**SCHEDULING STATUS**

S3

## 1. NAME OF THE MEDICINE

**JARINA**® 3 mg/0,03 mg film-coated tablets

## 2. QUALITATIVE AND QUNATITATIVE COMPOSITION

21 hormone-containing light yellow film-coated tablets:
Each film-coated tablet contains 3 mg drospirenone and 0,03 mg ethinylestradiol
Excipient: lactose 46 mg

7 hormone-free white film-coated tablets.
Excipient: lactose 50 mg

For full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Film-coated tablets.

The hormone-containing tablet is light yellow, round with convex faces, one side marked with the letters "DO" in a regular hexagon.
The hormone-free tablet is white, round with convex faces, one side marked with the letters "DP" in a regular hexagon.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

Oral contraception.

### 4.2 Posology and method of administration

**Method of administration**

Oral use

**Posology**

*How to take JARINA*

Combined oral contraceptives, 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 JARINA is started on the first day of the menstrual period (day 1 of the cycle) from the white 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 hormone-free white film-coated 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 JARINA during the latter part of the week, the very first cycle may be slightly shortened.

*How to start JARINA*

- 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 JARINA preferably on the day after the last hormone-containing 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 hormone-free tablet interval of her previous combined oral contraceptive. In case a vaginal ring or transdermal patch has been used, the woman should start using JARINA 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 an additional 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 combined oral contraceptive use or the woman has to wait for her first menstrual period.

*Management of missed tablets*

Missed hormone-free white film-coated 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 light yellow** film-coated tablets:

If the user is ***less than 12 hours*** late in taking any hormone-containing light yellow 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 hormone-containing light yellow 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 hormone-containing 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 hormone-containing 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 hormone-free white film-coated tablet phase, the higher the risk of a pregnancy.

- Second 7 days of hormone-containing 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 7 days of hormone-containing tablet-taking (Day 15 to 21)

The risk of reduced reliability is imminent because of the forthcoming hormone-free white film-coated 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 hormone-containing tablets are used up. The 7 hormone-free white film-coated 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 hormone-containing tablets section of the second pack, but she may experience spotting or breakthrough bleeding on hormone-containing tablet-taking days.
2. The woman may also be advised to discontinue hormone-containing 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 white section with the tablet for the appropriate day of the week.

If the woman missed hormone-containing tablets and subsequently has no withdrawal bleed in the hormone-free white film-coated tablet phase, the possibility of a pregnancy should be considered.

*Hormone-free white film-coated tablet-taking*

The white tablets are hormone-free tablets and missing these can be disregarded. However, they should be discarded to avoid unintentionally prolonging the hormone-free 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 taking a light yellow hormone-containing tablet, 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 JARINA without taking the hormone-free white film-coated tablets from her current pack. The extension can be carried on for as long as wished until the end of the hormone-containing light yellow tablets in the second pack. During the extension the woman may experience breakthrough bleeding or spotting. Regular intake of JARINA is then resumed after the hormone-free white film-coated tablet phase.

**Special populations**

*Children and adolescents*

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

*Geriatric patients*

Not applicable. JARINA is not indicated after menopause.

*Patients with hepatic impairment*

JARINA is contraindicated in women with severe hepatic diseases. See also sections 4.3 and 5.2.

*Patients with renal impairment*

JARINA is contraindicated in women with severe renal insufficiency or acute renal failure. See also sections sections 4.3 and 5.2.

## 4.3 Contraindications

JARINA 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 JARINA use, the product should be stopped immediately.

- Hypersensitivity to the active substances or to any of the excipients listed in section 6.1.
- 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.
- Presence or history of prodromata of a thrombosis (e.g. transient ischaemic attack, angina pectoris).
- A high risk of venous or arterial thrombosis (see section 4.4)
- History of migraine with focal neurological symptoms.
- Diabetes mellitus with vascular involvement.

- Severe hepatic disease as long as liver function values have not returned to normal.
- Use of direct-acting antiviral (DAA) medicines containing ombitasvir, peritaprevir, or dasabuvir, and combinations of these (see section 4.5).
- Severe renal insufficiency or acute renal failure with a creatinine clearance of less than 30 mL/minute.
- 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.

## 4.4 Special warnings and precautions for use

If any of the conditions/risk factors mentioned below are present, the benefits of JARINA 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 contact her medical practitioner. The medical practitioner should then decide on whether JARINA's use should be discontinued.

### Circulatory disorders

Epidemiological studies have demonstrated 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.

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. Data from a large, prospective 3-armed cohort study suggest that this increased risk is 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).

Venous thromboembolism, manifesting as deep venous thrombosis and/or pulmonary embolism, may occur.

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 JARINA users.

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 discolored 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.

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 potential for an increased synergistic risk of thrombosis should be considered in women who possess a combination of risk factors or exhibit a greater severity of an individual risk factor. This increased risk may be greater than a simple cumulative risk of the factors. A combined oral contraceptive should not be prescribed in case of a negative risk benefit assessment (see section 4.3).

The risk of venous or arterial thrombotic/thromboembolic events or of a cerebrovascular accident increases with:

- older 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.

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 associated with adverse circulatory events include diabetes mellitus, systemic lupus erythematosus, haemolytic uraemic syndrome, chronic inflammatory bowel disease (Crohn's disease or ulcerative colitis) 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. Some epidemiological studies have indicated that 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 finding is attributable to confounding effects, e.g. cervical screening and sexual behaviour including use of barrier contraceptives.

A meta-analysis from 54 epidemiological studies reported that there is a slightly increased relative risk (RR = 1,24) of having breast cancer diagnosed in women who are currently using combined oral contraceptives. The excess risk gradually disappears during the course of 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 led 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.

**Other conditions**

Potassium excretion capacity may be limited in patients with renal insufficiency. In a clinical study, drospirenone intake did not 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 JARINA.

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 JARINA then it is prudent for the medical practitioner to withdraw JARINA.

The following conditions have been reported to occur but the evidence of an association with JARINA 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 estrogens may induce or exacerbate symptoms of angioedema.

Acute or chronic disturbances of liver function may necessitate the discontinuation of JARINA, 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 JARINA.

Although JARINA may have an effect on peripheral insulin resistance and glucose tolerance, there is no evidence for a need to alter the therapeutic regimen in diabetics using JARINA, due to its low ethinylestradiol content of 0,03 mg. However, diabetic women should be carefully observed while taking JARINA.

Crohn's disease and ulcerative colitis have been associated with combined oral contraceptive use.

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 JARINA.

Respiratory: Asthma may deteriorate in women using JARINA.

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 physician in case of mood changes and depressive symptoms, including shortly after initiating the treatment.

Each light yellow film-coated tablet of JARINA contains 46 mg lactose per tablet and each white film-coated tablet contains 50 mg lactose per tablet. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption who are on a lactose-free diet should take this amount into consideration.

**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 "Contraindications" and "Warnings", 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 JARINA. 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 JARINA does not protect against HIV infections (AIDS) and other sexually transmitted diseases.**

**Reduced efficacy**

The efficacy of combined oral contraceptives such as JARINA may be reduced in the event of e.g. missed hormone-containing light yellow tablets, gastrointestinal disturbances during hormone-containing light yellow tablet taking (see section 4.2) or concomitant medication (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 hormone-free white film-coated tablet phase. If JARINA has been taken according to the directions described under "Dosage and directions for use", it is unlikely that the woman is pregnant. However, if JARINA 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 JARINA use is continued.

**4.5 Interactions with other medicines and other forms of interactions**

**Note: The prescribing information of concomitant medications should be consulted to identify potential interactions.**

**Effects of other medicines on JARINA**

Interactions can occur with medicines that induce microsomal enzymes which can result in increased clearance of sex hormones and which may lead to breakthrough bleeding and/or contraceptive failure.

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 drug therapy enzyme induction may be sustained for about 4 weeks.

Women on treatment with any of these medicines should temporarily use a barrier method in addition to JARINA or choose another method of contraception. The barrier method should be used during the time of concomitant medicine administration and for 28 days after their discontinuation. If the period during which the barrier method is used runs beyond the end of the hormone-containing tablets in the JARINA pack, the hormone-free white film-coated tablets should be omitted and the next JARINA pack should be started with the light yellow hormone-containing tablet in the white section (i.e. without the usual hormone-free white film-coated tablet interval).

*Substances increasing the clearance of JARINA (diminished efficacy by enzyme-induction), e.g.:*

Phenytoin, barbiturates, primidone, carbamazepine, rifampicin, and possibly also oxcarbazepine, topiramate, felbamate, griseofulvin and products containing St John's wort.

*Substances with variable effects on the clearance of JARINA, e.g.:*

When co-administered with JARINA, many HIV/HCV proteasae inhibitors and non-nucleoside reverse transcriptase inhibitors can increase or decrease plasma concentrations of estrogen or progestogen. These changes may be clinically relevant in some cases.

*Substances decreasing the clearance of JARINA (enzyme inhibitors)*
Strong and moderate CYP3A4 inhibitors such as azole antifungals (e.g. itraconazole, voriconazole, fluconazole), verapamil, macrolides (e.g. clarithromycin, erythromycin), diltiazem and grapefruit juice can increase plasma concentrations of the estrogen or the progestogen or both.

In a 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 2,68-fold (90 % CI: 2,44; 2,95) and 1,40-fold (90 % CI: 1,31; 1,49), respectively.

Etoricoxib doses of 60 to 120 mg/day have been shown 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.

**Effects of JARINA on other medicines**

JARINA may affect the metabolism of certain other medicines. Accordingly, plasma and tissue concentrations may either increase (e.g. ciclosporin) or decrease (e.g. lamotrigine).

In vitro, drospirenone is capable to inhibit weakly to moderately the cytochrome P450 enzymes CYP1A1, CYP2C9, CYP2C19 and CYP3A4.

Based on in vivo interaction studies in female volunteers using omeprazole, simvastatin or midazolam as marker substrates, clinically relevant interaction of drospirenone at doses of 3 mg with the cytochrome P450 enzyme mediated metabolism of other medicines is unlikely.

In vitro, ethinylestradiol is a reversible inhibitor of CYP2C19, CYP1A1 and CYP1A2 as well as a mechanism based inhibitor of CYP3A4/5, CYP2C8, and CYP2J2. In clinical studies, administration of a hormonal contraceptive containing ethinylestradiol did not lead to any increase or only to a weak increase in plasma concentrations of CYP3A4 substrates (e.g. midazolam) while plasma concentrations of CYP1A2 substrates can increase weakly (e.g. theophylline) or moderately (e.g. melatonin and tizanidine).

**Pharmacodynamic interactions**

Co-administration of ethinylestradiol-containing medicines with direct-acting antiviral (DAA) medicines containing ombitasvir, paritaprevir, or dasabuvir, and combinations of these has been shown to be associated with increases in ALT levels to greater than 20 times the upper limit of normal in healthy female subjects and hepatitis C virus (HCV) infected women (see section 4.3).

**Other forms of interaction**

*Serum potassium*

There is a theoretical potential for an increase in serum potassium in women taking JARINA 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 observed.

*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. Antimineralocorticoid activity of drospirenone causes an increase in plasma renin activity and induces plasma aldosterone.

**4.6 Pregnancy and lactation**

**Pregnancy**

JARINA is not indicated during pregnancy. If pregnancy occurs during treatment with JARINA, further intake must be stopped.

**Lactation**

Lactation may be influenced by combined oral contraceptives as they may reduce the quantity and change the composition of breast milk. Therefore, the use of JARINA is not 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.

### 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 performed. No effects on ability to drive and use machines have been observed in users of JARINA.

### 4.8 Undesirable effects

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

**Tabulated summary of adverse reactions**

The frequencies of side effects reported in clinical trials with JARINA (n=4 897) are summarised in the table below. Within each frequency grouping, side effects are presented in order of decreasing seriousness. Frequencies are defined as very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1 000 to < 1/100) and rare (≥ 1/10 000 to < 1/1 000).

| System organ class | Very common | Common | Uncommon | Rare |
|---|---|---|---|---|
| **Psychiatric disorders** | | depression/depressive mood<br>emotional lability<br>decrease and loss of libido | | |
| **Nervous system disorders** | | migraine | | |
| **Vascular disorders** | | | | venous and arterial thromboembolic events* |
| **Gastrointestinal disorders** | | nausea | | |
| **Reproductive system and breast disorders** | | breast pain<br>unscheduled uterine bleeding<br>genital tract bleeding not further specified | | |

Adverse events in clinical studies were coded using the MedDRA dictionary (version 12.1). Different MedDRA terms representing the same medical phenomenon have been grouped together as single adverse reactions to avoid diluting or obscuring the true effect.

* - Estimated frequency, from epidemiological studies encompassing a group of combined oral contraceptives. Frequency was borderline to Very Rare.
- 'Venous and arterial thromboembolic events' summarises the following Medical Entities: Peripheral deep venous occlusion, thrombosis and embolism/Pulmonary vascular occlusion, thrombosis, embolism and infarction/Myocardial infarction/Cerebral infarction and stroke not specified as haemorrhagic.

For venous and arterial thromboembolic events and migraine see also sections 4.3 and 4.4.

**The following adverse reactions have been identified during postapproval use of JARINA**

Skin and subcutaneous disorders: Erythema multiforme.

Because these reactions are reported from a population of uncertain size it is not always possible to reliably estimate their frequency or establish a causal relationship to medicine exposure.

**Description of selected adverse reactions**

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

*Tumours*

- The frequency of diagnosis of breast cancer is slightly increased among oral contraceptive 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*

- Erythema nodosum
- 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 estrogens 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.
- Hypersensitivity (including symptoms such as rash, urticaria)

*Interactions*

Breakthrough bleeding and/or contraceptive failure may result from interactions of other medicines (enzyme inducers) with JARINA (see section 4.5).

**Reporting of suspected adverse reactions**

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

**4.9 Overdose**

There has not been any clinical experience of overdose with JARINA. 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 withdrawal bleeding.

The last may even occur in girls before their menarche, if they have accidentally the medicine. There are no antidotes and further treatment should be symptomatic.

## 5. PHARMACOLOGICAL ACTION

### 5.1 Pharmacodynamic properties

Pharmacotherapeutic group (ATC): Progestogens and estrogens, fixed combinations
ATC Code: G03AA 12

The contraceptive effect of JARINA 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. JARINA is a combined oral contraceptive with ethinylestradiol and the progestogen drospirenone. In a therapeutic dosage, drospirenone also possesses antiandrogenic and mild antimineralocorticoid properties. It has no estrogenic, glucocorticoid and antiglucocorticoid activity.

There are indications from clinical studies that the mild antimineralocorticoid properties of JARINA result in a mild antimineralocorticoid 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. Peak serum concentrations of approximately 37 ng/mL are reached at about 1 to 2 hours after single ingestion. Bioavailability is about 76 to 85 %. Concomitant ingestion of food has no influence on bioavailability.

*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 drug 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.

*Metabolism*

Drospirenone is extensively metabolised after oral administration. The major metabolites in plasma are the acid form of drospirenone, generated by opening of the lactone ring, and the 4,5-dihydro-drospirenone-3-sulphate, formed by reduction and subsequent sulfatation. Drospirenone is-also subject to oxidative metaqbolsim catalysed by CYP-3A4.
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 found.

*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 drug 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 comparable to those of women with normal renal function (CLcr, > 80 mL/minute). The serum drospirenone levels were 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 well tolerated by all groups. 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 seen in volunteers with moderate hepatic impairment as compared to those with normal liver function. The observed 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 reduced the bioavailability of ethinylestradiol in about 25 % of the investigated subjects while no change was observed 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.

*Metabolism*

Ethinylestradiol is subject to significant gut and hepatic first-pass metaboism. Ethinylestradiol and its oxidative metabolites are primarily conjugated with glucuronides or 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 drug levels are higher by 40 to 110 % as compared to single dose.

### 5.3 Preclinical safety data

Not applicable

## 6. PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

ferric oxide pigment yellow (E172)
hydroxylpropylmethyl cellulose
lactose monohydrate
macrogol 6000
magnesium stearate
maize starch
modified starch (pregelatinised starch)
povidone 25000
talc
titanium dioxide (E171)

### 6.2 Incompatibilities

Not applicable.

### 6.3 Shelf life

3 years

### 6.4 Special precautions for storage

Store at or below 30 °C.
Keep the blister strips in the original carton until required for use.

### 6.5 Nature and contents of container

PVC/PE.EVOH.PE/PCTFE-Aluminium blister pack.

Pack sizes:
1x28 (21+7) tablets

### 6.6 Special preacutions for disposal

No special requirements.

## 7. HOLDER OF CERTIFICATE OF REGISTRATION

Bayer (Pty) Ltd
Reg. No.: 1968/011192/07
27 Wrench Road
Isando
1609

## 8. REGISTRATION NUMBER

43/18.8/0782

## 9. DATE OF FIRST AUTHORISATION

25 November 2011

## 10. DATE OF REVISION OF THE TEXT

11 July 2024