1.3.1.1 PROFESSIONAL INFORMATION FOR MEDICINES FOR HUMAN USE

SCHEDULING STATUS

S2

1. NAME OF THE MEDICINE

SYNAPAUSE VAGINAL CREAM 1 mg/g

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each gram of SYNAPAUSE VAGINAL CREAM contains 1 mg estriol.

Preservative: Chlorhexidine dihydrochloride 0,01 % *m/m*

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Cream.

A white to almost white, smooth, homogeneous, creamy mass.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

SYNAPAUSE VAGINAL CREAM is indicated in adults for:

- Hormone replacement therapy (HRT) for the treatment of atrophy of the lower urogenital tract related to estrogen deficiency associated with the natural or surgical menopause.
- Pre- and postoperative therapy in postmenopausal or ovariectomised women undergoing vaginal surgery.

4.2. Posology and method of administration

Posology

Adults

For atrophy of the lower urogenital tract in conditions of estrogen deficiency:

1 application per day for the first 2 to 3 weeks, followed by a gradual reduction based on relief of symptoms, until a maintenance dosage of 1 application twice a week is reached.

As pre- and postoperative therapy in post-menopausal or ovariectomised women undergoing vaginal surgery:

1 application per day in the 2 weeks before surgery; 1 application twice a week in the 2 weeks after surgery. Post-surgery treatment can be started as soon as application of the cream is possible.

One application (applicator filled to the ring mark) contains 0,5 g SYNAPAUSE VAGINAL CREAM, which corresponds with 0,5 mg estriol.

For initiation and continuation of treatment of post-menopausal symptoms, the lowest effective dose for the shortest duration should be used (see section 4.4).

For SYNAPAUSE VAGINAL CREAM the systemic exposure of estriol remains closely to the normal postmenopausal range when used in a twice weekly administration, it is not recommended to add a progestogen (see section 4.4).

In women not taking HRT or women who switch from a continuous combined HRT medicine, treatment with SYNAPAUSE VAGINAL CREAM may be started on any day.

Women who switch from cyclic HRT regimen should start SYNAPAUSE VAGINAL CREAM treatment one week after completion of the cycle.

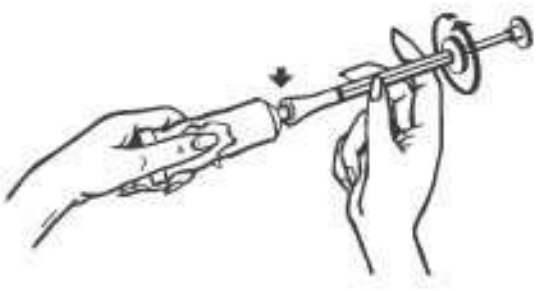
A missed dose should be administered as soon as remembered unless the missed dose is noticed at the day of the next dose. In the latter case the missed dose should be skipped, and the regular dosing scheme continued. Two doses must never be administered on the same day.

Method of administration

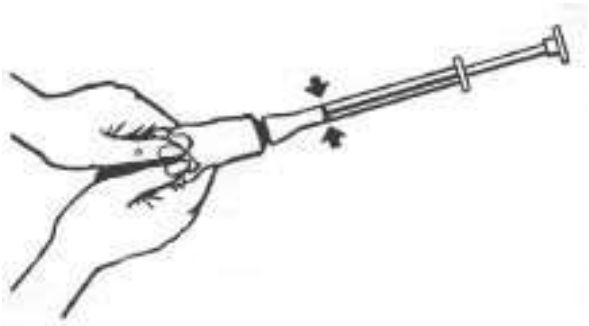
SYNAPAUSE VAGINAL CREAM should be administered intravaginally by means of a calibrated applicator before retiring at night.

1. Remove cap from the tube, invert it, and use the sharp point to open the tube.

2. Screw the end of the applicator onto the tube. Make sure the plunger is fully inserted into the barrel.



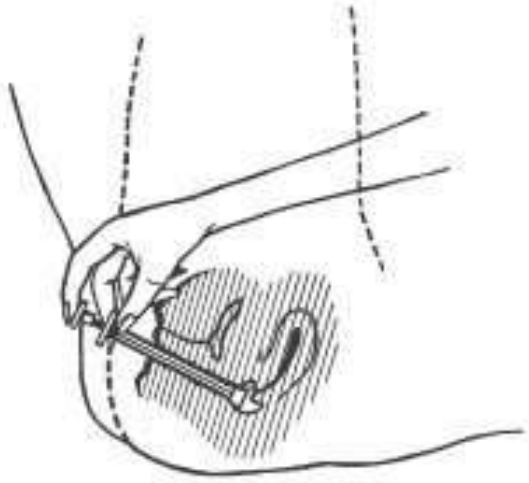
3. Squeeze tube slowly to fill the applicator with the cream until the plunger stops (see arrows in the picture below).



4. Unscrew applicator from tube and put cap back on tube.

5. To apply cream, lie down, insert end of applicator deep into the vagina.

6. Slowly push plunger all the way in until applicator is empty.



7. After use, pull plunger out of barrel beyond the point of resistance and wash both in warm, soapy water. Do not use detergents. Rinse well afterwards. DO NOT PUT THE APPLICATOR IN HOT OR BOILING WATER.

8. The applicator can be re-assembled by fully inserting the plunger into the barrel beyond the point where resistance is felt.

Discard the applicator once the tube is empty.

Cleaning the applicator

After use, pull the plunger out of the barrel. Wash the plunger and barrel in hot, soapy water. Do not use detergents. Rinse well with clean water afterwards.

DO NOT PUT THE APPLICATOR IN BOILING WATER.

Paediatric population

No data available.

4.3. Contraindications

SYNAPAUSE VAGINAL CREAM is contraindicated in:

- Patients with hypersensitivity to estriol or to any excipients in SYNAPAUSE VAGINAL CREAM (see section 2 and section 6.1).
- Patients with known, past or suspected breast cancer including a family history of breast cancer (see section 4.4).
- History of non-cancerous breast diseases (atypical hyperplasia or lobular carcinoma *in situ*).
- Patients with known or suspected estrogen-dependent malignant tumours (e.g. endometrial cancer) (see section 4.4).
- Patients with undiagnosed vaginal bleeding.
- Patients that started early menstrual periods (before the age of 12 years).
- Patients with untreated endometrial hyperplasia (see section 4.4).
- Patients with previous idiopathic or current venous thromboembolism (deep venous thrombosis, pulmonary embolism, or a risk factor thereof e.g. known thrombophilic disease) (see section 4.4).
- Patients with known or inherited thrombophilic disorders/diseases (e.g. protein C, protein S or antithrombin deficiency) (see section 4.4).
- Patients with active or recent arterial thromboembolic disease (e.g. angina, myocardial infarction).
- Patients with active liver disease, acute liver disease or a history of liver disease as long as liver function tests failed to return to normal.
- Patients with porphyria.
- Pregnancy and lactation (see section 4.6).
- Patients known with inherited genetic mutations: BRCA1 and BRCA 2 genes.
- Previous treatment using radiation therapy to the chest or breast.

Previous exposure to diethylstilbestrol (DES).

4.4. Special warnings and precautions for use

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.

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.

Medical examination/ follow-up

Before initiation or re-instituting treatment with SYNAPAUSE VAGINAL CREAM, a complete personal and family medical history should be taken, together with a thorough general and gynaecological examination. Physical (including pelvic and breast) examination should be guided by this, and by the contraindications (see section 4.3 and section 4.4). 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 and mammography should be carried out in accordance with currently

accepted screening practices, modified according to the clinical needs of the individual. In case of vaginal infections, these should be treated before therapy with SYNAPAUSE VAGINAL CREAM is started.

Conditions which need supervision

If any of the following conditions are present, have occurred previously and/or have 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 SYNAPAUSE VAGINAL CREAM, in particular:

- leiomyoma (uterine fibroids) or endometriosis,
- a history of, or risk factors for thromboembolic disorders (see *Venous thromboembolism* 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 (SLE),
- a history of endometrial hyperplasia (see *Endometrial hyperplasia and carcinoma* below),
- epilepsy,
- asthma,
- otosclerosis,
- severe pruritus

- cholestatic jaundice
- herpes gestations
- hypertriglyceridaemia (see *Other conditions* below).

Reasons for immediate withdrawal of therapy

Therapy should be discontinued in case a contraindication is discovered (see section 4.3) and in the following situations:

- Jaundice or deterioration in liver function.
- Significant increase in blood pressure.
- New onset of migraine-type headache.
- Pregnancy.

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 of time. 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. After stopping treatment, risk may remain elevated for at least 10 years.

The addition of a progestogen cyclically 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.

For SYNAPAUSE VAGINAL CREAM, the systemic exposure of estriol remains closely to the normal postmenopausal range when used in a twice weekly administration, it is not recommended to add a progestogen.

Unopposed estrogen stimulation may lead to premalignant transformation in the residual foci of endometriosis. Therefore, caution is advised when using SYNAPAUSE VAGINAL CREAM in women who have undergone hysterectomy because of endometriosis, especially if they are known to have residual endometriosis.

The endometrial safety of long-term or repeated use of topical vaginal estrogens is uncertain. Therefore, repeated treatment should be reviewed at least annually, with special consideration given to any symptoms of endometrial hyperplasia or carcinoma.

In order to prevent endometrial stimulation, the daily dose should not exceed 1 application (0,5 mg estriol), nor should this maximum dose be used for longer than several weeks **(maximum 4 weeks).**

Data has shown that long-term treatment with low doses of oral estriol, but not vaginal estriol, may increase the risk for endometrial cancer. This risk increased with the duration of treatment and disappeared within one year after the treatment was terminated. The increased risk mainly concerned less invasive and highly differentiated tumors.

If breakthrough bleeding or spotting appears at any time whilst on therapy, the reason should be investigated, which may include endometrial biopsy to exclude endometrial malignancy.
The patient should be informed to contact a doctor if vaginal bleeding occurs.

Breast cancer

SYNAPAUSE VAGINAL CREAM contains estriol 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 estrogen 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 SYNAPAUSE VAGINAL CREAM 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.

Combined estrogen-progestogen therapy

The randomized placebo-controlled trial (Women's Health Initiative study (WHI)), and epidemiological studies are consistent in finding an increased risk of breast cancer in women taking combined estrogen-progestogen, or tibolone for HRT for several years that becomes apparent after about 3 years.

Estrogen-only therapy

The WHI trial found no increase in the risk of breast cancer in hysterectomized women using estrogen-only HRT. Observational studies have mostly reported a small increase

in risk of having breast cancer diagnosed that is substantially lower than that found in users of estrogen-progestogen combinations.

An up to 2-fold increased risk of having breast cancer diagnosed is reported in women taking combined estrogen-progestogen therapy for more than 5 years. Any increased risk in users of estrogen-only therapy is substantially lower than that seen in users of estrogen-progestogen combinations. There was no evidence of a difference in risk between the different routes of administration.

In the WHI study, the continuous combined conjugated equine estrogen and medroxyprogesterone acetate medicine used, was associated with breast cancers that were slightly larger in size and had local lymph node metastases compared to placebo.

HRT may increase mammographic density. This may complicate the radiological detection of breast cancer. Clinical studies reported that the likelihood of developing increased mammographic density was lower in women treated with estriol, as contained in SYNAPAUSE VAGINAL CREAM than in women treated with other estrogens.

It is unknown whether SYNAPAUSE VAGINAL CREAM carries the same risk. In a population-based case control study in 3,345 women with invasive breast cancer and 3,454 controls, estriol was found not to be associated with an increased risk of breast cancer, in contrast to other estrogens. However, the clinical implications of these findings are yet unknown. Therefore, it is important that the risk of being diagnosed with breast cancer is discussed with the patient and weighed against the known benefits of HRT.

Venous thromboembolism

Systemic 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.

One randomised controlled trial and epidemiological studies found a 2 to 3-fold higher risk for users compared with non-users. For non-users it is estimated that the number of cases of VTE that will occur over a 5-year period is about 3 per 1 000 women aged 50 to 59 years, and 8 per 1 000 women aged 60 to 69 years. It is estimated that in healthy women who use HRT for 5 years, the number of additional cases of VTE over a 5-year period will be between 2 and 6 (best estimate = 4) per 1 000 women aged 50 to 59 years, and between 5 and 15 (best estimate = 9) per 1 000 women aged 60 to 69 years. 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 a personal or family history of VTE, obesity (Body Mass Index > 30 kg/m^2), use of estrogens, older age, major surgery, prolonged immobilisation, 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 4 to 6 weeks earlier is recommended. Treatment should not

be re-started until the woman is completely mobilised.

Consideration should be given to prophylactic treatment against thrombosis.

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. Patients with a history of recurrent VTE or known thrombophilic states have an increased risk of VTE. SYNAPAUSE VAGINAL CREAM may add to this risk. Personal or strong family history of thromboembolism or recurrent spontaneous abortion should be investigated in order to exclude a thrombophilic predisposition. Until a thorough evaluation of thrombophilic factors has been made or anticoagulant treatment initiated, use of HRT in such patients should be viewed as contraindicated (see section 4.3).

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

If VTE develops after initiating SYNAPAUSE VAGINAL CREAM therapy, the medicine should be discontinued. Patients should be told to contact their doctors immediately when they are aware of potential thromboembolic symptoms (e.g. painful swelling of a leg, sudden pain in the chest, dyspnoea).

Coronary artery disease (CAD)

The risk of coronary artery disease is increased in users of combined estrogen-progestogen HRT over the age of 60.

Two large clinical trials (WHI and HERS i.e. Heart and Estrogen/progestin Replacement Study) showed a possible increased risk of cardiovascular morbidity in the first year of use and no overall benefit. For other HRT medicines there are only limited data from randomised controlled trials examining effects in cardiovascular morbidity or mortality.

There is no evidence from randomized 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.

Estrogen-only

Randomized controlled data found no increased risk of CAD in hysterectomized women using estrogen-only therapy.

Ischaemic stroke

Systemic estrogen-only therapy is associated with an up to 1,5-fold increased relative risk of ischaemic stroke. The risk of haemorrhagic stroke is not increased during use of HRT.

This relative risk is not dependent on age on duration of use, or time since menopause, but as the baseline risk is strongly age-dependent, the overall risk of stroke in women who use HRT will increase with age.

One large randomised clinical trial (WHI-trial) found as a secondary outcome, an increased risk of ischaemic stroke in healthy women during treatment with continuous combined conjugated estrogens and medroxyprogesterone acetate. For women who do not use HRT, it is estimated that the number of cases of stroke that will occur over a 5-year period is about 3 per 1 000 women aged 50 to 59 years, and 11 per 1 000 women aged 60 to 69 years. It is estimated that for women who use conjugated estrogens and medroxyprogesterone acetate for 5 years, the number of additional cases will be between 0 and 3 (best estimate = 1) per 1 000 users aged 50 to 59 years, and between 1 and 9 (best estimate = 4) per 1 000 users aged 60 to 69 years.

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 systemic HRT, which becomes apparent within 5 years of use and diminishes over time after stopping.

Long-term (at least 5 to 10 years) use of estrogen-only and combined estrogen-progestogen HRT-medicines in hysterectomised women has been associated with an increased risk of ovarian cancer in some epidemiological studies. In the Million Women Study (MWS) 5 years of HRT resulted in 1 extra case per 2 500 users. It is not known whether long term use of SYNAPAUSE VAGINAL CREAM confers similar risks.

Some studies including the WHI trial suggest that the long-term use of combined HRT may confer a similar, or slightly smaller, risk.

Hereditary and Acquired Angioedema:

Exogenous estrogens may induce or exacerbate symptoms of hereditary and acquired angioedema.

ALT elevations

During clinical trials with patients treated for hepatitis C virus (HCV) infections with the combination medicine regimen ombitasvir hydrate/paritaprevir hydrate/ritonavir with or without dasabuvir, alanine aminotransferase (ALT) elevations to greater than 5 times the upper limit of normal (ULN) were significantly more frequent in women using ethinyl estradiol-containing medicines such as Combined Hormonal Contraceptives (CHCs). Additionally, also in patients treated with glecaprevir/ pibrentasvir, ALT elevations were observed in women using ethinylestradiol-containing medicines such as CHCs.
Women using medicines containing estrogens other than ethinyl estradiol, such as estradiol, estriol and conjugated estrogens had a rate of ALT elevation similar to those not receiving any estrogens; however, due to the limited number of women taking these other estrogens, caution is warranted for co administration with the combination medicine regimen ombitasvir hydrate/paritaprevir hydrate/ritonavir with or without dasabuvir and also the regimen glecaprevir /pibrentasvir (see section 4.5).

Other conditions

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

Patients with terminal renal insufficiency should be closely observed, since it is expected that the level of circulating active ingredient in SYNAPAUSE VAGINAL

CREAM is increased.

Estriol, as contained in SYNAPAUSE VAGINAL CREAM, is a weak gonadotropin inhibitor without other significant effects on the endocrine system.

Benign hepatic adenoma and hepato-cellular carcinoma appear to be associated with the use of oral contraceptives, but such lesions have not been reported with the use of other estrogen preparations.

A two-fold increase has been reported in the risk of gall bladder disease in women receiving oral estrogen preparations (including oral contraceptives). However, there have been no reports of gall bladder disease in association with estriol tablets, cream or pessaries.

Susceptible women may experience a rise in blood pressure. Care should be exercised in prescribing estrogens for patients with hypertension; regular measurement of blood pressure and careful observation for progressive hypertension is recommended.

Because estrogens may increase the size of uterine fibroids, the pathologist should be advised of estrogen therapy when relevant specimens are submitted.

Patients with diabetes, severe migraine, epilepsy, asthma, fibrocystic mastopathy, significant cardiac or renal dysfunction should be observed carefully during administration of estrogens.

Patients with metabolic bone disease or renal insufficiency should be treated with caution because of the effect of estrogens on the metabolism of calcium and phosphorus.

Women with pre-existing hypertriglyceridaemia should be followed closely during estrogen replacement or hormone replacement therapy, since rare cases of large increases of plasma triglycerides leading to pancreatitis have been reported with estrogen therapy in this condition.

Estrogens, as contained in SYNAPAUSE VAGINAL CREAM, increase thyroid binding globulin (TBG), leading to increased circulating total thyroid hormone, as measured by protein-bound iodine (PBI), T4 levels (by column or radio-immunoassay) or T3 levels (by radio-immunoassay). T3 resin uptake is decreased, reflecting the elevated TBG. Free T4 and free T3 concentrations are unaltered. Other binding proteins may be elevated in serum, i.e. corticoid binding globulin (CBG), sex-hormone-binding globulin (SHBG) leading to increased circulating corticosteroids and sex steroids, respectively. Free or biological active hormone concentrations are unchanged. Other plasma proteins may be increased (angiotensinogen/renin substrate, alpha-l-antitrypsin, ceruloplasmin).

With vaginal administration, stimulation of the liver by the first-pass effect is avoided and thus, transvaginal estrogens might affect hormone binding proteins and other serum proteins produced by the liver less than oral hormones (see section 4.5).
There is no conclusive evidence for improvement of cognitive function. There is some evidence from the WHI trial of increased risk of probable dementia in women who start using continuous combined conjugated estrogens (Conjugated Equine Estrogens) and medroxyprogesterone acetate after the age of 65. It is unknown whether the findings apply to younger post-menopausal women or other HRT medicines.

In case of vaginal infections, these should be treated before therapy with SYNAPAUSE VAGINAL CREAM is started.

Excipients

SYNAPAUSE VAGINAL CREAM contains cetyl alcohol and stearyl alcohol. This may cause local skin reactions (e.g. contact dermatitis) (see section 4.8).

4.5. Interaction with other medicines and other forms of interaction

Due to the vaginal administration and minimal systemic absorption, it is unlikely that any clinically relevant medicines interactions will occur with SYNAPAUSE VAGINAL CREAM. However, interactions with other locally applied vaginal treatments should be considered.

Although data are limited, interactions between SYNAPAUSE VAGINAL CREAM and other medicines may occur. The following interactions have been described with use of combined oral contraceptives which may also be relevant for SYNAPAUSE VAGINAL CREAM.

The metabolism of estrogens, as contained in SYNAPAUSE VAGINAL CREAM, may be increased and the efficacy may be decreased by concomitant use of substances known to induce drug-metabolising enzymes, specifically, cytochrome P450 enzymes, such as anticonvulsants (e.g. hydantoins, phenobarbital, phenytoin, barbiturates, carbamazepine), and herbal preparations containing St John's wort (*Hypericum perforatum*), anti-infectives (e.g. griseofulvin, rifamycins, rifabutin, the antiretroviral medicines nevirapine and efavirenz) as well as bosentan. Caution is warranted for co-administration with the combination drug regimen ombitasvir hydrate/paritaprevir hydrate/ritonavir with or without dasabuvir.

Ritonavir and nelfinavir although known as strong inhibitors, by contrast exhibit inducing properties when used concomitantly with steroid hormones.

With intravaginal administration, the first-pass effect in the liver is avoided and thus, estriol, as contained in SYNAPAUSE VAGINAL CREAM, given intravaginally might be less affected by enzyme inducers than oral hormones (see section 4.4).

Clinically, an increased metabolism of estrogens, as contained in SYNAPAUSE VAGINAL CREAM, may lead to decreased effect and changes in the uterine bleeding profile.

Conversely, estriol, as contained in SYNAPAUSE VAGINAL CREAM, may possibly change the effectiveness of insulins and oral anticoagulants, and increase the pharmacological effects of beta-adrenergic blockers, corticosteroids, succinylcholine, theophyllines and troleandomycin.

SYNAPAUSE VAGINAL CREAM is not intended for contraceptive use.
Contact between contraceptive diaphragms or condoms and the cream must be avoided since the rubber may be damaged by SYNAPAUSE VAGINAL CREAM.

Effect of HRT with oestrogens on other medicines
Estrogen-containing oral contraceptives have been shown to significantly decrease plasma concentrations of lamotrigine when co-administered due to induction of lamotrigine glucuronidation. This may reduce seizure control. Although the potential interaction between estrogen-containing hormone replacement therapy and lamotrigine has not been studied, it is expected that a similar interaction exists, which may lead to a reduction in seizure control among women taking both medicines together. Therefore, dose adjustment of lamotrigine may be necessary.

Pharmacodynamic interactions
During clinical trials with the HCV combination medicine regimen ombitasvir hydrate/paritaprevir hydrate/ritonavir with-and without dasabuvir, ALT elevations to greater than 5 times the upper limit of normal (ULN) were significantly more frequent in women using ethinyl estradiol-containing medicines such as CHCs. Women using

estrogens other than ethinyl estradiol, such as estradiol, estriol, as contained in SYNAPAUSE VAGINAL CREAM, and conjugated estrogens had a rate of ALT elevation similar to those not receiving any estrogens; however, due to the limited number of women taking these other estrogens, caution is warranted for co-administration with the combination medicine regimen ombitasvir hydrate/paritaprevir hydrate/ritonavir with or without dasabuvir and also the regimen with glecaprevir/pibrentasvir (see section 4.4).

4.6. Fertility, pregnancy and lactation

Pregnancy

SYNAPAUSE VAGINAL CREAM is contraindicated during pregnancy (see section 4.3).

The results of most epidemiological studies to date, relevant to inadvertent foetal exposure to estrogens indicate no teratogenic or fetotoxic effect.

If pregnancy occurs during treatment with SYNAPAUSE VAGINAL CREAM, treatment should be withdrawn immediately.

Breastfeeding

SYNAPAUSE VAGINAL CREAM is excreted into breast milk and may decrease milk production. Mothers breastfeeding their infants should not be treated with SYNAPAUSE VAGINAL CREAM (see section 4.3).

Fertility

There is no fertility data.

4.7. Effects on ability to drive and use machines

SYNAPAUSE VAGINAL CREAM has no or negligible influence on the ability to drive and use machines.

Patients should not drive, use machinery or perform any tasks that require concentration until they are certain that SYNAPAUSE VAGINAL CREAM does not adversely affect their ability to do so safely (see section 4.4 and/or 4.8).

4.8. Undesirable effects

(a) Summary of the safety profile

The following adverse reactions, associated with estrogen treatment may occur during estriol therapy or overdose: Nausea and vomiting, breast tenderness or pain in the breasts, vaginal bleeding or spotting during or on withdrawal of therapy, excessive production of cervical mucus, headache.

(b) Tabulated list of adverse reactions

System organ class	***Frequent***	***Less frequent***	***Frequency unknown*** (cannot be estimated from the available data)
Neoplasms benign and malignant (including cysts and polyps)		Endometrial cancer, breast cancer*, ovarian cancer*	
Nervous system disorders		Ischaemic stroke*	
Vascular disorders		Venous thromboembolism*	

*See section (c) for additional information.

Post-marketing data

System organ class	Frequent	Less frequent	Frequency unknown (cannot be estimated from the available data)
Infections and infestations			Cystitis
Metabolism and nutrition disorders			Fluid retention
Psychiatric disorders			Dementia* (depression is a well-known risk factor for suicidal behavior and suicide)
Nervous system disorders			Headache
Cardiac disorders			Palpitations, coronary artery disease
Gastrointestinal disorders			Nausea, vomiting, lower abdominal pain
Hepato-biliary disorder			Gallbladder disease*
Skin and subcutaneous tissue disorders			Itching chloasma/melasma*, erythema multiforme*, erythema nodosum*,, vascular purpura*, exacerbation of the symtoms of hereditary and acquired angioedema
Musculoskeletal and connective tissue disorders			Pain in the leg
Renal and urinary disorders			Increased frequency of micturition
Reproductive system and breast disorders			Breast tension, tenderness, discomfort, pain and enlargement, breakthrough bleeding/spotting, vaginal/cervical discharge, pre-menstrual tension, endometrial hyperplasia
General disorders and administrative site conditions			Flu-like symptoms, application site irritation, pruritis

(c) Description of selected adverse reactions

These adverse reactions are usually transient but may also be indicative of too high a dosage.

Class effects associated with systemic HRT

The following risks have been associated with systemic HRT and apply to a lesser extent for SYNAPAUSE VAGINAL CREAM of which the systemic exposure to estriol remains closely to the normal postmenopausal range when used in a twice weekly administration.

Breast cancer risk

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

• Any increased risk in users of estrogen-only therapy is substantially lower than that seen in users of estrogen-progestagen combinations.

• The level of risk is dependent on the duration of use (see section 4.4).

• Results of the largest randomised placebo-controlled trial (WHI-study) and largest epidemiological study (MWS) are presented.

Million Women study– Estimated additional risk of breast cancer after 5 years' use

Age range (yrs.)	Additional cases per 1000 never-users of HRT over a 5 year period*	Risk ratio#	Additional cases per 1000 HRT users over 5 years (95%CI)
Estrogen only HRT			
50-65	*9-12*	*1.2*	*1-2 (0-3)*
#Overall risk ratio. The risk ratio is not constant but will increase with increasing duration on use ** Taken from baseline incidence rates in developed countries.* Note: Since the background incidence of breast cancer differs by EU country, the number of additional cases of breast cancer will also change proportionately.			

US WHI studies - additional risk of breast cancer after 5 years' use

Age range (yrs.)	Incidence per 1000 women in placebo arm over 5 years	Risk ratio & 95%CI	Additional cases per 1000 HRT users over 5 years (95%CI)
CEE estrogenic-only			
50-79	*21*	*0.8 (0.7 – 1.0)*	*-4 (-6 – 0)**

* WHI study in women with no uterus, which did not show an increase in risk of breast cancer.

Ovarian cancer

Use of **systemic** HRT has been associated with a slightly increased risk of having ovarian cancer diagnosed (see Section 4.4).

A meta-analysis from 52 epidemiological studies reported an increased risk of ovarian cancer in women currently using systemic HRT compared to women who have never used HRT (RR 1.43, 95% CI 1.31-1.56). For women aged 50 to 54 years taking 5 years of HRT, this results in about 1 extra case per 2000 users. In women aged 50 to 54 who are not taking HRT, about 2 women in 2000 will be diagnosed with ovarian cancer over a 5-year period.

Risk of venous thromboembolism

Systemic

HRT is associated with a 1.3-3-fold increased relative risk of developing venous thromboembolism (VTE), i.e. deep vein thrombosis or pulmonary embolism. The occurrence of such an event is more likely in the first year of using HT (see section 4.4).

Results of the WHI studies are presented:

WHI Studies - Additional risk of VTE over 5 years' use

Age range (yrs.)	Incidence per 1000 women in placebo arm over 5 years	Risk ratio & 95%CI	Additional cases per 1000 HRT users
Oral estrogenic-only			
50-59	**7**	*1.2 (0.6 – 2.4)*	*1 (-3 – 10)*

Study in women with no uterus

Risk of ischaemic stroke

• The use of **systemic** HRT is associated with an up to 1,5-fold increased relative risk of ischaemic stroke. The risk of haemorrhagic stroke is not increased during use of HRT.

• This relative risk is not dependent on age or on duration of use, but as the baseline risk is strongly age-dependent, the overall risk of stroke in women who use HRT will increase with age, see section 4.4.

Age range (years)	Incidence per 1000 women in placebo arm over 5 years	Risk ratio and 95%CI	Additional cases per 1000 HRT users over 5 years
50-59	8	1.3 (1.1– 1.6)	3 (1-5)

*no differentiation was made between ischaemic and haemorrhagic stroke.

Other adverse reactions have been reported in association with estrogen-only and estrogen/progestagen combined treatment:

• Estrogen-dependent neoplasms benign and malignant, e.g. endometrial cancer. For further information see sections 4.3 and 4.4.

• Gall bladder disease.

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

• Probable dementia over the age of 65 (see section 4.4).

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

Aspen Pharmacare:
E-mail: Drugsafety@aspenpharma.com
Tel: 0800 118 088

4.9. Overdose

Symptoms

Overdose with SYNAPAUSE VAGINAL CREAM after vaginal administration is unlikely. Should large quantities be ingested nausea, vomiting, breast tenderness or pain in the breasts, headache, excessive production of cervical mucus, abdominal cramps and/or bloating and vaginal bleeding or spotting may develop.

Treatment

No specific antidote is known.

Vaginal lavage should be considered. If accidental ingestion of large quantities of the medicine occurs, an appropriate method of gastric emptying may be considered.

Symptomatic treatment can be given if necessary.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Classification: A.18.6 Vaginal preparations

Pharmacotherapeutic group: Hormonal contraceptives for systemic use, progestogens and estrogens, fixed combinations

ATC code: G03AA06

Mechanism of action

Estriol is a natural short acting female hormone which substitutes for the loss of estrogen production in menopausal women and alleviates menopausal symptoms such

as atrophic vaginitis.

In the years just before and after the menopause (whether naturally or surgically induced) estriol can be used in the treatment of urogenital symptoms and complaints related to estrogen deficiency. In cases of vaginal atrophy estriol induces normalisation of the vaginal epithelium and thus helps to restore the normal microflora and a physiological pH in the vagina. As a result, it increases the resistance of the vaginal epithelial cells to infection and inflammation reducing vaginal complaints such as dyspareunia, dryness, itching, vaginal and urinary infections, miction complaints and mild urinary incontinence.

Estriol is a relatively short-acting estrogen due to its short nuclear retention time in endometrial cells, its low affinity for plasma proteins and partly because of this, its rapid metabolic clearance. Endometrial proliferation is not expected when estriol is given in a single daily dose, since this requires sustained occupancy of the nuclear estrogen receptor.

5.2. Pharmacokinetic properties

Absorption

During the vaginal use of estriol, systemic absorption of estriol occurs shown by a sharp rise in plasma estriol, followed by a gradual decline.

Distribution

Peak plasma levels are reached 1 to 2 hours after application. After vaginal application of 0,5 mg estriol, C_{max} is approximately 100 pg/ml, C_{min} is approximately 25 pg/ml and

$C_{average}$ is approximately 70 pg/ml. After 3 weeks of daily administration of 0,5 mg vaginal estriol, $C_{average}$ has decreased to 40 pg/ml.

Biotransformation

Nearly all (90 %) estriol is bound to albumin in the plasma and, in contrast with other estrogens, hardly any estriol is bound to sex hormone-binding globulin. The metabolism of estriol consists principally of conjugation and deconjugation during the enterohepatic circulation.

Elimination

Estriol, being a metabolic end medicine is mainly excreted via the urine in the conjugated form. Only a small part (± 2 %) is excreted via the faeces, mainly as unconjugated estriol.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Cetyl alcohol, cetyl palmitate, chlorhexidine dihydrochloride, glycerol, lactic acid, octyldodecanol, polysorbate 60, purified water, sodium hydroxide (for pH adjustment), sorbitan stearate, stearyl alcohol.

6.2. Incompatibilities

Not applicable.

6.3. Shelf life

36 months

6.4. Special precautions for storage

Store in a cool place at or below 25 °C.

Do not freeze.

6.5. Nature and contents of container

SYNAPAUSE VAGINAL CREAM is filled in collapsible aluminium tubes containing 15 g of cream. The tubes are provided with a HDPE screw cap. The delivery device consists of a colourless styrene acrylonitrile syringe applicator with a white polyethylene cap and a white polyethylene plunger rod. Each tube is packed, together with an applicator in a carton.

6.6. Special precautions for disposal and other handling

No special requirements.

7. NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION

PHARMACARE LIMITED

Healthcare Park

Woodlands Drive

Woodmead 2191

Tel: 0800 122 912

8. REGISTRATION NUMBER

V/18.6/201

9. DATE OF FIRST AUTHORISATION

Date of registration: 05 December 1989

10. DATE OF REVISION OF TEXT

12 March 2026