Ministry of Health of the Republic of Belarus

Stamp:
AGREED BY
Ministry of Health of the Republic of Belarus
Order of the Ministry of Health of the Republic of Belarus
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Stamp:
JLLC "TriplePharm",
Development, Registration and Standardization Department
Controlled Copy

Package leaflet

Paulina
film-coated tablets, 2 mg/0.03 mg

Trade name Paulina
International nonproprietary name Dienogest/Ethinylestradiol
Pharmaceutical form Coated tablets, 2 mg/0.03 mg
Description
Active tablet: Round biconvex white coated tablets.
Placebo tablet: Round biconvex green coated tablets.
Composition per 1 tablet
Active substances:
Dienogest – 2 mg
Ethinylestradiol – 0.03 mg
Excipients: lactose monohydrate, corn starch, povidone K-30 (E1201), magnesium stearate (E470b).
Coat composition: hypromellose 2910, polyethyleneglycol (E 1521), titan dioxide (E 171).
Composition per 1 placebo tablet
Lactose monohydrate, corn starch, povidone K-30 (E1201), colloidal anhydrous silicon dioxide (E 551), magnesium stearate (E470b).
Coat composition: hypromellose 2910, triacetin (E 1518), Polysorbate (E 433), titan dioxide (E 171), Blue Aluminum Lake No. 2 (E 132), yellow iron oxide (E 172).
Pharmacotherapeutic group. Hormonal contraceptives for systemic use. Combinations of progestagens and estrogens.
ATC-code G03AA16
Pharmacological properties
Pharmacodynamics
Paulina is a medicinal preparation for oral contraception, consisting of estrogen - ethinylestradiol and progestagen – dienogest.
Contraceptive action of Paulina is based on the combined interaction of various factors, the most important of which are suppression of ovulation and change of vaginal secretion viscosity.
Contraceptive action can be decreased in case of violation of dosage regimen (for example, in case of tablet omission).
Unadjusted Pearl Index is 0.454 (upper 95% confidence interval: 0.701).
Adjusted Pearl Index is 0.182 (upper 95% confidence interval: 0.358).
Dienogest is a derivative from nortestosterone which has affinity to progesterone receptors in vitro in 10-30 times less in comparison with other progestins. In animal studies in vivo, a high gestagenic and antiandrogenic action of dienogest has been demonstrated.
Dienogest dose suppressing ovulation is 1 mg/day.
Administration of hormonal contraceptives with a 50 μg ethinylestradiol dose decreases the risk of endometrial cancer and ovarian cancer. There is no data on contraceptives with lower dosage of ethinylestradiol.
Pharmacokinetics
Ethinylestradiol
Absorption
After oral administration ethinylestradiol is quickly and almost completely absorbed. The highest concentration in blood serum, which is about 67pg/ml, is reached in 1.5-4 hours after oral administration.

Ethinylestradiol is subject to extensive metabolism during absorption and "first passing" in liver, which results in average peoral distribution approximately 44%.

Distribution

Ethinylestradiol (approximately 98%) is not specifically linked to serum albumin, and induces increase of sex hormone binding globulin in blood serum. Apparent volume of ethinylestradiol distribution is 2.8 to 8.6 l/kg.

Metabolism

Ethinylestradiol is eliminated by presystemic conjugation in small intestine mucous membrane and liver. Ethinylestradiol is primarily metabolized by aromatic hydroxylation; in the process of it various hydroxylated and methylated metabolites are formed, which can be observed as free metabolites or as conjugates of glucuronidsulphates in serum. Ethinylestradiol is subject to enterohepatic cycle.

Elimination

Decrease of concentration of ethinylestradiol in blood serum has a two-phase character: the first phase is characterized by a half-life period about 1 hour, the second - 10-20 hours. Ethinylestradiol is not eliminated in unchanged form. Metabolites are excreted with urine and bilis in the ratio 4:6.

Equilibrium concentration

The state of equilibrium concentration is reached during the second half of cycle of administration when ethinylestradiol level in blood serum increases approximately in 2.0-2.3 times.

Dienogest

Absorption

After oral administration dienogest is quickly and almost completely absorbed. The highest concentration in blood serum, which is 51 ng/ml, is achieved approximately in 2.5 hours. Absolute bioavailability is approximately 96%.

Distribution

Dienogest links to serum albumin and links neither to sex hormone binding globulin, nor to corticosteroid binding globulin. About 10% of general concentration of dienogest in serum is present as free steroid, 90% - as not specifically bound to serum albumin. The average apparent volume of dienogest distribution is 37-45 l/kg.

Metabolism

Dienogest is generally destroyed by hydroxylation and conjugation with formation of endocrinologically inactive metabolites. These metabolites are quickly eliminated from plasma. General clearance (C1/F) after single administration is 3.6 l/h.

Elimination

Half-life period of dienogest is 9 hours. Only insignificant quantity is eliminated through kidneys in unchanged form. After administration of 0.1 mg of dienogest per 1 kg of weight, the ratio of renal excretion to faecal is 3.2. Within 6 days 86% of the aministered dose are excreted, from which 42% are excreted in the first 24 hours with urine.

Equilibrium concentration

Pharmacokinetics of dienogest is not influenced by the level of sex hormone binding globulin. In case of daily administration, concentration of dienogest in blood serum is increased approximately by 1.5 times and after a 4-day administration it reaches an equilibrium state.

Indications

Hormonal contraception.

When deciding on indication of Paulina medicinal preparation, current individual risk factors of each woman, in particular, concerning venous thromboembolism, should be considered. It is necessary to compare risk of venous thromboembolism during use of Paulina medicinal preparation to the risk of venous thromboembolism for other combined hormonal contraceptives.

Contraindications

- hypersensitivity to any of components of Paulina medicinal product;
- venous thromboembolism for anticoagulants at the present time or in the anamnesis (e.g., deep venous thrombosis or pulmonary embolism);
- revealed genetic or acquired predisposition to venous thromboembolism, such as resistance to activated protein C (including Factor V Leiden), insufficiency of antithrombin-III, insufficiency of protein C, insufficiency of protein S;
- serious surgical intervention with prolonged immobilization;
- high risk of the development of venous thromboembolism in presence of multiple risk factors;
- arterial thromboembolism at the present time or in anamnesis (e.g., myocardial infarction) or in anamnesis (e.g., stenocardia);
- cerebrovascular disease - current stroke, stroke in anamnesis or primary disease (e.g., transient ischaemic attack);
- revealed genetic or acquired predisposition to arterial thromboembolism, such as hyperhomocisteinemia and antiphospholipidic antibodies (anticardiolipin antibodies, lupus anticoagulant);
- present or history of focal neurological symptoms;
- high risk of development of arterial thromboembolism because of presence of one of serious risk factors (diabetes mellitus with vascular complications, severe form of hypertensive disease, severe form of dislipoproteinemia, smoking);
- presence in history of hepatic diseases if indicators of hepatic function haven't returned to normal, Dubin-Johnson syndrome, liver tumors;
- revealed or suspected hormone-dependent malignant diseases (e.g., of mammary gland or endometrium);
- vaginal bleeding of unclear genesis;
- pregnancy or suspicion of it;
- absence of menstruation for unspecified cause;
- menopause.

Precautionary measures

Administration during pregnancy and breastfeeding

Administration of Paulina during pregnancy is contraindicated.

Pregnancy should be eliminated before administration of medicinal preparation. If pregnancy occurs during administration of medicinal preparation, it should be immediately excluded. Epidemiological studies haven't revealed the increased risk of development of defects in the children born by the women who received oral contraceptives before pregnancy or teratogenic action in cases of careless administration of oral contraceptives during pregnancy. Similar studies have not been carried out for Paulina medicinal preparation. There are too limited data on administration of Paulina medicinal preparation during pregnancy to make conclusion on its negative influence on pregnancy and health of fetus and neonate. Relevant epidemiological data are absent.

Animal studies showed undesirable influences of combination of dienogest and ethinylestradiol during pregnancy and in the period of lactation. On the basis of these experimental data, it is impossible to exclude undesirable hormonal action of active components. In case of prescription of Paulina medicinal preparation, an increased risk of development of venous thromboembolism (VTE) during postpartum period should be considered. Paulina medicinal preparation shouldn't be administered during breastfeeding as it penetrates into breast milk, and also can reduce its production. If possible nonhormonal

methods of contraception should be used, until the child is ablactated completely.

Special instructions

Before the beginning or renewing of administration of combined oral contraceptive, it is necessary to study the complete medical anamnesis (including family anamnesis) of patient. Blood pressure should be measured and medical examination should be performed. It is important to pay attention of the patient to information on venous and arterial thrombosis, to high risk of development of arterial thromboembolism in the presence of critical factors, symptoms of VTE and ATE, and also to explain an operations procedure in case of suspicion of thrombosis.

Also, the patient should be instructed to read package leaflet attentively, and to adhere to the recommendations given in it. The frequency and nature of studies should be based on the accepted practical guidance and adapted to the specific woman.

Patient should be warned that hormonal contraceptives do not protect from HIV infection (AIDS) and other sexually transmitted diseases. If any of the conditions or risk factors provided below exist at the present moment, then it is necessary to discuss with the patient acceptability of use of Paulina medicinal preparation.

In case of aggravation or first manifestation of any of these conditions, the patient is recommended to consult with the doctor to define whether Paulina medicinal preparation administration should be withdrawn.

Risk of development of venous thromboembolism (VTE)

Administration of any combined hormonal contraceptives increases the risk of development of venous thromboembolism (VTE). Medicinal preparations containing levonorgestrel, norelgestromin or norethisterone, are associated with lower risk of development of VTE. It is unknown yet, how the risk during administration of Paulina medicinal preparation is comparable to medicinal products which have lower risk. The decision on administration of Paulina medicinal preparation should be made only after discussion with the patient of a possibility of development of VTE during administration of hormonal contraceptives, the risk factors leading to development of VTE, and the fact that her risk of development of VTE is maximum in the first year of administration of preparation. There are also some proofs that the risk increases, in case of renewal of use of combined hormonal contraceptives (CHC) after a break between administrations in 4 weeks and more.

Among women who do not receive hormonal contraceptives and are not pregnant, approximately in 2 of 10.000 VTE will be developed within the period equal to one year. In certain women the risk of emergence of VTE can be much higher if there are risk factors (see below).

During epidemiological studies of the women receiving combined oral contraceptives in small doses (< 50 μg of ethinylestradiol), it has been found out that from 10000 women, approximately in 6-12 VTE will be developed within the first year of administration. It is considered that from 10000 women who receive CHC containing levonorgestrel approximately in 6[1] VTE will be developed within the first year of administration.

Limited epidemiological data show that the risk of development of VTE during administration of contraceptives containing dienogest can be comparable to the risk during administration of CHC containing levonorgestrel.

Such number of cases of VTE in a year appears less, than the number of VTE expected during pregnancy or during postpartum period.

VTE can lead to lethal outcome in 1-2% of cases.

[1] - The average value from the range is 5-7 women of 10000 women/year, on the basis of the relative risk for CHC, containing levonorgestrel in comparison with absence of their use, which is equal approximately to 2.3 to 3.6.

Factors of VTE development

The risk of development of thromboembolic disorders in patients receiving CHC can be significantly increased in women who have additional risk factors, particularly if there are many risk factors (see the table).

Paulina medicinal preparation is contraindicated, if woman has several risk factors, and if the ratio between risk and benefit is negative.

Table: Risk factors of development of VTE

Risk factor	**Comment**
Obesity (body mass index more than 30 kg/m^2).	The risk is significantly increased with increase of BMI. It is particularly important to consider in presence of other risk factors.
Long-term immobilization, serious surgical intervention, anu surgery on legs on legs or in pelvis area, neurosurgical intervention or extensive wounds. *Note:* temporary immobilization, including flights in the plane during > 4 hours, can also be VTE risk factor, particularly in women with other risk factors.	In these situations it is desirable to discontinue CHC administration (in case of planned surgery, at least, in four weeks before it) and not to renew during two weeks after complete remobilization. It is necessary to use other method of contraception to avoid accidental pregnancy. It is necessary to consider a possibility of antithrombotic therapy if CHC administration was discontinued beforehand.
VTE in family history (venous thromboembolism in close relatives or parents, especially in relatively young age, for example, under 50 years).	If genetic predisposition is suspected, patient should be directed to specialist for consultation before making a decision on administration of any CHC.
Other medical conditions, connected with VTE.	Cancer, systemic lupus erythematosis, hemolytic-uremic syndrome, chronic inflammatory bowel disease (Crohn's disease or ulcerative colitis) and sickle cell anaemia.
Age.	Particularly over 35 years.

It is necessary to consider the increased risk of thromboembolism development during pregnancy, and particularly during a 6-week postpartum period.

VTE symptoms (deep venous thrombosis and pulmonary embolism)

In case of symptoms emergence, woman is recommended to address emergency medical care and to report to medical specialist that she receives CHC. Symptoms of deep venous thrombosis (DVT):

- unilateral hypostasis of leg and/or foot or along a vein on a leg;
- pain or discomfort in legs which can be felt only in vertical position or when walking;
- temperature increase in the affected leg, redness or change of coloring of skin integument on legs.

Symptoms of pulmonary embolism (PE):

- sudden emergence of inexplicable difficulty or acceleration of breathing;
- sudden cough which can be followed by blood spitting;
- acute pain in thorax;
- severe dizziness;
- hurried or irregular heartbeat.

Some of these symptoms (e.g., "shortbreathing", "cough") are nonspecific and can be incorrectly interpreted as signs of other less severe events (e.g., respiratory tract infection).
Other signs of vascular occlusion can include: sudden pain, edema and mild blue discoloration of extremities.
If occlusion happens in the eyes, symptoms can vary from painless blurring of vision which can progress, to loss of vision. Sometimes loss of vision can suddenly occur.
Risk of development of arterial thromboembolism (ATE)
Epidemiological studies associate CHC administration with a higher risk of development of arterial thromboembolism (myocardial infarction) or cerebrovascular disorders (e.g., transient ischemic attack, disorder of cerebral circulation). Emergence of arterial thromboembolism can lead to lethal outcome.
Risk factors of ATE development
The risk of development of arterial tromboembolic events or cerebrovascular disorders in patients receiving CHC increases in women who have risk factors (see the table). Paulina medicinal preparation is contraindicated if several risk factors are present and if the ration between benefit and risk is considered negative.
Table: Risk factors of ATE development

Risk factor	**Comment**
Age.	Particularly over 35 years.
Smoking.	Women are not recommended to smoke, if they want to receive CHC. Women over 35, who continue smoking, should be strongly recommended to use other method of contraception.
Hypertension.	
Obesity (body mass index more than 30 kg/m^2).	The risk is significantly increased with increase of BMI. It is particularly important to consider in presence of other risk factors.
VTE in family history (venous thromboembolism in close relatives or parents, especially in relatively young age, for example, under 50 years).	If genetic predisposition is suspected, patient should be directed to specialist for consultation before making a decision on administration of any CHC.
Migraine.	Increase of frequency or severity of migraine (which can be precoursor of cerebrovascular disorder) during CHC administration can be the reason for immediate termination of contraceptive administration.
Other medical conditions, connected with pathology of vessels.	Diabetes mellitus, hyperhomocisteinemia, valvular diseases of the heart and atrial fibrillation, dislipoproteinemia and systemic lupus erythematosis.

ATE symptoms:
In case of symptoms emergence, woman is recommended to address emergency medical care and to report to medical specialist that she receives CHC.
Symptoms of cerebrovascular disorder:
- sudden weakness or loss of sensitivity of face, arms or legs, especially on one half of the body;
- sudden gait disturbance, dizziness, loss of balance or coordination of movements;

- sudden mental confusion, problem with speech and understanding;
- sudden one- or bilateral loss of vision;
- sudden, severe or long headache without clear reason;
- loss of consciousness or faint with epileptic seizure or without it.

Temporary symptoms show that the event represents transient ischemic attack (TIA).

Symptoms of myocardial infarction (MI):

- pain, discomfort, pressure, heaviness, feeling of compression or spreading in breast, in arm or behind breast;
- discomfort with irradiation in back, cheekbone, throat, arm, stomach;
- feeling of fullness, indigestion or asthma;
- cold sweat, nausea, vomiting or dizziness;
- strong weakness, disturbance or shortbreathing;
- hurried or irregular heartbeat.

Administration in children and adolescents

Administration of Paulina medicinal preparation is possible only after the onset of menarche.

The conditions and risk factors requiring special medical examination:

- Cardiac and renal diseases as active substance ethinylestradiol can cause liquid retention in the body.
- Phlebitis of superficial veins, a strong tendency to venous varices, problems of peripheral breakthrough bleedings as they can be associated with the development of thrombosis.
- Increased blood pressure (higher than 140/90 mm hg).
- Lipid storage disease. In patients with lipid storage disease, ethinylestradiol can cause gradual increase in triglycerides in plasma and therefore, pancreatitis and other complications.
- Sickle cell anaemia.
- Hepatic diseases in anamnesis.
- Disease of gall bladder.
- Migraine.
- Depression. It is necessary to find out whether depression is connected with the use of Paulina medicinal preparation. If necessary, other non-hormonal methods of contraception should be used.
- Decrease in tolerance of glucose/diabetes mellitus. As combined oral contraceptives can influence peripheral resistance to insulin and tolerance of glucose, a correction of dosage of insulin or other medicinal preparations for treatment of diabetes will possibly be required.
- Smoking.
- Epilepsy. If increase in epileptic seizures during administration of Paulina medicinal preparation is observed, it is necessary to consider an option of use of other methods of contraception.
- Sydenham's chorea.
- Chronic inflammatory bowel disease (Crohn's disease, ulcerative colitis).
- Hemolytic-uremic syndrome.
- Uterine fibroid.
- Otosclerosis.
- Long-term immobilization.
- Obesity.
- Systemic lupus erythematosis.
- Women over 40 years.

Mammary gland

Meta-analysis of 54 epidemiological studies showed that there is a little increase of relative risk (RR = 1.24) of development of breast cancer, diagnosed in the women who receive combined oral contraceptives at the present time. The increased risk gradually disappears within 10 years after

discontinuation of administration of combined oral contraceptives. As breast cancer is rarely observed in women under 40 years, the increase in the number of breast cancer diagnoses in patients receiving combined oral contraceptives at the present time, or those who have been administered recently, is insignificant in relation to the general risk of breast cancer.

Uterine cervix

The results of several epidemiological researches show that a long-term use of hormonal contraception by the women infected with human papilloma virus (HPV), is a risk factor of development of cervical cancer. However it is still not clear, how much other factors (e.g., distinctions in the number of sexual partners or use of mechanical methods of contraception) influence such result.

Liver

In rare cases it was reported on benign hepatic tumors during administration of combined oral contraceptives. In some cases such tumors led to life-threatening intra-abdominal bleeding. In case of severe abdominal pain upper, hepatomegalia or symptoms of intra-abdominal bleeding in the women receiving combined oral contraceptives, hepatic tumor should be considered during carrying out differential diagnosis.

The studies revealed an increased risk of development of cancer in hepatocytes during a long-term administration of combined oral contraceptives; however such tumor is developed extremely rarely.

Mammary glands

Increase in frequency of breast cancer diagnosis among the women receiving oral contraceptives has been recorded. As breast cancer is rare in women under 40 years, secondary to general risk of development of breast cancer, the number of additional cases of diseases is small. Causal relationship has been not established with administration of CHC.

Other conditions

Hypertension

It was reported about hypertension during administration of combined oral contraceptives, particularly by the patients of increased age and in case of prolonged use of preparation. The studies has shown that the frequency of hypertension increases depending on progesterone content. The women sho have the diseases connected with hypertension in the anamnesis should be recommended to use other methods of contraception.

Pancreatitis

In patients with hypertriglyceridemia or in the presence of this condition in family anamnesis increase of risk of pancreatitis development is possible during administration of CHC.

Hepatic dysfunction

Acute or chronic hepatic dysfunction can require discontinuation of CHC administration until hepatic function values return to normal. Recrudescent cholestatic jaundice and/or pruritus connected with cholestasis which is developed for the first time during pregnancy or during the previous administration of sex hormones, requires discontinuation of CHC administration.

Chloasma

Chloasma can sometimes emerge, especially in the women in whose anamnesis there was chloasma gravidarum. Women with predisposition to chloasma should avoid action of sunlight or ultraviolet radiation when they receive combined oral contraceptives.

Hereditary angioedema

In women with hereditary angioedema, exogenetic estrogen can cause or aggravate symptoms of angioedema.

Diabetes mellitus

Although CHC can affect peripheral insulin resistance and glucose tolerance, there are no proofs for need of change of therapeutic regimen in the patients with diabetes mellitus using a low-dosed CHC

(containing <0.05 mg of ethinylestradiol). Nevertheless, in the presence of diabetes mellitus it is necessary to be carefully observed, especially at early stages of CHC administration.

Lactase deficiency

Paulina at the average contains 60 mg of lactose in one tablet. Patients with intolerance of galactose, Lapp lactase deficiency or glucose-galactose malabsorption adhering to lactose-free diet, should consider this quantity.

Irregular menstruation

Breakthrough bleedings or spotting were observed during administration of combined oral contraceptives, especially in the first months of treatment. On this account, it is reasonable to estimate similar irregular menstruations only after three months of use of Paulina medicinal preparation. Therefore the information on type and dose of progesterone can be essential. When long-term or recrudescent irregular bleeding occurs after the previous regular cycles of menstruations, it is necessary to consider non-hormonal reasons and, also as well as during unusual vaginal bleeding, the appropriate diagnostic measures should be taken to exclude malignant disease and pregnancy. If both of these factors are excluded, it is possible to continue receiving Paulina medicinal preparation or to switch to the other hormonal contraceptive. Blood-tinged discharge between menstruations can evidence the reduced contraceptive effectiveness.

In some patients withdrawal bleedings may not occur during phase of administration of green inactive tablets. If Paulina medicinal preparation was received irregularly before the first absent withdrawal bleeding, or if withdrawal bleeding does not happen two times in succession, pregnancy should be excluded before further administration of medicinal preparation.

After discontinuation of administration of hormonal contraceptives, some time can be required before menstrual cycle normalization.

Decreased effectiveness

Contraceptive effectiveness of Paulina medicinal product can be decreased in the following cases:

- if administration of active tablet is missed,
- in cases of vomiting or diarrhea,
- during concomitant administration of some medicinal preparations.

Reasons for immediate discontinuation of administration

- Confirmed or suspected pregnancy.
- First signs of venous inflammation or symptoms of possible thrombosis (including retinal vein thrombosis), embolism or myocardial infarction.
- Constantly increased blood pressure (higher than 140/90 mm hg). Renewal of administration of combined oral contraceptive can be considered after normalization of blood pressure as a result of hypotensive treatment.
- Planned surgery (at least in 4 weeks) and/or long-term immobilization (e.g., after accidents). Administration of preparation should be renewed not earlier than in 2 weeks after complete remobilization.
- Emergence or aggravation of migraine.
- If headaches occur with unusual frequency, duration or intensity or if focal neurological symptoms suddenly appear (possibly the first symptom of stroke).
- Severe pain in stomach upper, hepatomegalia or signs of internal bleeding (possible symptoms of hepatic tumor).
- Developing of jaundice, hepatitis, pruritus generalisatus, cholestasis and abnormal values of hepatic. In case of restricted function of liver, steroid hormones are digested worse.
- Acute diabetes mellitus.
- Recent or recrudescent porphyria.

Effects on ability to drive and use machines

Paulina medicinal preparation does not influence the ability to drive and use machines.

Mode of administration and dosage

Medicinal preparation is administered orally daily, one tablet within 28 days approximately at the same time, if necessary, washing down with small amount of water.

Each subsequent package is started on the next day after completion of the previous package. Withdrawal bleeding usually begins on the 2-3 day after the beginning of administration of green placebo tablets (in the last row), and may not end before the beginning of use of new package.

Beginning of administration

In the absence of the history of hormonal contraceptives administration in the previous month, administration of tablets should be started on the first day of menstrual cycle (the first day of menstruation). In case of correct administration, contraception starts on the first day of use of medicinal preparation.

Administration of Paulina is possible on the 2-5 day of menstruation. In this case during the first 7 days of administration of tablets, additional non-hormonal methods of contraception should be used (barrier methods).

Upon switching from other contraceptives (combined oral contraceptives, vaginal ring, contraceptive patch). Depending on the type of previous contraceptive, administration of Paulina should be started either on the next day after usual break in administration of tablets following the use of the last active tablet, or on the next day after administration of the last inactive tablet (placebo) of combined oral contraceptive used earlier. When vaginal ring or contraceptive patch were used, then it is necessary to begin administration of Paulina on the next day after usual break without ring or patch.

Upon switching from "only progestagen" method ("mini pills", implants, injection forms) or from endometrial system. If earlier "mini-pills" have been administered, switching can be made in any day. Transition from implant or endometrial system should happen at the date of their removal. After administration of injection form - on the day when the next injection should be made. Anyway, during the first 7 days of administration of Paulina medicinal preparation, a non-hormonal method of protection should be used (barrier method).

After abortion in the first trimester of pregnancy, administration of Paulina can be started immediately. In this case, there is no need for taking additional measures of contraception.

After the act of delivery or abortion in the second trimester of pregnancy, administration should be initiated not earlier than in 21-28 days after the delivery for not nursing mothers or after abortion in the second trimester of pregnancy. During the first 7 days of administration of tablets, it is necessary to use additionally a non-hormonal method of contraception (barrier method).

If sexual contact has already happened, pregnancy should be excluded, or the first spontaneous menstruation should be waited for, before the beginning of administration of this medicinal product.

Administration of missed tablets

If from the moment of routine time of administration less than 12 hours passed, contraceptive protection is not decreased. All the following tablets should be taken in usual time.

If the tablet is taken after more than 12 hours from the moment of the last administration, contraception protection cannot be guaranteed. A possibility of pregnancy becomes the higher, the closer the forgotten tablet is to green placebo tablets.

If routine menstruation does not happen after administration of the last active tablet from package, pregnancy should be excluded before new package is started.

If the tablet is missed from the 1 to the 7 day of administration, then administration of the last missed tablet should be renewed as soon as possible, even if it means administration of 2 tablets in one day.

Further administration of tablets happens in usual time. In addition, it is necessary to use a non-hormonal method of contraception during the next 7 days.

If the tablet is missed only once from the 8 to the 14 day of administration, there is no need to use additional methods of contraception. If more than one tablet is missed, prior to the following withdrawal bleeding, it is necessary to use an additional non-hormonal method of contraception.

If the tablet is missed from the 15 to the 24 day of administration, the risk of decrease in contraceptive effect is inevitable because of the coming break in administration of active tablets. In this case, it is necessary to adhere to one of two schemes strictly:

If the tablet is missed from the 15 to the 24 day of administration, the risk of decrease in contraceptive effect is inevitable because of the coming break in administration of active tablets. In this case, it is necessary to adhere to one of two schemes strictly:

Scheme 1. If from the moment of omission of the tablet and to the last active tablet from the current blister pack, than 7 tablets remain, it is necessary to start a new blister pack instead of receiving green placebo tablets. At the same time withdrawal bleeding will be absent, until the second package ends, however withdrawal bleedings or spotting can be observed.

Scheme 2. As an alternative, administration of tablets from the current package can be discontinued, and administration of green placebo tablets can be started. After administration of green placebo tablets within 7 days, including days of omission of tablets, administration from new blister pack can be started.

Administration during gastrointestinal disorders

In a case vomiting or severe diarrhea during the first 4 hours after administration of Paulina medicinal preparation, absorption of active components can be not full, and additional contraceptive measures should be used. In these cases it is necessary to follow the rules of administration in case of omission of one tablet. If it is necessary to adhere to routine schedule of administration of tablets, additional tablet from other package should be administered. In case of continuous or recrudescent gastrointestinal disorders, additional non-hormonal methods of contraception should be used.

Delay of the beginning of withdrawal bleeding

To delay the beginning of menstruation, administration of active tablets should be continued from a new package, instead of green placebo tablets. Menstruation can be prolonged on any desired term until the end of active tablets from the second package. During this time, breakthrough bleedings or spotting can be observed. After administration of the following green placebo tablets, administration can be continued as usual.

Adverse effects

Common adverse reactions (≥1/100 to <1/10):

Nervous system disorders: headache.

Reproductive system disorders: breast tenderness and swelling.

Uncommon adverse reactions (≥1/1000 to <1/100):

Cardiovascular system disorders: hypertension, hypotension.

Gastrointestinal tract disorders: abdominal pain, nausea, vomiting, diarrhea, hyperorexia.

Skin and subcutaneous tissue disorders: acne, pruritus, alopecia, rash.

Reproductive system disorders: vaginitis, vulvovaginitis, vaginal candidiasis, irregular menstrual bleedings, parent bleedings, breast augmentation, edema of mammary gland, dysmenorrhea, vulval discharge, ovarian cyst, pain in pelvis..

General disorders: fatigability, fluid retention, change of body mass.

Rare adverse reactions (≥1/10000 to <1/1000):

Immune system disorders: salpingo-oophoritis, infections of urinary tract, cystitis, mastitis, cervicitis, fungal infections, herpes, influenza, bronchitis, sinusitis, upper respiratory tract infections, viral infections, allergy, asthma..

Ear and labyrinth disorders: sudden hearing loss, buzzing in ears, dizziness, diminished hearing.

Eye disorders: eye dryness, eye irritation, oscillopsia, visual loop.
Blood circulatory system disorders: anemia.
Endocrine disorders: virilism.
Nervous system disorders: depression, mental deterioration, insomnia, sleep disorders, aggression, ischemic stroke, cerebrovascular disorders, dystonia. Cardiovascular system disorders: tachycardia, thrombophlebitis, venous / arterial thromboembolism, pulmonary embolism, diastolic hypertension, orthostatic hypotension, hyperemia, varicosity.
Respiratory system disorders: overventilation.
Gastrointestinal tract disorders: gastritis, enteritis, dyspepsia.
Skin and subcutaneous tissue disorders: allergic dermatitis, atopic dermatitis, eczema, psoriasis, hyperhidrosis, chloasma, discoloration of skin/hyperpegmentation, seborrhea, dandruff, hirsutism, skin nevus.
Supporting-motor system disorders: backache, myalgia, extremity pain.
Reproductive system disorders: uterine neck dysplasia, adnexal cysts, cyst of mammary gland, fibrocystic mastopathy, dyspareunia, galactorrhea, menstrual disorders.
General disorders: thorax pain, peripheral hypostasis, influenza like illnesses, hyperthermia.
Laboratory findings: increase of level of blood triglycerides, hypercholesteremia.
Congenital and hereditary defects: asymptomatic manifestation of polymastism.
Adverse reactions with unknown frequency:
Eye disorders: intolerance of contact lenses.
Skin and subcutaneous tissue disorders: urticaria, erythema nodosum, erythema multiform.
Nervous system disorders: mood swings, change of libido.
Reproductive system disorders: secretion from mammary glands.
General disorders: fluid retention in the body.
(for more details see "*Special instructions*").

Overdose

During overdose there can be the following symptoms: nausea, vomiting, spotting or metrorrhagia. There is no specific antidote, it is necessary to carry out symptomatic treatment.

Interaction with other medicinal preparations

Concomitant use of Paulina medicinal preparation with some other medicinal preparations can either increase, or decrease concentration of ethinylestradiol and dienogest in blood serum. Concentration decrease can lead to more frequent breakthrough bleedings, failures in menstruation cycle, and decrease of contraceptive effectiveness of Paulina medicinal preparation. Increased level of ethinylestradiol/ dienogest can lead to the increase of frequency of emergence and higher intensity of adverse reactions.
Medicinal preparations decreasing concentration of ethinylestradiol/ dienogest in blood serum
- medicinal preparations increasing intestinal peristalsis, e.g. metoclopramide;
- medicinal preparations inducing microsomal hepatic enzymes, such as rifampicin, rifabutin, anticonvulsion drugs (such as barbexaclone, carbamazepine, oxcarbazepine, phenytoin, primidone, topiramate and felbamate), griseofulvin, modafinil, St. John's Wort (Hypericum perforatum). It was reported that HIV protease inhibitors (e.g., ritonavir), and non nucleoside reverse transcriptase inhibitor (e.g., nevirapine), and combinations of both, can influence hepatic metabolism;
- several antibiotics (e.g., ampicillin, tetracyclin).

In case of simultaneous treatment by the specified medicinal products and Paulina, additional non-hormonal method of contraception should be used throughout the treatment and within 7 days after its discontinuation.

For medicinal products reducing concentration of sex steroid hormones in blood serum by induction of microsomal hepatic enzymes, additional non-hormonal method of contraception should be used up to 28 days after discontinuation of their administration. If use of such medicinal preparations continues for a longer period, than the last tablet in blister pack of Paulina ends, a new blister pack should be started immediately, without usual phase of administration of green placebo tablets.

If long-term treatment is required with these medicinal preparations, non-hormonal methods of contraception should be used.

Medicinal preparations increasing concentration of ethinylestradiol/ dienogest in blood serum

- medicinal preparations which inhibit sulphating of ethinylestradiol in gastrointestinal wall, e.g. ascorbic acid or paracetamol;
- atorvastatin (increases ethinylestradiol PPK by 20%);
- pharmaceuticals which inhibit microsomal hepatic enzymes, such as antimicotic drugs on the basis of imidasole (e.g., fluconazole), indinavir and troleandomycin.

The influence of Paulina medicinal preparation on metabolism of other medicinal preparations:

- by inhibition of microsomal enzymes that leads to increased concentration in blood serum of such active substances as diazepam (and some other benzodiazepines), cyclosporine, theophyllin and glucocorticoids;
- by induction of glucuronidation of liver that leads to the increased concentrations in blood serum, e.g., of clofibrate, paracetamol, morphine, lorazepam (as well as some other benzodiazepines) and lamotrigine.

The studies in-vitro showed what dienogest in this concentration does not inhibit enzymes of cytochrome P450 system, so from this side no adverse reactions are expected.

Information on each indicated medicinal preparation should be checked regarding possible interactions with Paulina.

Changes in laboratory values

Administration of combined oral contraceptives can influence the results of some laboratory values, including liver, thyroid gland, adrenal glands and kidneys function tests, level of transport proteins in plasma, e.g. globulin binding corticosteroid and fractions of lipids/lipoproteins, values of carbohydrate metabolism, parameters of coagulation and fibrinolysis. Character and degree of this event partially depends on a dose of administered hormones.

Storage conditions and shelf-life

Protect from light; store at a temperature not exceeding 25 °C.

Keep out of the reach of children.

Shelf life is 3 years. Do not use after termination of shelf life specified on the package.

Prescription status

Medicinal preparation is on prescription.

Package

28 tablets (21 white tablet with active substances + 7 white inactive tablets) in blister pack. 1, 2, or 3 blisters with a package insert in cardboard package.

Information on manufacturer

Manufactured by: Laboratorios Leon Farma, S.A, Spain

Packed by: JLLC “TriplePharm”, Minskaya St., 2B, 223141, Logoysk, Minsk region, Republic of Belarus,

ph./fax: (+375) 1774 43 181, e-mail: triplepharm@gmail.com