SCHEDULING STATUS
S2

1. NAME OF THE MEDICINE
GYNOFLOR vaginal tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Each vaginal tablet contains at least 1 x 10^8 colony forming units (cfu) 900 mg viable *Lactobacillus acidophilus* and 0,03 mg estriol.

Contains sugar “lactose monohydrate”.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM
Vaginal tablets.

The vaginal tablets are white to beige, spotted, oval and biconvex.

4. CLINICAL PARTICULARS
4.1 Therapeutic indications
Atrophic vaginitis and symptomatic vaginal atrophy due to oestrogen deficiency during menopause and post-menopause.

4.2 Posology and method of administration
One vaginal tablet daily for at least 12 days.

Subsequently a maintenance dose of 1 vaginal tablet 2 to 3 days per week is recommended.

For the initiation and continuation of treatment of postmenopausal symptoms, the smallest effective dose should be used for the shortest period of time (see section 4.4).

Method of administration
The vaginal tablets should be inserted deeply (about the depth of one finger) into the vagina in the evening before retiring. This is best performed in a reclining position with the knees slightly bent towards the chest.

Special populations
Elderly patients
Age-related dose adjustment is not necessary.

Renal insufficiency
GYNOFLOR has not been studied in patients with renal insufficiency, however it is probably not necessary to adjust the dose.

Hepatic insufficiency
GYNOFLOR has not been studied in patients with hepatic insufficiency. As with all sex hormones, **GYNOFLOR** is also contraindicated in the presence of severe hepatic insufficiency.

Paediatric population
The use of **GYNOFLOR** is contraindicated in girls before menarche (see section 4.3).

If indicated for adolescents who have had their first period, the same dose is recommended as for adults.

4.3 Contraindications
- Hypersensitivity to the active substances or to any of the excipients listed in section 6.1.
- Existing or suspected breast cancer or a history of breast cancer.
- Known or suspected oestrogen-dependent malignant tumours (especially endometrial carcinoma).
- Known or suspected endometriosis.
- Untreated endometrial hyperplasia.
- Unexplained bleeding in the genital area.
- Vaginitis with severe inflammation and purulent infiltrates.
- Previous idiopathic or existing venous thromboembolic disease (especially deep vein thrombosis, pulmonary embolism).
- Known thrombophilia (e.g. protein C, protein S or antithrombin deficiency).
- Existing or recent arterial embolic disease (especially angina pectoris, myocardial infarction).
- Acute liver disease or a history of liver disease if the relevant liver enzyme values have not returned to normal.
- Porphyria.
- **GYNOFLOR** should not be used in girls before puberty (see section 4.2).

4.4 Special warnings and precautions for use
GYNOFLOR contains only a small amount of estriol of which only a small amount is absorbed.

Only slight risks exist during short-term use of this medicine (i.e. over a period of 6 – 12 days) in the presence of severe impairment of hepatic, renal and cardiac function, epilepsy or migraine (or history thereof), hypertension, diabetes mellitus, porphyria and hyperlipidaemia. This also applies to patients with severe pruritus, gestational herpes or exacerbation of otosclerosis during early pregnancy and those with a history of thrombophlebitis or thromboembolic events.

In the event of a deterioration in any of these conditions, treatment with **GYNOFLOR** should be discontinued. This also applies if abnormal vaginal bleeding occurs during use.

The following warnings are applicable during long-term treatment with **GYNOFLOR**.

Topical oestrogen therapy should be started only in order to treat postmenopausal symptoms that have a negative impact on quality of life. As with all oestrogen-based medicinal products, there should be a careful assessment of the risks and benefits at least once a year. Treatment should be continued only while the benefits outweigh the risks.

Medical/follow-up examinations
Before the start/resumption of treatment, a complete personal and family history must be obtained from the patient.

Furthermore, the patient should undergo a thorough physical and gynaecological examination at regular intervals during treatment with **GYNOFLOR**. The frequency and nature of the examination should be based on the patient's individual risk situation. Patients should be made aware of what types of changes (e.g. unexpected genital bleeding or changes in the breast) they must report to their doctor.

The examinations, including imaging procedures such as mammography, must be carried out in accordance with currently standard screening practice and the clinical needs of the individual patient.

Situations in which special medical surveillance is required
Postmenopausal patients with vaginal atrophy receiving maintenance therapy with **GYNOFLOR** should be monitored closely if any of the following situations/conditions are present or existed in the past or got worse during a pregnancy or previous hormone therapy.

This also applies where one of the situations or conditions mentioned below occurs or deteriorates during the current course of treatment with **GYNOFLOR**:
- Risk factors for oestrogen-dependent tumours, e.g. occurrence of breast cancer in a first-degree relative.
- History of endometrial hyperplasia.
- Leiomyoma (fibroids) or endometriosis.
- Risk factors for thromboembolic disorders.
- Migraine or severe headaches.
- Systemic lupus erythematosus.
- Liver disease (e.g. hepatic adenoma).
- Diabetes mellitus with or without vascular involvement.
- Cholelithiasis.
- Hypertension.
- Epilepsy.
- Asthma.
- Otosclerosis.

Reasons for immediate withdrawal of maintenance therapy
Treatment must be discontinued in the presence of a contraindication (see section 4.3) and in the following situations:
- Jaundice or deterioration in liver function.
- Significant increase in blood pressure.
- First-time occurrence of migraine-like headaches or more frequent occurrence of severe headaches.

Endometrial hyperplasia
The risk of endometrial hyperplasia and carcinoma is increased under oral oestrogen monotherapy depending on the duration of treatment and on the oestrogen dose. An increased risk of endometrial hyperplasia or uterine cancer has not been established for monotherapy with vaginal estriol. If long-term treatment is necessary, regular examinations are recommended, with particular attention being paid to symptoms suggestive of endometrial hyperplasia or a malignant disease of the endometrium.

If breakthrough bleeding occurs during treatment or persists after the end of treatment, the causes must be investigated. In order to rule out malignant degeneration, an endometrial biopsy may be necessary.

Unhindered oestrogen stimulation can lead to premalignant transformation of residual endometrial lesions. This medicine should therefore be used with caution in women who have undergone a hysterectomy because of endometriosis and in whom residual endometriosis is present.

Breast, uterine and ovarian cancer
Systemic oestrogen treatment may increase the risk of certain cancers, especially uterine, ovarian and breast cancer. **GYNOFLOR** vaginal tablets are administered topically, contain a

low dose of estriol, and systemic absorption of estriol after administration of **GYNOFLOR** is minimal and transient. Therefore, the risk of cancer is not expected to increase as a result of **GYNOFLOR** therapy.

Venous thromboembolic disease, stroke and coronary artery disease
Hormone replacement therapy with systemic effects is associated with an increased risk of venous thromboembolism (VTE), stroke and coronary artery disease. **GYNOFLOR** vaginal tablets, which contain a low dose of estriol and are administered topically, should not increase the risk of VTE, stroke or coronary artery disease.

The generally acknowledged risk factors for VTE include a personal or family history of VTE, being significantly overweight (BMI > 30 kg/m^2) and systemic lupus erythematosus (SLE). There is no consensus regarding the possible role of varicose veins in VTE. Close monitoring of these patients is recommended.

Other disease states
Oestrogens with systemic effects may cause fluid retention or lead to an increase in plasma triglyceride levels. Patients with heart disease, renal impairment or pre-existing hypertriglyceridaemia should be monitored closely during the first few weeks of treatment.

GYNOFLOR vaginal tablets contain a low dose of estriol for topical treatment. Systemic effects are therefore not expected.

Patients with severe renal insufficiency should be monitored closely because this may result in increased levels of estriol in the blood.

4.5 Interaction with other medicines and other forms of interaction
Lactobacillus acidophilus is sensitive to various anti-infective medicines (local or systemic). Simultaneous treatment with such medicines may lead to a reduction in the efficacy of **GYNOFLOR**.

Because of the very low estriol content in **GYNOFLOR** and the topical method of administration, clinically relevant interactions are unlikely.

No studies are available on possible interactions between **GYNOFLOR** vaginal tablets and latex products (e.g. condoms, diaphragms, etc.). As a precaution, other methods of contraception should be used during **GYNOFLOR** use and for the first few days after discontinuation of treatment.

4.6 Fertility, pregnancy and lactation
Pregnancy
There are limited data from studies on the use of **GYNOFLOR** in pregnancy. They provide no evidence of negative effects on the pregnancy or the health of the foetus/new-born child.

Endogenous production by the placenta itself results in a significant increase in estriol levels during pregnancy, about 1 000 times as compared to non-pregnant women. Because estriol is present in a very low dose in **GYNOFLOR** and undergoes only limited absorption (see section 5.2), adverse effects on the foetus/new-born are unlikely following use of this medicine during pregnancy.

Pharmacovigilance data compiled over many years also fail to show any increased risk.

Animal studies show adverse effects on the foetus after oral administration of estriol. However, these can be extrapolated to humans only to a limited extent(see section 5.3).

GYNOFLOR may be used during pregnancy after careful assessment of the risks and benefits by a medical practitioner.

Breastfeeding
Estriol is secreted in breast milk. Because of the small quantity and the low vaginal absorption rate of estriol in **GYNOFLOR** (see section 5.2), **GYNOFLOR** may be used during lactation.

Fertility
No studies on effects on fertility have been conducted in animals.

4.7 Effects on ability to drive and use machines
No studies have been conducted on the effect of **GYNOFLOR** on the ability to drive and use machines.

4.8 Undesirable effects
In clinical studies, no serious adverse reactions have been observed. Most of the adverse reactions were local reactions and were experienced shortly after the administration of **GYNOFLOR**. The most commonly reported adverse reactions during treatment are vulvovaginal burning sensation and vulvovaginal pruritus, both occurring in slightly less than 1 % of patients.

The adverse effects observed in clinical trials involving **GYNOFLOR** and in the course of post-marketing surveillance are listed below according to organ system and frequency, with frequency being defined as follows:
Uncommon (≥ 1/1 000, < 1/100), rare (≥ 1/10 000, < 1/1 000).

Infections and infestations
Uncommon: Vaginitis.

Immune system
Rare: Allergic reaction with redness and pruritus.

Reproductive system and breast disorders
Uncommon: Vulvovaginal pruritus, vaginal discharge, vulvovaginal burning sensation (especially at the start of treatment).

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

4.9 Overdose
No adverse effects occur following a vaginal overdose. There is simply an increase in the number of lactobacilli in the environment of the vagina which is the desired effect of the product.

With regards to estriol, a transient increase in serum concentrations is possible. Systemic effects do not usually occur.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and class: A 21.13 Others
Pharmacotherapeutic group: Vaginal therapeutic agent, gynaecological anti-infective and antiseptic.
ATC code: G01AX99, G03CC06

Mechanism of action

GYNOFLOR has a unique dual mechanism of action. Estriol as contained in **GYNOFLOR** stimulates the proliferation and maturation of the vaginal epithelium, which result in an increase in the amount of glycogen and glycogen by-products in vaginal secretions. Glycogen and by-products are a nourishment source for lactobacilli bacteria and estriol promotes *Lactobacillus* adhesion to vaginal epithelium. *Lactobacillus acidophilus* metabolises the glycogen and by-products to lactic acid, helping to maintain the local vaginal pH in the normal range (below 4,5) and create a healthy vaginal ecosystem.

Lactobacillus is a species of bacteria that naturally inhabits a healthy vagina. Lactobacilli are non-pathogenic bacteria which inhibit the colonisation and growth of pathogenic microorganisms in the vagina. They ferment glycogen stored in the vaginal epithelium to lactic acid. The resulting acidic environment (pH 3,8 – 4,5) provides unfavourable conditions for the colonisation and growth of pathogenic microorganisms and provides an optimal medium for the proliferation of the lactobacilli.

In addition to lactic acid, lactobacilli produce hydrogen peroxide and bacteriocins, which also inhibit the growth of pathogenic microorganisms.

The strain of *Lactobacillus acidophilus* contained in **GYNOFLOR** is sensitive to beta-lactam antibiotics, as well as to aminoglycosides, tetracyclines and macrolides. It is resistant to metronidazole, cotrimoxazole, as well as some quinolones (e.g. nalidixic acid and ofloxacin).

Estriol is an endogenous oestrogenic hormone, naturally found in humans, and the major metabolite of estradiol and estrone. Estriol cannot be transformed into estradiol and estrone.

Estriol has been defined as a short-acting oestrogen, having the shortest receptor occupancy (about 10 times lower than for estradiol) of all natural oestrogens. Oestrogens act through binding to nuclear oestrogen receptors, DNA-binding proteins which are found in oestrogen-responsive tissues and by regulating the transcription of a limited number of genes. Some oestrogenic effects, so-called early effects, can be observed after a single administration of estriol, whereas others, the late effects, are seen only with estradiol – which has a longer retention time in the target organ – but not with estriol.

Pharmacodynamic effects

The therapeutic concept of **GYNOFLOR** is to restore a healthy vaginal epithelium and a physiological lactobacillary flora and re-establish the natural defence mechanisms against atrophy and infection, by local treatment with a tablet combining estriol and *Lactobacillus acidophilus*.

Disturbance or deterioration of the vaginal lactobacillary flora can occur mainly as a result of fluctuations in oestrogen levels, local or systemic treatment with anti-infective medicines, serious general illnesses, improper hygienic measures, and vaginal infections. In a non-physiological vaginal environment, the number of lactobacilli is reduced or absent, and their protective function is no longer assured.

Estriol in **GYNOFLOR** ensures proliferation and maturation of the vaginal epithelium. A

proliferated and matured vaginal epithelium acts as physical barrier and stores glycogen, a nutritional substrate for lactobacilli. In the case of hormonal disorders, more commonly observed at advanced age, the vaginal epithelium is disturbed, and the glycogen content decreased. Vaginal infections can also lead to a damaged vaginal epithelium. Exogenous estriol, even in the very low dose contained in **GYNOFLOR**, improves the proliferation and maturation of the epithelium, and thus provides the optimal conditions for the restoration of the vaginal lactobacillary flora.

GYNOFLOR provides *L. acidophilus* to restore the vaginal lactobacillary flora to a healthy state when dysbiosis occurs due to atrophy, infection or use of an anti-infective. *L. acidophilus* produces substances such as lactic acid and hydrogen peroxide, which inhibit the growth of pathogenic microorganisms. Furthermore, *L. acidophilus* can adhere to the vaginal epithelium preventing colonisation by pathogens.

Lactobacillus acidophilus and estriol exert their actions locally within the vagina. Lactose, used for the manufacturing of the vaginal tablets, can also be fermented to lactic acid by the lactobacilli. Replication of the lactobacilli and re-colonisation of the vagina by these bacteria start after the first application of **GYNOFLOR**.

Lactose monohydrate does not directly modulate the vaginal bacterial flora. The lactose contained in the vaginal tablet as well as the local glycogen) is metabolised by the lactobacilli to lactic acid. This induces acidification of the vaginal milieu, reducing the pH and inhibiting the growth of other bacterial species.

Clinical efficacy and safety
Clinical studies with **GYNOFLOR** conducted in postmenopausal women with vaginal atrophy symptoms have demonstrated the significant improvement of the symptoms, the vaginal maturation index (VMI) and the lactobacillary flora. In a double-blind, randomised, placebo-controlled study, postmenopausal women were treated for 12 days once daily with **GYNOFLOR** (n = 44) or placebo (n = 43), followed by an open-label maintenance therapy with **GYNOFLOR** twice per week for 12 weeks (n = 87). The VMI increased significantly more with **GYNOFLOR** (35,2 %) as compared to placebo (9,9 %, $p < 0,001$). The percentage of women with moderate to severe vaginal dryness decreased significantly more and the lactobacillary grade improved significantly more with **GYNOFLOR** as compared to placebo ($p < 0,001$). The maintenance dose of 2 **GYNOFLOR** vaginal tablets weekly was sufficient to maintain the improved maturation and to prevent relapse of symptomatic vaginal atrophy.

In a randomised, double-blind, active-controlled study, 48 post-menopausal women with atrophic vaginitis were treated daily for 12 days either with **GYNOFLOR** or a high dose (0,5 mg) vaginal estriol. Symptoms, degree of epithelial proliferation and vaginal pH improved similarly in both groups.

In a randomised, placebo-controlled study, a total of 360 pre- and postmenopausal women with vaginal infections were enrolled. All women first received an anti-infective therapy and were then randomised 2:1 to receive **GYNOFLOR** or placebo once daily for 6 days (premenopausal) or 12 days (postmenopausal). The normal flora index (NFI), considering numbers of lactobacilli, pathogens, leucocytes and vaginal pH, improved significantly more with **GYNOFLOR** than with placebo ($p < 0,005$).

In a randomised, placebo-controlled study, 32 premenopausal women diagnosed with bacterial vaginosis were included to receive either **GYNOFLOR** or placebo once daily for 6 days. In the **GYNOFLOR** group 77 % of women were cured after the treatment, compared to 25 % in the placebo group ($p < 0,05$).

Lactose intolerance is due to the lack of the enzyme that breaks down lactose in the gastrointestinal tract, resulting in the incapacity to digest milk and food made with milk (dairy products). This is not a concern upon vaginal application.

5.2 Pharmacokinetic properties
As soon as the vaginal tablet comes into contact with vaginal secretions, the tablet begins to disintegrate, and *Lactobacillus acidophilus* as well as estriol are released. *In vitro* experiments have demonstrated that the *Lactobacillus acidophilus* resume their metabolism and cause a reduction in pH within a few hours.

The positive oestrogenic effect induced by estriol is also quickly initiated, and the proliferation and maturation status of the vaginal epithelium improves progressively over the course of treatment (6 – 12 days).

Due to the low dose of estriol (0,03 mg), the local application and the limited absorption, no accumulation of estriol occurs and systemic oestrogen effects are very unlikely.

Absorption
The absorption of estriol from **GYNOFLOR** was investigated in healthy, postmenopausal women with atrophic epithelia. After a single, intravaginal application of **GYNOFLOR**, there was an increase in the plasma concentration of unconjugated estriol (biologically active form) above the basal level, and the maximum estriol concentration was reached after 5 hours. After 8 hours, the plasma concentration of unconjugated estriol was no longer elevated.

After 12 days of once-daily treatment, a single dose of **GYNOFLOR** produced a peak plasma level of unconjugated estriol that was significantly less pronounced, 2,3 pg/mL (baseline subtracted), and was nearly indistinguishable from the normal range of baseline values. During the 12-day treatment, no accumulation of estriol was observed. The plasma concentrations observed after repeated application of **GYNOFLOR** were within the normal range of the endogenous, postmenopausal plasma level of unconjugated estriol.

The absorption of estriol from **GYNOFLOR** was measured in 16 women on non-steroidal aromatase inhibitor with severe vaginal atrophy. The women applied 1 vaginal tablet of **GYNOFLOR** daily for 28 days followed by a maintenance therapy of 3 tablets weekly for 8 weeks. Pharmacokinetic parameters were assessed at day 1 and day 28, and pre-dose, baseline values at day 56 and day 84.

Compared with baseline, serum E1 (estrone) and E2 (estradiol) did not increase in any of the women at any time following vaginal application. Serum E3 (estriol) transiently increased after the first application in 15 of 16 women, with a mean C_{max} of 104,5 pg/mL occurring at 2 – 3 hours after administration. After 4 weeks, serum E3 was slightly increased in 8 women with a mean C_{max} 15,8 pg/mL. No accumulation of serum estriol was observed.

Distribution
The distribution of exogenous oestrogens is similar to that of endogenous oestrogens. Oestrogens are distributed in the body and generally found in higher concentration in the sex hormone target organs. Oestrogen circulate in the blood largely bound to sex hormone binding globulin (SHBG) and albumin.

Metabolism
The main metabolites of estriol are the 16α-glucuronide, 3-glucuronide, 3-sulphate and 3-sulphate-16-glucuronide, which circulate in blood in high concentrations. These conjugates are pharmacologically inactive.

Elimination
The elimination half-life of estriol has been shown to be 9 – 10 hours. More than 95 % of estriol is eliminated via urine, predominantly in the form of glucuronides.

5.3 Preclinical safety data
Two toxicological aspects must be considered for medicines administered by the vaginal route: local tolerance and the possibility of systemic toxicity due to absorption of the components.

Lactobacilli are the predominant microorganisms in the healthy human vagina and are regarded as non-pathogenic. For this reason, the introduction of these bacteria into the vagina is not expected to cause any local irritation or epithelial damage.

Estriol is a steroid sex hormone that is found almost exclusively in humans. Consequently, the extrapolation of data from animal studies to humans has little meaning.

Results of animal experiments (Wistar rats) have demonstrated that only high doses of estriol can lead to a feminisation of the male foetus.

Considering the low dose of estriol in **GYNOFLOR**, no acute or chronic toxicity is to be expected.

6. PHARMACEUTICAL PARTICULARS
6.1 List of excipients
Dibasic sodium phosphate (anhydrous)
Lactose monohydrate
Magnesium stearate
Microcrystalline cellulose (PH102)
Sodium starch glycolate (Type A)

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
36 months

6.4 Special precautions for storage
- Store at 2 °C – 8 °C (in a refrigerator).
- Storage of **GYNOFLOR** at room temperature for 1 – 2 weeks does not affect its efficacy.
- Keep the blister strips in the outer carton until required for use.

6.5 Nature and contents of container
PVC/PE/PVdC-aluminium foil blister strips.
Each blister strip contains 6 vaginal tablets.
Packs sizes: 6, 12, or 36.

6.6 Special precautions for disposal
GYNOFLOR contains excipients which do not dissolve completely, and tablet remains are occasionally found in the underwear. This is of no importance to the efficacy of **GYNOFLOR**.

In rare cases of a very dry vagina, it is possible that the vaginal tablet does not dissolve at all and is discharged by the vagina as an intact tablet. Consequently, the treatment is not optimal. However, this is not harmful to the vagina. For prevention, the vaginal tablet can be moistened with a drop of water before insertion into a very dry vagina.

Patients should use a sanitary towel or panty liner.

7. HOLDER OF CERTIFICATE OF REGISTRATION
Adcock Ingram Limited
1 New Road,
Erand Gardens,
Midrand, 1685
South Africa
Customer Care: 0860 ADCOCK / 232625

8. REGISTRATION NUMBER
55/21.13/0343

9. DATE OF FIRST AUTHORISATION
15 August 2023