Professional information for GINORELLE

SCHEDULING STATUS

S3

1. NAME OF THE MEDICINE

GINORELLE 3 mg / 0,03 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

21 yellow (active) film-coated tablets:

Each tablet contains 3 mg drospirenone and 0,03 mg ethinylestradiol.

Contains sugar.

Each tablet contains 62 mg lactose monohydrate.

7 white placebo (inactive) film-coated tablets:

The tablet does not contain active substances.

Contains sugar.

Each tablet contains 89,5 mg lactose.

For the full list of excipients, see section 6 .1.

3. PHARMACEUTICAL FORM

Film-coated tablets.

The active tablets are round, yellow film-coated tablets.

The inactive tablets are round, white film-coated tablets.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Oral contraception.

4.2 Posology and method of administration

How to take GINORELLE:

Combined oral contraceptives (COC), when taken correctly, have a failure rate of approximately 1 % per year. The failure rate may increase when pills are missed or taken incorrectly.

The first course of GINORELLE is started on the first day of the menstrual period (day 1 of the cycle) from the silver section of the pack by selecting the appropriate tablet for that day of the week (e.g. "MO" for Monday). The tablet is swallowed whole with some liquid. Thereafter one tablet must be taken daily for 28 days following the direction shown by the arrows. It does not matter at what time of the day the tablet is taken, but once the patient has selected a particular time, the tablet should be taken as near as possible at the same time each day. Withdrawal bleeding usually starts on day 2 to 3 after starting the inactive (hormone-free) tablets and may not have finished before the next pack is started. Each subsequent pack is started the day after the last tablet of the current pack. If a patient starts GINORELLE during the latter part of the week, the very first cycle may be slightly shortened.

How to start GINORELLE:

No preceding hormonal contraceptive use (in the past month):

Tablet-taking has to start on day 1 of the woman’s natural cycle (i.e. the first day of her menstrual bleeding). Starting on days 2 to 5 is allowed, but during the first cycle a barrier method is recommended in addition for the first 7 days of tablet-taking.

Changing from a combined hormonal contraceptive (combined oral contraceptive), vaginal ring or transdermal patch:

The woman should start with GINORELLE preferably on the day after the last active tablet (the last tablet containing the active substances) of her previous combined oral contraceptive, but at the latest on the day following the usual tablet-free or inactive tablet interval of her previous combined

oral contraceptive. In case a vaginal ring or transdermal patch has been used, the woman should start using GINORELLE preferably on the day of removal, but at the latest when the next application would have been due.

Changing from a progestogen-only method (minipill, injection, implant) or from a progestogen-releasing intrauterine system (IUS):
The woman may switch any day from the minipill, from an implant or the intrauterine system on the day of its removal and from an injectable when the next injection would be due, but should in all of these cases be advised to additionally use a barrier method for the first 7 days of tablet-taking.

Following first-trimester abortion:
The woman may start immediately. When doing so, she need not take additional contraceptive measures.

Following delivery or second-trimester abortion:
For breastfeeding women see section 4.6.
Women should be advised to start at day 21 to 28 after delivery or second-trimester abortion. When starting later, the woman should be advised to additionally use a barrier method for the first 7 days of tablet-taking. However, if intercourse has already occurred, pregnancy should be excluded before the actual start of GINORELLE use or the woman has to wait for her first menstrual period.

Management of missed tablets:
Missed hormone-free white tablets can be disregarded. However, they should be discarded to avoid unintentionally prolonging the hormone-free white tablet phase. The following advice only refers to missed hormone-containing yellow film-coated tablets:

If the user is **less than 12 hours** late in taking any active tablet, contraceptive protection is not

reduced. The woman should take the tablet as soon as she remembers and should take further tablets at the usual time.

If she is **more than 12 hours** late in taking any active tablet, contraceptive protection may be reduced. The management of missed tablets can be guided by the following two basic rules:

1. Active tablet-taking must never be discontinued for longer than 7 days;
2. 7 days of uninterrupted active tablet-taking are required to attain adequate suppression of the hypothalamic-pituitary-ovarian-axis.

Accordingly the following advice can be given in daily practice:

First 7 days of active tablet-taking (Day 1 to 7):

The user should take the last missed tablet as soon as she remembers, even if this means taking two tablets at the same time. She then continues to take tablets at her usual time. In addition, a barrier method such as a condom should be used for the next 7 days. If intercourse took place in the preceding 7 days, the possibility of a pregnancy should be considered. The more tablets that are missed and the closer they are to the inactive tablet phase, the higher the risk of a pregnancy.

Second 7 days of active tablet-taking (Day 8 to 14):

The user should take the last missed tablet as soon as she remembers, even if this means taking two tablets at the same time. She then continues to take tablets at her usual time. Provided that the woman has taken her tablets correctly in the 7 days preceding the first missed tablet, there is no need to use extra contraceptive precautions. However, if this is not the case, or if she missed more than 1 tablet, the woman should be advised to use extra precautions for 7 days.

Third seven days of tablet-taking (Day 15 to 21):

The risk of reduced reliability is imminent because of the forthcoming inactive tablet phase. However, by adjusting the tablet-intake schedule, reduced contraceptive protection can still be prevented. If either of the following two options is adhered to, there is no need to use extra

contraceptive precautions, provided that in the 7 days preceding the first missed tablet the woman has taken all tablets correctly. If this is not the case, the woman should be advised to follow the first of these two options, and also to use extra precautions for the next 7 days.

1. The user should take the last missed tablet as soon as she remembers, even if this means taking two tablets at the same time. She then continues to take tablets at her usual time until the active tablets are used up. The 7 inactive tablets must be discarded. The next pack must be started right away. The user is unlikely to have a withdrawal bleed until the end of the active tablets section of the second pack, but she may experience spotting or breakthrough bleeding on active tablet-taking days.
2. The woman may also be advised to discontinue active tablet-taking from the current pack. She should then have a tablet-free interval of up to 7 days, including the days she missed tablets, and subsequently continue with the next pack, starting in the silver section with the tablet for the appropriate day of the week.

If the woman missed active tablets and subsequently has no withdrawal bleed in the inactive tablet phase, the possibility of a pregnancy should be considered.

Inactive tablet-taking

The white tablets are inactive tablets and missing these can be disregarded. However, they should be discarded to avoid unintentionally prolonging the inactive tablet phase.

Advice in case of gastrointestinal disturbances:

In case of severe gastrointestinal disturbances, absorption may not be complete and additional contraceptive measures should be taken.

If vomiting occurs within 3 to 4 hours after active tablet-taking, the advice concerning missed tablets is applicable. If the woman does not want to change her normal tablet-taking schedule, she must take the extra tablet(s) needed from another pack.

How to delay a period:

To delay a period the woman should continue with another pack of GINORELLE without taking the inactive tablets from her current pack. The extension can be carried on for as long as wished until the end of the active tablets in the second pack. During the extension the woman may experience breakthrough bleeding or spotting. Regular intake of GINORELLE is then resumed after the inactive tablet phase.

Additional information on special populations

Children and adolescents:

GINORELLE is only indicated after menarche. There are no reported data suggesting the need for a dosage adjustment.

Elderly patients:

Not applicable. GINORELLE is not indicated after menopause.

Patients with hepatic impairment:

GINORELLE is contraindicated in women with severe hepatic diseases (see section 4.3 and section 5.2).

Patients with renal impairment:

GINORELLE is contraindicated in patients with severe renal insufficiency or acute renal failure (see section 4.3 and section 5.2).

Method of administration

For oral use only.

4.3 Contraindications

GINORELLE should not be used in the presence of any of the conditions listed below. Should any of the conditions appear for the first time during GINORELLE use, the product should be stopped immediately.

- Hypersensitivity to active substances, drospirenone and ethinylestradiol, or to any of the excipients listed in section 6.1.
- Hereditary or acquired predisposition for venous or arterial thrombosis, such as activated protein C-resistance (including Factor V Leiden), antithrombin-III-deficiency, protein C deficiency, protein S deficiency, hyperhomocysteinaemia and antiphospholipid antibodies (anticardiolipin-antibodies, lupus anticoagulant).
- Presence or a history of venous or arterial thrombotic / thromboembolic events (e.g. deep venous thrombosis, pulmonary embolism, myocardial infarction) or of a cerebrovascular accident (current stroke, history of stroke).
- Presence or history of prodroma of a thrombosis (e.g. transient ischaemic attack, angina pectoris), major surgery with prolonged immobilisation.
- The presence of a severe or multiple risk factor(s) for venous or arterial thrombosis may also constitute a contraindication (see section 4.4).
- History of migraine with focal neurological symptoms.
- Diabetes mellitus with vascular involvement.
- Severe hypertension.
- Severe dyslipoproteinaemia.
- Severe hepatic disease as long as liver function values have not returned to normal.
- Severe renal insufficiency or acute renal failure with a creatinine clearance of less than 30 mL/min.
- Presence or history of liver tumours (benign or malignant).
- Known or suspected sex-steroid influenced malignancies (e.g. of the genital organs or the breasts).
- Undiagnosed vaginal bleeding.

- Known or suspected pregnancy.
- Depression not well-controlled with treatment.
- A history of depression with the use of hormonal contraception.

GINORELLE is contraindicated for concomitant use with the medicines containing ombitasvir / paritaprevir / ritonavir and dasabuvir (see section 4.5).

4.4 Special warnings and precautions for use

If any of the conditions or risk factors mentioned below is present, the benefits of GINORELLE should be weighed against the possible risks for each individual woman and discussed with the woman before she decides to start using it.
In the event of aggravation, exacerbation or first appearance of any of these conditions or risk factors, the woman should be advised to contact her doctor to determine whether the use of GINORELLE should be discontinued.

In case of suspected or confirmed venous thromboembolism (VTE) or arterial thromboembolism (ATE), combined hormonal contraceptives (CHC) use should be discontinued. In case anticoagulant therapy is started, adequate alternative contraception should be initiated because of the teratogenicity of anticoagulant therapy (coumarins).

Circulatory disorders

An association between the use of combined oral contraceptives and an increased risk of arterial and venous thrombotic and thromboembolic diseases such as myocardial infarction, deep venous thrombosis, pulmonary embolism and of cerebrovascular accidents has been reported.

The risk for venous thromboembolism is highest during the first year of use. This increased risk is present after initially starting a combined oral contraceptive or restarting (following a 4 week or greater pill free interval) the same or a different combined oral contraceptive. The increased risk is reported to be mainly present during the first 3 months.

Overall, the risk for venous thromboembolism (VTE) in users of low combined oral contraceptives is two to threefold higher than for non-users of combined oral contraceptives who are not pregnant.

Venous thromboembolism (VTE) may be life-threatening or may have a fatal outcome (in 1 to 2 % of the cases).

The occurrence of thrombosis has been reported in other blood vessels, e.g., hepatic, mesenteric, renal, cerebral or retinal veins and arteries, in combined oral contraceptive including GINORELLE users. There is no consensus as to whether the occurrence of these events is associated with the use of combined oral contraceptives such as drospirenone 3 mg and ethinylestradiol 0,03 mg as in GINORELLE:

Symptoms of deep venous thrombosis (DVT) can include unilateral swelling of the leg or along a vein in the leg; pain or tenderness in the leg which may be felt only when standing or walking, increased warmth in the affected leg; red or discoloured skin on the leg.

Symptoms of pulmonary embolism (PE) can include sudden onset of unexplained shortness of breath or rapid breathing; sudden coughing which may bring up blood; sharp chest pain which may increase with deep breathing; sense of anxiety; severe light headedness or dizziness; rapid or irregular heartbeat. Some of these symptoms (e.g., shortness of breath, coughing) are non-specific and might be misinterpreted as more common or less severe events (e.g. respiratory tract infections).

An arterial thromboembolic event can include cerebrovascular accident, vascular occlusion or myocardial infarction (MI). Symptoms of a cerebrovascular accident can include sudden numbness or weakness of the face, arm or leg, especially on one side of the body; sudden confusion, trouble speaking or understanding; sudden trouble seeing in one or both eyes; sudden trouble walking, dizziness, loss of balance or coordination; sudden, severe or prolonged headache with no known

cause; loss of consciousness or fainting with or without seizure. Other signs of vascular occlusion can include sudden pain, swelling and slight blue discoloration of an extremity; acute abdomen. If the occlusion occurs in the eye symptoms can range from painless blurring of vision which can progress to loss of vision. Sometimes loss of vision can occur almost immediately.
Symptoms of myocardial infarction (MI) can include pain, discomfort, pressure, heaviness, sensation of squeezing or fullness in the chest, arm, or below the breastbone; discomfort radiating to the back, jaw, throat, arm, stomach; fullness, indigestion or choking feeling; sweating, nausea, vomiting or dizziness; extreme weakness, anxiety, or shortness of breath; rapid or irregular heartbeats.

Arterial thromboembolic events may be life-threatening or may have a fatal outcome. The risk of venous or arterial thrombotic/thromboembolic events or of a cerebrovascular accident increases with:

- age.
- smoking (with heavier smoking and increasing age the risk increases further, especially in women over 35 years of age).
- a positive family history (i.e., venous, or arterial thromboembolism ever in a sibling or parent at a relatively early age). If a hereditary predisposition is known or suspected, the woman should be referred to a specialist for advice before deciding about any combined oral contraceptive use.
- obesity (body mass index over 30 kg/m^2).
- dyslipoproteinaemia.
- hypertension.
- migraine.
- valvular heart disease.
- atrial fibrillation.
- prolonged immobilisation, major surgery, any surgery to the legs, or major trauma. In these situations, it is advisable to discontinue combined oral contraceptive use (in the case of elective

surgery at least four weeks in advance) and not to resume until two weeks after complete remobilisation.

- hyperhomocysteinaemia.

There is no consensus about the possible role of varicose veins and superficial thrombophlebitis in venous thromboembolism.

The increased risk of thromboembolism in the puerperium must be considered (see section 4.6).

Other medical conditions which have been reported to be associated with adverse circulatory events include diabetes mellitus, systemic lupus erythematosus, haemolytic uraemic syndrome, chronic inflammatory bowel disease (Crohn's disease or ulcerative colitis), cancer and sickle cell disease.
An increase in frequency or severity of migraine during combined oral contraceptive use (which may be prodromal of a cerebrovascular event) may be a reason for immediate discontinuation of the combined oral contraceptive.

Biochemical factors that may be indicative of hereditary or acquired predisposition for venous or arterial thrombosis include Activated Protein C (APC) resistance, hyperhomocysteinaemia, antithrombin-III deficiency, protein C deficiency, protein S deficiency, antiphospholipid antibodies (anticardiolipin antibodies, lupus anticoagulant).

Tumours

The most important risk factor for cervical cancer is persistent human papilloma virus infection. Long-term use of combined oral contraceptives may further contribute to this increased risk but there continues to be controversy about the extent to which this reported finding is attributable to confounding effects, e.g., cervical screening and sexual behaviour including use of barrier contraceptives.

A slightly increased relative risk (RR = 1,24) of having breast cancer diagnosed has been reported in women who are currently using combined oral contraceptives. The excess risk has been reported to gradually disappear during the 10 years after cessation of combined oral contraceptive use. Because breast cancer is rare in women under 40 years of age, the excess number of breast cancer diagnoses in current and recent combined oral contraceptive users is small in relation to the overall risk of breast cancer.

Benign liver tumours, and malignant liver tumours have been reported in users of combined oral contraceptives. These tumours have been reported to lead to life-threatening intra-abdominal haemorrhages. A hepatic tumour should be considered in the differential diagnosis when severe upper abdominal pain, liver enlargement or signs of intra-abdominal haemorrhage occur in women taking combined oral contraceptives.

Malignancies may be life-threatening or may have a fatal outcome.

With the use of the higher-dosed COCs (50 µg ethinylestradiol) the risk of endometrial and ovarian cancer is reduced. Whether this also applies to lower-dosed COCs remains to be confirmed.

Other conditions

Potassium excretion capacity may be limited in patients with renal insufficiency. Drospirenone intake did not reportedly show an effect on the serum potassium concentration in patients with mild or moderate renal impairment. A theoretical risk for hyperkalaemia can be assumed only for patients with renal impairment whose pre-treatment serum potassium is in the upper reference range, and who are additionally using potassium-sparing medicines.

Women with hypertriglyceridaemia, or a family history thereof, may be at an increased risk of pancreatitis when using drospirenone 3 mg and ethinylestradiol 0,03 mg, as in GINORELLE.

Small increases in blood pressure have been reported in many women taking combined oral

contraceptives containing ethinylestradiol, clinically relevant increases may occur. If a sustained clinically significant hypertension develops during the use of GINORELLE then it is prudent for the medical practitioner to withdraw it.

The following conditions have been reported to occur but the evidence of an association with GINORELLE: is inconclusive: jaundice and/or pruritus related to cholestasis; gallstone formation; porphyria; systemic lupus erythematosus; haemolytic uraemic syndrome; Sydenham's chorea; herpes gestationis; otosclerosis-related hearing loss.
In women with hereditary angioedema exogenous oestrogens may induce or exacerbate symptoms of angioedema.
Acute or chronic disturbances of liver function may necessitate the discontinuation of GINORELLE: until markers of liver function return to normal. Recurrence of cholestatic jaundice which occurred first during pregnancy or previous use of sex steroids necessitates the discontinuation of GINORELLE.
Although drospirenone 3 mg and ethinylestradiol 0,03 mg, as in GINORELLE: may have an effect on peripheral insulin resistance and glucose tolerance, there is no reported evidence for a need to alter the therapeutic regimen in diabetics using GINORELLE due to its low ethinylestradiol content of 0,03 mg. However, diabetic women should be carefully observed while taking GINORELLE.

Worsening of endogenous depression, of epilepsy, of Crohn's disease and of ulcerative colitis has been reported during COC use.

Depressed mood and depression are well-known undesirable effects of hormonal contraceptive use. 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.

Chloasma may occasionally occur, especially in women with a history of chloasma gravidarum.

Women with a tendency to chloasma should avoid exposure to the sun or ultraviolet radiation whilst taking GINORELLE.

Respiratory: Asthma may deteriorate in women using GINORELLE.

ALT elevations

In patients treated for hepatitis C virus infections (HCV) with the medicines containing ombitasvir/paritaprevir/ritonavir and dasabuvir with or without ribavirin, transaminase (ALT) elevations higher than 5 times the upper limit of normal (ULN) has been reported to occur significantly more frequent in women using ethinylestradiol-containing medicines such as combined hormonal contraceptives (CHCs).

Special precautions

Medical examination/consultation

A complete medical history and physical examination should be taken prior to the initiation or reinstitution of combined oral contraceptive use, guided by the section 4.3 and section 4.4, and should be repeated periodically. Periodic medical assessment is also of importance because contraindications (e.g., a transient ischaemic attack, etc.) or risk factors (e.g., a family history of venous or arterial thrombosis) may appear for the first time during the use of a combined oral contraceptive such as drospirenone 3 mg and ethinylestradiol 0,03 mg as in GINORELLE. The frequency and nature of these assessments should be based on established practice guidelines and be adapted to the individual woman, but should generally include special reference to blood pressure, breasts, abdomen and pelvic organs, including cervical cytology.

Women should be advised that GINORELLE does not protect against HIV infections (AIDS) and other sexually transmitted diseases.

Reduced efficacy

The efficacy of combined oral contraceptives such as drospirenone 3 mg and ethinylestradiol 0,03 mg may be reduced in the event of e.g., missed active tablets, gastrointestinal disturbances during active tablet taking (see section 4.2) or concomitant medicines (see section 4.5).

Reduced cycle control

Irregular bleeding (spotting or breakthrough bleeding) may occur, especially during the first months of use. Therefore, the evaluation of any irregular bleeding is only meaningful after an adaptation interval of about three cycles.

If bleeding irregularities persist or occur after previously regular cycles, then non-hormonal causes should be considered, and adequate diagnostic measures are indicated to exclude malignancy or pregnancy. These may include curettage.

In some women withdrawal bleeding may not occur during the inactive tablet phase. If GINORELLE has been taken according to the directions described under section 4.2, it is unlikely that the woman is pregnant. However, if GINORELLE has not been taken according to these directions prior to the first missed withdrawal bleed or if two withdrawal bleeds are missed, pregnancy must be ruled out before GINORELLE use is continued.

Excipients

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

4.5 Interaction with other medicines and other forms of interaction

Effects of other medicines on GINORELLE

Interactions between GINORELLE and other medicines (enzyme inducers, some antibiotics) may lead to breakthrough bleeding and/or contraceptive failure.

Management

Enzyme induction can already be observed after a few days of treatment. Maximal enzyme induction is generally seen within a few weeks. After the cessation of medicine therapy, enzyme induction may be sustained for about 4 weeks.

Short-term treatment

Women on treatment with enzyme-inducing medicines should temporarily use a barrier method or another method of contraception in addition to GINORELLE. The barrier method must be used during the whole time of the concomitant therapy and for 28 days after its discontinuation. If the medicine therapy runs beyond the end of the tablets in the COC pack, the next COC pack should be started right after the previous one without the usual tablet-free interval.

Long-term treatment

In women on long-term treatment with hepatic enzyme-inducing active substances, another reliable, non-hormonal, method of contraception is recommended.

The following interactions have been reported in the literature.

Medicines diminishing the efficacy of combined oral contraceptives such as drospirenone 3 mg and ethinylestradiol 0,03 mg (enzyme-inducers and antibiotics)

Enzyme induction (increase of hepatic metabolism):

Interactions can occur with medicines that induce microsomal enzymes, which can result in increased clearance of sex hormones (e.g., phenytoin, barbiturates, primidone, carbamazepine, bosentan, rifampicin, efavirenz and possibly also oxcarbazepine, topiramate, felbamate, griseofulvin and products containing St John’s Wort).

Also, HIV protease inhibitors (e.g., ritonavir) and non-nucleoside reverse transcriptase inhibitors (e.g., nevirapine), and combinations of them, have been reported to potentially affect hepatic metabolism.

Concomitant administration of strong CYP3A4 inhibitors can increase plasma concentrations of the

oestrogen or the progestin or both.
In a reported multiple dose study with a drospirenone (3 mg/day) / ethinylestradiol (0,02 mg/day) combination, co-administration of the strong CYP3A4 inhibitor ketoconazole for 10 days increased the AUC(0-24h) of drospirenone and ethinylestradiol 2,7-fold and 1,4-fold respectively.
Etoricoxib doses of 60 to 120 mg/day have been reported to increase plasma concentrations of ethinylestradiol 1,4 to 1,6-fold, respectively when taken concomitantly with a combined hormonal contraceptive containing 0,035 mg ethinylestradiol.

Antibiotics (interference with enterohepatic circulation):
Enterohepatic circulation of oestrogens may decrease when certain antibiotics are given, which may reduce ethinylestradiol concentrations (e.g., penicillins, tetracyclines).
Women on treatment with any of these medicines should temporarily use a barrier method in addition to GINORELLE or choose another method of contraception. With microsomal enzyme-inducing medicines, the barrier method should be used during the time of concomitant medicine administration and for 28 days after their discontinuation. Women on treatment with antibiotics (except rifampicin and griseofulvin) should use the barrier method until 7 days after discontinuation. If the period during which the barrier method is used runs beyond the end of the active tablets in the GINORELLE pack, the white inactive tablets should be omitted and the next GINORELLE pack should be started with the yellow active tablet in the silver section (i.e., without the usual inactive tablet interval).

Substances interfering with the metabolism of combined oral contraceptives such as drospirenone 3 mg and ethinylestradiol 0,03 mg, as in GINORELLE (enzyme inhibitors)
The main metabolites of drospirenone in human plasma are generated without involvement of the cytochrome P450 system. Inhibitors of this enzyme system are therefore unlikely to influence the metabolism of drospirenone.

Effects of combined oral contraceptives such as GINORELLE on other medicines

GINORELLE may affect the metabolism of certain other medicines. Accordingly, plasma and tissue concentrations may either increase (e.g., ciclosporin) or decrease (e.g., lamotrigine).
Based on reported in vitro inhibition studies and in vivo interaction studies in female volunteers using omeprazole, simvastatin and midazolam as marker substrates, an interaction of drospirenone at doses of 3 mg with the metabolism of other medicines is unlikely.

Clinical data suggest that ethinylestradiol may inhibit the clearance of CYP1A2 substrates leading to a weak (e.g. theophylline) or moderate (e.g. tizanidine) increase in their plasma concentration.

Other interactions

There is a theoretical potential for an increase in serum potassium in women taking drospirenone 3 mg and ethinylestradiol 0,03 mg, as in GINORELLE with other medicines that may increase serum potassium levels. Such medicines include angiotensin-II-receptor antagonists, potassium-sparing diuretics, and aldosterone antagonists. However, in studies evaluating the interaction of drospirenone (combined with estradiol) with an ACE inhibitor or indomethacin, no clinically or statistically significant differences in serum potassium concentrations were reported.

Concomitant use with the medicines containing ombitasvir / paritaprevir / ritonavir and dasabuvir, with or without ribavirin may increase the risk of ALT elevations.
Therefore, GINORELLE users must switch to an alternative method of contraception (e.g., progestogen-only contraception or non-hormonal methods) prior to starting therapy with this combination regimen. GINORELLE can be restarted 2 weeks following completion of treatment with this combination regimen.

Note: The package insert information of concomitant medicines should be consulted to identify potential interactions.

Laboratory tests

The use of contraceptive steroids may influence the results of certain laboratory tests including biochemical parameters of liver, thyroid, adrenal and renal function, plasma levels of (carrier) proteins, e.g., corticosteroid-binding globulin and lipid/lipoprotein fractions, parameters of carbohydrate metabolism and parameters of coagulation and fibrinolysis. Changes generally remain within the normal laboratory range. Anti-mineralocorticoid activity of drospirenone causes an increase in plasma renin activity and induces plasma aldosterone.

4.6 Fertility, pregnancy and lactation

Pregnancy

GINORELLE is contraindicated during pregnancy.

If pregnancy occurs during use of with GINORELLE, further intake must be stopped.

The increased risk of VTE during the postpartum period should be considered when re-starting GINORELLE.

Breastfeeding

Lactation may be influenced by GINORELLE as it may reduce the quantity and change the composition of breast milk. Therefore, the use of GINORELLE should not be recommended until the breastfeeding mother has completely weaned her child. Small amounts of the contraceptive steroids and/or their metabolites may be excreted with the milk. These amounts may affect the child.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been reported. No effects on ability to drive and use machines have been reported in users of GINORELLE tablets. However GINORELLE may cause migraine. Patients should be advised that they should determine how GINORELLE affects them before they can engage in these activities.

4.8 Undesirable effects

The most serious adverse effects associated with the use of combined oral contraceptives are also listed under section 4.4.

The frequencies of side effects reported with GINORELLE tablets are summarised in the table below. Within each frequency grouping, side effects are presented in order of decreasing seriousness.

System Organ Class (MedDRA)	**Frequent**	**Less frequent**
Immune system disorders		Hypersensitivity
Metabolism and nutrition disorders		Fluid retention
Psychiatric disorders	Depression/depressive mood, emotional lability, decrease and loss of libido	Increased libido
Nervous system disorders	Headache	
Eye disorders		Contact lens intolerance
Ear and labyrinth disorders		Hypoacusis
Vascular disorders	Migraine	Venous and arterial thromboembolic events (peripheral deep venous occlusion, thrombosis and embolism / pulmonary vascular occlusion, thrombosis, embolism and infarction / myocardial infarction / cerebral infarction and stroke not specified as haemorrhagic), hypertension,

		hypotension
Respiratory, thoracic and mediastinal disorders		Asthma
Gastrointestinal disorders	Nausea, abdominal pain	Vomiting, diarrhoea
Skin and subcutaneous tissue disorders		Rash, urticaria, erythema nodosum, erythema multiforme, acne, eczema, pruritus, alopecia
Reproductive system and breast disorders	Breast pain, unscheduled uterine bleeding, genital tract bleeding not further specified, breast tenderness, menstrual disorders, vaginal discharge, vulvovaginal candidiasis	Breast hypertrophy, vaginal infection, breast discharge
Investigations	Increased weight	Decreased weight

Description of selected adverse reactions

Adverse reactions with low frequency or with delayed onset of symptoms which are considered related to the group of combined oral contraceptives, including GINORELLE tablets, are listed below (see section 4.3 and section 4.4):

Tumours

The frequency of diagnosis of breast cancer is slightly increased among OC users. As breast cancer is rare in women under 40 years of age the excess number is small in relation to the overall risk of breast cancer.

- Liver tumours (benign and malignant)

Other conditions

- Women with hypertriglyceridaemia (increased risk of pancreatitis when using COCs).
- Hypertension.
- Occurrence or deterioration of conditions for which association with COC use is not conclusive: jaundice and/or pruritus related to cholestasis; gallstone formation; porphyria; systemic lupus erythematosus; haemolytic uremic syndrome; Sydenham's chorea; herpes gestationis; otosclerosis-related hearing loss.
- In women with hereditary angioedema exogenous oestrogens may induce or exacerbate symptoms of angioedema.
- Liver function disturbances.
- Changes in glucose tolerance or effect on peripheral insulin resistance.
- Crohn's disease, ulcerative colitis.
- Chloasma

Reporting of suspected adverse reactions:

Reporting suspected adverse reactions after authorisation of GINORELLE is important. It allows continued monitoring of the benefit/risk balance of GINORELLE. Health care 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:

https://www.sahpra.org.za/Publications/Index/8

4.9 Overdose

There has not yet been any experience of overdose with GINORELLE. There have been no reports of serious deleterious effects from overdose in preclinical studies. On this basis of general experience with combined oral contraceptives, symptoms that may occur in this case are nausea, vomiting and, in young girls, slight vaginal bleeding.

Withdrawal bleeding may even occur in girls before their menarche if they accidentally take the medicine. There are no antidotes and further treatment should be symptomatic.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

A 18.8 Ovulation controlling agents

Pharmacotherapeutic group: Progestogens and oestrogens, fixed combinations

ATC code: G03AA12

The contraceptive effect of drospirenone 3 mg and ethinylestradiol 0,03 mg tablets is based on the interaction of various factors, the most important of which are seen as the inhibition of ovulation and the changes in the cervical secretion. GINORELLE is a combined oral contraceptive with ethinylestradiol and the progestogen, drospirenone. In a therapeutic dosage, drospirenone also possesses antiandrogenic and mild anti-mineralocorticoid properties. It has no oestrogenic, glucocorticoid and anti-glucocorticoid activity.

There are indications from clinical studies that the mild anti-mineralocorticoid properties of drospirenone 3 mg and ethinylestradiol 0,03 mg tablets result in a mild anti-mineralocorticoid effect.

With the use of the higher dosed combined oral contraceptives (50 µg ethinylestradiol) the risk of endometrial and ovarian cancer is reduced. Whether this also applies to lower dosed combined oral contraceptives remains to be confirmed.

5.2 Pharmacokinetic properties

Drospirenone

Absorption

Orally administered drospirenone is rapidly and almost completely absorbed. Maximum concentrations of the active substance in serum of about 37 ng/mL are reached at about 1 to 2 hours after single ingestion. Bioavailability is between 76 and 85 %. Concomitant ingestion of food has no influence on the bioavailability of drospirenone.

Distribution

Drospirenone is bound to serum albumin and does not bind to sex hormone binding globulin (SHBG) or corticoid binding globulin (CBG). Only 3 to 5 % of the total serum medicine concentrations are present as free steroid, 95 to 97 % are non-specifically bound to albumin. The ethinylestradiol-induced increase in SHBG does not influence the serum protein binding of drospirenone. The apparent volume of distribution of drospirenone is about 3,7 to 4,2 L/kg.

Biotransformation

Drospirenone is completely metabolised. The major metabolites in the plasma are the acid form of drospirenone, generated by opening of the lactone ring, and the 4,5-dihydro-drospirenone-3-sulphate, both of which are formed without involvement of the P450 system. Drospirenone is metabolised to a minor extent by cytochrome P450 3A4 based on in vitro data. The clearance rate from serum is about 1,2 to 1,5 mL/min/kg. When drospirenone was acutely co-administered with ethinylestradiol, no direct interaction was reported.

Elimination

Drospirenone serum levels decrease in two phases. The terminal disposition phase is characterised by a half-life of approximately 31 hours. Drospirenone is not excreted in unchanged form. Its metabolites are excreted at a biliary to urinary ratio of about 1,2 to 1,4. The half-life of metabolite excretion with the urine and faeces is about 1,7 days.

Steady-state conditions

Drospirenone pharmacokinetics are not influenced by SHBG levels. Following daily ingestion medicine serum levels increase about two to threefold reaching steady-state conditions during the second half of a treatment cycle.

Special populations

Effect of renal impairment

Steady-state serum drospirenone levels in women with mild renal impairment (creatinine clearance CLcr, 50 to 80 mL/minute) were reported to be comparable to those of women with normal renal function (CLcr, > 80 mL/minute). The serum drospirenone levels were reported to be on average 37 % higher in women with moderate renal impairment (CLcr, 30 to 50 mL/minute) compared to those in women with normal renal function. Drospirenone treatment was reported to be well tolerated by all groups. It has been reported that drospirenone treatment did not show any clinically significant effect on serum potassium concentration. Severe renal impairment was not studied.

Effect of hepatic impairment

In women with moderate hepatic impairment (Child-Pugh B), mean serum drospirenone concentration-time profiles were comparable to those of women with normal hepatic function during the absorption/distribution phases, with similar C_{max} values.

The mean terminal half-life of drospirenone for the volunteers with moderate hepatic impairment was about 1,8 times greater than for the volunteers with normal hepatic function.

An about 50 % decrease in apparent oral clearance (CL/f) was reported in volunteers with moderate hepatic impairment as compared to those with normal liver function. The reported decline in drospirenone clearance in volunteers with moderate hepatic impairment compared to normal volunteers did not translate into any apparent difference in terms of serum potassium concentrations between the two groups of volunteers.

Ethinylestradiol

Absorption

Orally administered ethinylestradiol is rapidly and completely absorbed. Peak serum concentrations of about 54 to 100 pg/mL are reached within 1 to 2 hours. During absorption and first-liver passage, ethinylestradiol is metabolised extensively, resulting in a mean oral bioavailability of about 45 % with a large interindividual variation of about 20 to 65 %.

Concomitant intake of food has been reported to reduce the bioavailability of ethinylestradiol in about 25 % of the investigated subjects while no change was reported in the others.

Distribution

Ethinylestradiol is highly but non-specifically bound to serum albumin (approximately 98 %) and induces an increase in the serum concentrations of SHBG. An apparent volume of distribution of about 2,8 to 8,6 L/kg was determined.

Biotransformation

Ethinylestradiol is subject to pre-systemic conjugation in both the small bowel mucosa and the liver. Ethinylestradiol is primarily metabolised by aromatic hydroxylation but a wide variety of hydroxylated and methylated metabolites are formed, and these are present as free metabolites and as conjugates with glucuronides and sulphate. The clearance rate was reported to be about 2,3 to 7 mL/min/kg.

Elimination

Ethinylestradiol serum levels decrease in two disposition phases characterised by half-lives of about 1 hour and 10 to 20 hours, respectively. Unchanged medicine is not excreted, ethinylestradiol metabolites are excreted at a urinary to biliary ratio of 4:6. The half-life of metabolite excretion is about 1 day.

Steady-state conditions

Steady-state conditions are reached during the second half of a treatment cycle when serum medicine levels are higher by 40 to 110 % as compared to single dose.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Yellow active film-coated tablets:

Tablet core:

Crospovidone

Lactose monohydrate

Magnesium stearate

Maize starch

Polysorbate 80

Povidone

Pregelatinised starch

Film-coating:

Opadry yellow (containing iron oxide yellow (E172), macrogol 3350, talc (E553b) and titanium dioxide (E171)).

White placebo film-coated tablets:

Tablet core:

Lactose, anhydrous

Magnesium stearate

Povidone.

Film-coating:

Opadry white (containing titanium dioxide (E171), macrogol 3350 and talc (E553b)).

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

Store at or below 25 °C.

Keep the blister strip in the outer carton until required for use.

6.5 Nature and contents of container

PVC/PVDC/Aluminium foil blister strip, placed in an outer carton.

Pack size: 28 tablets.

6.6. Special precautions for disposal and other handling

Return all unused or expired medicines to your pharmacist for safe disposal. Do not dispose of unused medicines in drains or sewerage systems (e.g., toilets).

7. HOLDER OF CERTIFICATE OF REGISTRATION

Actor Pharma (Pty) Ltd [1]

Unit 7, Royal Palm Business Estate

646 Washington Street, Halfway House,

Midrand, 1685,

Gauteng, South Africa

8. REGISTRATION NUMBER

50/18.8/0343

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

04 August 2022

10. DATE OF REVISION OF THE TEXT

[1] **Company Registration number:** 2008/008787/07