplementation of the luteal phase during IVF cycles:**

The recommended dosage is 400 mg - 600 mg per day, over two to three doses per day, from the date of HCG injection until week 12 of pregnancy.

- **Supplementation of the luteal phase in cases of spontaneous or induced cycles, in subjects with sub-fertility or primary or secondary sterility, particularly due to dysovulation:**

The recommended dosage is 200 mg - 300 mg per day, over two doses, for ten days, from day 17 of the cycle. If menstruation does not resume and pregnancy is diagnosed, treatment should be quickly resumed until week 12 of pregnancy.

- **Threatened early miscarriage or repeated miscarriage due to luteal phase insufficiency**:

The recommended dosage is 200 mg - 400 mg per day, split over two doses, until week 12 of pregnancy.

Paediatric population

TANILIVE VAGINAL CAPSULES are not indicated in paediatric patients.

Method of administration

Vaginal route:

Each capsule should be inserted deep into the vagina.

4.3 Contraindications

TANILIVE VAGINAL CAPSULES are contraindicated in:

- known hypersensitivity to progesterone or to any of the ingredients of TANILIVE VAGINAL CAPSULES (see section 6.1)
- severe liver disease such as cholestatic jaundice, or hepatitis, or a history of severe liver disease, hepatic cell tumours, Rotor syndrome, or Dubin-Johnson syndrome.
- undiagnosed vaginal bleeding
- conditions of rare occurrence known to be affected by sex steroids i.e. herpes gestationis, jaundice of pregnancy, otosclerosis, severe pruritus, or porphyria
- personal and family history of breast cancer
- previous or current thromboembolism disorders (e.g. deep venous thrombosis, pulmonary embolism) or thrombophlebitis
- known thrombophilic disorders.
- cerebral haemorrhage
- patients known with inherited genetic mutation: BRCA 1 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)
- breastfeeding (see section 4.6).

4.4 Special warnings and precautions for use

PROFESSIONAL INFORMATION

In the event that results of liver function tests become abnormal or if cholestatic jaundice appears, therapy with TANILIVE VAGINAL CAPSULES should be discontinued.

More than half early spontaneous abortions are due to genetic defects. Moreover, infections and mechanical disorders may cause early miscarriages. In these cases, the only effect of progesterone administration will be to delay the expulsion of the dead egg (or interruption of a terminated pregnancy).
Upon diagnosis of a missed abortion, therapy should be discontinued.

A pre-treatment physical examination, including a complete personal and family medical history, prior to the initiation of hormone replacement treatment should include special attention to breast and pelvic organs as well as Papanicolaou smear 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.

The use of TANILIVE VAGINAL CAPSULES must be reserved for cases with insufficient secretion of the corpus luteum.

TANILIVE VAGINAL CAPSULES has no contraceptive effect when taken under the recommended conditions of use.

PROFESSIONAL INFORMATION

The use of progesterone during pregnancy is restricted to the first trimester and only via the vaginal route. TANILIVE VAGINAL CAPSULES are not a treatment for the threat of preterm birth.

During the second and third trimesters of pregnancy, exceptional cases of cytolytic hepatitis and intrahepatic cholestasis of pregnancy have been reported in patients taking TANILIVE VAGINAL CAPSULES.

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

Evidence regarding the risks associated with HRT 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.

Conditions requiring 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 TANILIVE VAGINAL CAPSULES, in particular:

- leiomyoma (uterine fibroids) or endometriosis
- risk factors for thromboembolic disorders (see below)

- risk factors for estrogen 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
- depression
- photosensitivity.

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
- pregnancy
- sudden or gradual, partial or complete loss of vision
- proptosis or diplopia
- papilloedema

- retinal vascular lesions

Endometrial hyperplasia and carcinoma

In women with an intact uterus the risk of endometrial hyperplasia and carcinoma is increased when estrogens are administered alone for prolonged periods. The reported increase in endometrial cancer risk among estrogen-only users varies from 2-to 12-fold greater compared with non-users, depending on the duration of treatment and estrogen dose (see section 4.8). After stopping treatment risk may remain elevated for at least 10 years.

The addition of progesterone for at least 12 days per month/28- day cycle or continuous combined estrogen-progestogen therapy in non-hysterectomised women prevents the excess risk associated with estrogen-only HRT.

Breakthrough bleeding and spotting may occur during the first months of treatment. If breakthrough bleeding persists, a lower dose of TANILIVE VAGINAL CAPSULES for 25 days per cycle could be considered (see section 4.2).

Persistent breakthrough bleeding or after discontinuation of treatment may be an indication for endometrial assessment, which may include biopsy to exclude endometrial malignancy.

Breast cancer

Combined estrogen and progesterone or estrogen only which, 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 estrogen-progestogen than estrogen only preparations, and the risk persisted for more than 10 years after stopping the treatment. The relative risk (RR) to develop breast cancer for estrogen-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 developing breast cancer in women who started MHT at 60 years of age.

All women on TANILIVE VAGINAL CAPSULES 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. Epidemiological evidence from a large meta-analysis suggests a slightly increased risk in women taking estrogen-only or combined estrogen-progestogen HRT, which becomes apparent within 5 years of use and diminishes over time after stopping. Some other studies, including the Women's Health initiative (WHI) trial, suggest that use of combined Hormone replacement therapy (HRTs) may be associated with a similar or slightly smaller risk (see section 4.8).

Venous thromboembolism

PROFESSIONAL INFORMATION

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).

Patients with known thrombophilic states have an increased risk of VTE and HRT 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 estrogens, 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 be considered to prevent VTE following surgery. If prolonged immobilisation is to follow elective surgery, temporarily stopping HRT 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. anti-thrombin, protein S, or protein C deficiencies or a combination of defects) HRT is contraindicated.

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

If VTE develops after initiating therapy, TANILIVE VAGINAL CAPSULES 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 estrogen-progestogen or estrogen-only HRT.

Combined estrogen-progestogen therapy:

The relative risk of CAD during use of combined estrogen + progestogen HRT is slightly increased. As the baseline absolute risk of CAD is strongly dependent on age, the number of extra cases of CAD due to estrogen + progestogen use is very low in healthy women close to menopause, but will rise with more advanced age.

Ischaemic stroke

Combined estrogen-progestogen and estrogen-only therapy are associated with an up to 1,5-fold increase in risk of ischaemic stroke. The relative risk does not change with age or time since menopause. However, as the baseline risk of stroke is strongly age-dependent, the overall risk of stroke in women who use HRT will increase with age (see section 4.8).

Depression

Depressed mood and depression are well-known undesirable effects of hormonal contraceptive use (see section 4.8). Depression can be serious and is a well-known risk factor for suicidal behaviour and suicide. Women should be advised to contact their medical practitioner in case of mood changes and depressive symptoms, including shortly after initiating the treatment.

Other conditions

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.

Excipients with known effect

TANILIVE VAGINAL CAPSULES contains soy lecithin and may cause hypersensitivity reactions (urticarial and anaphylactic shock in hypersensitive patients). As there is a possible relationship between allergy to soya and allergy to peanut, patients with peanut allergy should avoid taking TANILIVE VAGINAL CAPSULES.

4.5 Interaction with other medicines and other forms of interaction

Enzyme inducers

The efficacy of TANILIVE VAGINAL CAPSULES may be decreased due to an enhanced metabolism of progesterone by hepatic enzyme inducing-medicines, such as carbamazepine, phenobarbital, phenytoin, rifabutin or rifampicin, griseofulvin, some antibiotics (ampicillin,

tetracyclines), phenylbutazone, bromocriptine, spironolactone and also herbal products containing St. John's wort (*Hypericum perforatum*).

Enzyme inhibitors

The bioavailability of TANILIVE VAGINAL CAPSULES may be increased by hepatic metabolic enzyme inhibitors such as ketoconazole, ritonavir and nelfinavir. The metabolism of progesterone by human liver microsomes was inhibited by ketoconazole (IC50 <0,1 µM).

Immunosuppressants

TANILIVE VAGINAL CAPSULES may raise the plasma concentration of ciclosporin.

Xanthines

TANILIVE VAGINAL CAPSULES may raise the plasma concentration of theophyllines.

Macrolide antibiotics

TANILIVE VAGINAL CAPSULES may raise the plasma concentration of troleandomycin.

Anti-steroidal medicines

Aminoglutethimide markedly reduces the plasma concentrations of medroxyprogesterone acetate and megestrol, possibly through a hepatic enzyme-inducing effect.

Anticoagulants

TANILIVE VAGINAL CAPSULES may enhance or reduce the anticoagulant effect of coumarins. TANILIVE VAGINAL CAPSULES antagonises the anticoagulant effect of phenindione.

Diabetic medicines

An adjustment in anti-diabetic dosage may be required for women being treated concomitantly with TANILIVE VAGINAL CAPSULES.

Emergency contraceptives

The concomitant use of ulipristal acetate with progesterone may result in reduced efficacy of TANILIVE VAGINAL CAPSULES.

Diazepam

TANILIVE VAGINAL CAPSULES may increase the plasma concentration of diazepam.

Tizanidine

TANILIVE VAGINAL CAPSULES may increase the plasma concentration of tizanidine.

Terbinafine

There have been occasional reports of breakthrough bleeding when terbinafine is used concomitantly with TANILIVE VAGINAL CAPSULES.

Laboratory tests

TANILIVE VAGINAL CAPSULES may affect the results of laboratory tests of hepatic and/or endocrine functions.

4.6 Fertility, pregnancy and lactation

Pregnancy

Safety in pregnancy has not been established. The use of progesterone during pregnancy is restricted to the first trimester via the vaginal route.

Cases of hepatic cytolysis and cases of cholestasis of pregnancy have been reported during administration of micronized progesterone during the 2nd and 3rd trimesters of pregnancy.

If pregnancy occurs whilst on therapy, TANILIVE VAGINAL CAPSULES should be withdrawn immediately.

Therapy with TANILIVE VAGINAL CAPSULES beyond the first trimester of pregnancy may reveal gravidic cholestasis.

Breastfeeding

PROFESSIONAL INFORMATION

TANILIVE VAGINAL CAPSULES are contraindicated when breastfeeding (see section 4.3).

Fertility

TANILIVE VAGINAL CAPSULES are indicated to support luteal deficiency in sub-fertile or infertile women.

4.7 Effects on ability to drive and use machines:

Drowsiness, dizziness and vertigo are possible side effects of TANILIVE VAGINAL CAPSULES. Patients should be warned to avoid driving or using machines until they know how TANILIVE VAGINAL CAPSULES affects them.

4.8 Undesirable effects

a). Summary of adverse reactions

Vaginal route:

- no local intolerances (such as burning, pruritus or fatty discharge) have been observed during various clinical trials
- no general side effects, including drowsiness or transient feelings of dizziness, have been reported during clinical studies, at the recommended dosages.

The information given below is based on extensive post marketing experience from vaginal administration of progesterone.

System Organ Class	**Frequency**	**Side effects**
Skin and subcutaneous tissue disorders	Frequency unknown	Pruritus
Reproductive system and breast disorders	Frequency unknown	Vaginal haemorrhage, vaginal discharge

PROFESSIONAL INFORMATION

c). Description of selected adverse reactions

Somnolence or transient dizziness may occur 1 to 3 hours after intake of TANILIVE VAGINAL CAPSULES. Dosing upon retiring and dose reduction may reduce these effects.

The following adverse reactions have also been reported in association with systemic estrogen/progestogen treatment:

System Organ Class	**Frequency**	**Side effects**
Metabolism and nutrition disorders	Frequency unknown	Weight changes
Psychiatric disorders	Frequency unknown	Insomnia, depression, probable dementia over the age of 65 (see section 4.4)
Gastrointestinal disorders	Frequency unknown	Gall bladder disease
Skin and subcutaneous tissue disorders	Frequency unknown	Rash, urticaria chloasma/melasma, alopecia , erythema multiforme, erythema nodosum, vascular purpura
Reproductive system and breast disorders	Frequency unknown	Irregular menstruation,

		amenorrhoea, breast pain/oedema, changes in libido
General disorders and administrative site conditions	Frequency unknown	Pyrexia, Fluid retention/oedema

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 professionals are asked to report any suspected adverse reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc-org) found on the SAHPRA website

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:

Symptoms of overdosage may include nausea, vomiting, somnolence, dizziness, fatigue, euphoria or dysmenorrhoea.

Management of overdose:

Treatment of overdosage consists of discontinuation of TANILIVE VAGINAL CAPSULES and institution of appropriate symptomatic and supportive care.

5. PHARMACOLOGICAL PROPERTIES

PROFESSIONAL INFORMATION

5.1 Pharmacodynamic properties

Pharmacotherapeutic groups: Genitourinary system and sex hormones, Sex hormones and modulators of the genital system

ATC code: G03DA04

Pharmacological classification: A 21.8.2 Progesterones with or without estrogens

The properties of progesterone are comparable to those of natural progesterone, in particular being a progestogen, estrogen antagonist, mild androgen antagonist, and aldosterone antagonist.

Mechanism of action

Progesterone is a natural progestogen, the main hormone of the corpus luteum and the placenta. It acts on the endometrium by converting the proliferating phase to the secretory phase.

This medicine has all the properties of endogenous progesterone, in particular gestagenic, antiestrogenic, slightly anti-androgenic and antialdosterone effects.

Clinical efficacy and safety

As estrogens promote the growth of the endometrium, unopposed estrogens increase the risk of endometrial hyperplasia and cancer. The addition of progesterone greatly reduces the estrogen-induced risk of endometrial hyperplasia in non-hysterectomised women.

5.2 Pharmacokinetic properties

Vaginal route:

PROFESSIONAL INFORMATION

Absorption:

Following vaginal insertion, progesterone is rapidly absorbed by the vaginal mucosa, as shown by the rise in plasma progesterone levels within one hour of administration.

The maximum plasma progesterone concentration is reached two to six hours after insertion, and remains at an average concentration of 9,7 ng/mL over the 24 hours following the administration of 100 mg in the morning and evening. This recommended average dose therefore leads to stable, physiological plasma progesterone concentrations similar to those observed during the luteal phase of a normal ovulatory menstrual cycle. Small inter-individual variations in progesterone levels make it possible to accurately predict the expected effect of a standard dose.

At doses of more than 200 mg per day, the resulting progesterone concentrations are comparable with those described during the first trimester of pregnancy.

Biotransformation:

The plasma concentration of 5β-pregnanolone does not increase.

It is primarily 3α, 5β-(pregnanediol) that is eliminated via the urine, as demonstrated by gradual increase in its concentration (until reaching a maximum concentration of 142 ng/mL after six hours). Following vaginal administration, only low plasma levels of pregnanolone and 5α-dihydroprogesterone are detected.

Linearity/non-linearity:

The pharmacokinetics of progesterone is independent of the dose administered. Although there were some inter-individual's variations, the same individual pharmacokinetic

characteristics were maintained over several months permitting appropriate individual adaptation of the posology and indicating predictable responses to the medicine.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Grapeseed oil

Soy Lecithin

Soft gelatin capsule:

Gelatin

Glycerol

Titanium dioxide

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months

6.4 Special precautions for storage

Store at or below 25 ºC.

Protect from excessive moisture.

Do not remove from outer carton until required for use.

6.5 Nature and contents of container

Transparent thermoformed PVC/PE/PVDC/Aluminum blister.

TANILIVE 100 mg VAGINAL CAPSULES: Each carton contains 30 capsules.

TANILIVE 200 mg VAGINAL CAPSULES: Each carton contains 15 capsules.

6.6 Special precautions for disposal

No special precautions.

7. HOLDER OF THE CERTIFICATE OF REGISTRATION

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8. REGISTRATION NUMBERS

TANILIVE 100 mg VAGINAL CAPSULES: 58/21.8.2/0036

TANILIVE 200 mg VAGINAL CAPSULES: 58/21.8.2/0037

9. DATE OF FIRST AUTHORISATION

17 June 2025