Ministry of Health of the Republic of Belarus

Package leaflet

Stamp:
JLLC "TriplePharm",
Development, Registration and Standardization Department
Controlled Copy

Ivonna Forte
film-coated tablets, 3 mg/0.03 mg

cl. No.11 dated 12.11.2015

Trade name Ivonna Forte
International nonproprietary name Drospirenone/Ethinylestradiol
Pharmaceutical form Film-coated tablets, 3 mg/0.03 mg
Description Round biconvex yellow coated tablets

Stamp:
AGREED BY
Ministry of Health of the Republic of Belarus
Order of the Ministry of Health of the Republic of Belarus
dated 25.11.2015, No. 1178

Composition per 1 tablet
Active substances:
Drospirenone – 3 mg
Ethinylestradiol – 0.03 mg
Excipients: lactose monohydrate, corn starch, peptized corn starch, crospovidone (Plasdone XL-10, B type), crospovidone (Plasdone XL-10, A type), povidone K-30 (E1201), polysorbate 80 (E433), magnesium stearate (E470).
Coat composition: polyvinyl alcohol, titan dioxide (E171), macrogol (E3350), talc (E553), iron (III) oxide yellow (E172).
Pharmacotherapeutic group. Hormonal contraceptives for systemic use. Combinations of progestagens and estrogens.
ATC-code G03AA12
Pharmacological properties
Pharmacodynamics
Ivonna Forte is a medicinal preparation for oral contraception consisting of estrogen - ethinylestradiol and progestagen - drospirenone.
Contraceptive action of Ivonna Forte is based on the combined interaction of various factors, the most important of which are suppression of ovulation and change of endometrium.
In therapeutic doses drospirenone has antiandrogenic and moderate antimineralocorticoid properties. Drospirenone doesn't show estrogenic, glucocorticoid and antiglucocorticoid effects. Owing to these properties, pharmacological profile of drospirenone is close to the properties of natural hormone progesterone.
Pharmacokinetics
Drospirenone
Absorption
After oral administration, drospirenone is quickly and almost completely absorbed. The highest concentration in blood serum is reached approximately in 1-2 h and is about 38 ng/ml. Bioavailability is 76-85%. Simultaneous food ingestion doesn't influence bioavailability of drospirenone.
Distribution
After oral administration, the level of drospirenone in serum is decreased with the final half-life period 31 hour. Drospirenone binds to serumal albumine and doesn't bind to sex hormone binding globulin, or corticosteroid-binding globulin. Only 3-5% of general concentration of drospirenone in serum is present as free steroid. The increase of sex hormone binding globulin induced by ethinylestradiol doesn't influence linking of drospirenone with proteins of serum. The average apparent volume of distribution of drospirenone is 3.7±1.2 l/kg.
Metabolism
Drospirenone is metabolized extensively. The main metabolites in plasma are acid forms of drospirenone which is formed as a result of opening of lactone ring and 4,5-dihydro-drospirenone-Z-sulphate. Both metabolites are formed without participation of P450 system. Drospirenone in insignificant degree is

metabolized by cytochrome P450 3A4 and demonstrates an ability in vitro to inhibit this enzyme, as well as cytochrome 450 1A1, cytochrome P450 2C9 and cytochrome P450 2C19.

Elimination

The rate of metabolic clearance of drospirenone in serum is 1.5±0.2 ml/min. In unchanged form drospirenone is eliminated only in trace quantities. Metabolites of drospirenone are is excreted with faeces and urine in the ratio about 1.2:1.4. The half-life period for excretion of metabolites with urine and faeces is about 40 hours.

Equilibrium concentration

During cyclic treatment maximum equilibrium concentration of drospirenone in serum is approximately 70 ng/ml, and it is reached in around 8 days of administration of medicinal preparation. The increase in concentration of drospirenone in blood serum approximately by 3 times was noted owing to accumulation which resulted from the rate of half-life period in terminal phase and dosing interval.

Pharmacokinetics in special clinical cases

Equilibrium concentration of drospirenone in blood serum in women with mild renal failure (clearance of creatinine 50-80 ml/min) is comparable with the corresponding indicators in women with normal function of kidneys. In women with moderate renal failure (clearance of creatinine 30-50 ml/min.), the level of drospirenone in blood serum was observed by 37% higher than in women with normal function of kidneys. Drospirenone treatment was well tolerated in women with mild and moderate renal failure. Reception of drospirenone didn't have clinically significant influence on concentration of potassium in blood serum.

Drospirenone is well tolerated by the patients with mild and moderate hepatic failure (class B according to Child-Pugh score). In the study of single dose administration, drospirenone clearance in case of oral administration by the patients with moderate hepatic failure decreased by 50% in comparison with women with normal hepatic function. There were no distinctions in concentration of potassium in blood serum in the studied groups. Even in case of diabetes mellitus and concomitant treatment by spironolactone, no increase in concentration of potassium in blood serum to the level above standard was noted.

Ethinylestradiol

Absorption

After oral administration, ethinylestradiol is quickly and almost completely absorbed. The highest concentration in blood serum after administration of 30 μg is about 100 pg/ml, and is reached in 1-2 hours after oral administration. Ethinylestradiol undergoes extensive presystemic metabolism at “first penetration”, which has more individual variability. Absolute bioavailability is approximately 45%.

Distribution

Apparent volume of ethinylestradiol distribution is 5l/kg, and binding to serumal albumin is approximately 98%. Ethinylestradiol causes globulin synthesis in liver, binding sex hormones, and corticosteroid-binding globulin. During the treatment with 30 μg of ethinylestradiol, globulin concentration binding sex hormones in plasma increases from 70 to 350nmol/l.

Ethinylestradiol is excreted in small amount with breast milk (0.02% of dose).

Metabolism

Ethinylestradiol is completely metabolized (metabolic clearance rate in blood plasma is 5 ml/min/kg).

Elimination

Ethinylestradiol is practically not excreted in unchanged form. Metabolites of ethinylestradiol are excreted with urine and bilis in the ratio 4:6. A half-life period for metabolites excretion is approximately 1 day. Elimination half-life period is 20 hours.

Equilibrium concentration

Equilibrium concentration status is achieved during the second half of treatment cycle, and serum level of ethinylestradiol is increased approximately in 1.4-2.1 times.

Indications

Oral contraception.

The assessment of individual risk factors in woman is necessary for making decision on Ivonna Forte administration, in particular concerning venous thromboembolism (VTE). Besides, the risk of development of VTE during Ivonna Forte administration should be compared to the risk connected with other combined hormonal contraceptives (CHC) (see the section “Precautionary measures”).

Contraindications

CHC shouldn't be used, in case of presence of any conditions / diseases which are listed below:

- hypersensitivity to any of components of Ivonna Forte medicinal product;
- venous thromboembolism 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 pre-existing conditions (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 due to presence of one of serious risk factors (diabetes with vascular complications, severe form of hypertensive disease, severe form of dislipoproteinemia);
- presence in history of hepatic diseases if indicators of hepatic function haven't returned to normal, hepatic tumors;
- severe or acute renal failure;
- revealed or suspected hormone-dependent malignant diseases (e.g., of genitals or mammary gland);
- 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 Ivonna Forte during pregnancy is contraindicated.

In case of pregnancy detection during Ivonna Forte administration, medicinal product should be immediately cancelled. Extensive epidemiological studies haven't revealed the increased risk of development of defects in the children born by the women who received CHC before pregnancy or teratogenic action in cases of careless administration of CHC during pregnancy.

CHC administration can decrease the amount of breast milk and change its composition, therefore, it is not recommended to receive medicinal preparation during lactation period.

Effects on ability to drive and use machines has been not studied by the present time. However, a long-term experience of CHC administration evidences the absence of influence of their administration on the ability to drive and use machines.

Special instructions

With care

During prescription of Ivonna Forte medicinal preparation in each individual case, risk factors should be considered, particularly the risk of venous thromboembolism (VTE), and differences in the degree of VTE among CHC (see article "Cardiovascular diseases" in the section "Precautionary measures").

It is necessary to weigh carefully potential risk and the expected advantage of CHC administration in each individual case in the presence of the following diseases / conditions and risk factors:

- risk factors of development of thrombosis and thromboembolism: smoking; obesity; dyslipoproteinemia, arterial hypertension; migraine; valvular heart disease; long-term immobilization, serious surgical interventions, extensive trauma; genetic predisposition to thrombosis (thromboses, myocardial infarction or disorder of cerebral circulation at a young age in any of immediate family members); the age above 35 years;
- other diseases in case of which disorders of peripheral blood circulation can be noted: diabetes; systemic lupus erythematosis; hemolytic uraemic syndrome; Crohn's disease and nonspecific ulcerative colitis; sickle-cell anaemia; phlebitis of superficial veins;
- genetic angioneurotic edema;
- hypertriglyceridemia;
- hepatic disorders;
- the diseases which for the first time occurred or aggravated during pregnancy or secondary to the history of reception of sex hormones (for example, jaundice and/or pruritus connected with cholestasis, cholelithiasis, otosclerosis with impairment of hearing, porphyria, herpes gestationis, Sydenham's chorea);
- postpartum period.

If any of the conditions or risk factors provided below is present now, it is necessary to discuss possible advantage and risk of administration of Ivonna Forte with woman. In case of weighting or the first development of any of these conditions or risk factors, the woman should consult a doctor to make the decision on drug withdrawal.

Cardiovascular diseases

In case of possible or established *venous thromboembolism* (VTE) or *arterial thromboembolism* (ATE), administration of CHC should be stopped. In case of the beginning of anticoagulant therapy, it is necessary to consider an option of swithing to a more suitable method of contraception as anticoagulant therapy has teratogenic effect (coumarins).

Administration of any CHC increases the risk of emergence of VTE in comparison with the case of non-use of this group of medicinal agents. According to the available data, medicinal preparations containing, norgestimate and norethisterone are associated with the lowest risk of emergence of VTE. During administration of other medicinal products, such as, for example, Ivonna Forte, the risk increases twofold. The decision on administration of any medicinal preparation including those having the lowest risk of emergence of VTE, should be made only after discussion with the woman of possibility of VTE emergence, as well as the fact that risk of disease is the highest in the first year of administration of medicinal preparation. Also there is the data that the risk increases in case of renewal of CHC administration after a break in reception for 4 weeks and more.

In women who don't receive CHC, the risk of development of VTE is 2 of 10000 women per year. However, this risk can considerably increase depending on individual risk factors of each woman. It is established, that in women receiving CHC containing drospirenone the risk of development of VTE is 9 to 12 cases of 10000 women a year that is comparable to the risk 5 to 7 cases of 10000 women per year for levonorgestrel. In both cases the frequency of development of VTE is lower, than expected during pregnancy and in postpartum period. VTE can lead to death in 1-2% of cases. Very seldom during administration of CHC, thrombosis of other blood vessels can occur, for example, hepatic, mesenteric, renal, cerebral veins and arteries, retinal vessels. Symptoms of deep venous thrombosis (DVT) include the following: unilateral hypostasis of lower extremity or along a vein on a leg, pain or discomfort in a leg only in vertical position or when walking, local temperature increase in the affected leg, redness or change of coloring of skin integument on a leg.

Symptoms of pulmonary artery thromboembolism (PATE) lie in the following: laboured or hurried breathing; sudden cough, including with blood spitting; acute pain in thorax which can increase during deep breathing; anxious feeling; 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 more or less severe events (e.g., respiratory tract infections).

Other signs of vascular occlusion: sudden pain, edema and mild blue discoloration of extremities.

Signs of vascular occlusion of amphiblestrodes: painless blurring of vision, progressing up to loss of vision. Sometimes loss of vision can happen immediately. The risk of VTE emergence increases in women with additional risk factors: obesity (index of body mass is higher than 30 kg/sq.m); long immobilization, extensive surgical intervention, surgeries on legs or in pelvis area, neurosurgical intervention, extensive wounds; burdened familial history (VTE in close relatives at the age less than 50 years), other conditions connected with venous thromboembolism: cancer, systemic lupus erythematosis; hemolytic uraemic syndrome, chronic inflammatory disease of intestinal tract (Crohn's disease or ulcerative colitis) and sickle-cell anaemia; the age above 35 years.

The question of possible role of varicosity and superficial thrombophlebitis in development of VTE remains disputable.

During epidemiological studies it has been established that administration of CHC increases the risk of development of ATE.

Arterial thromboembolism can lead to stroke, vascular occlusion or myocardial infarction. Symptoms of stroke are as follows: sudden weakness or loss of sensitivity of face, arms or legs, especially on one half of the body, sudden mental confusion, problem with speech and understanding; sudden one- or bilateral loss of vision; sudden gait disturbance, dizziness, loss of balance or coordination of movements; sudden, severe or long headache without clear reason; loss of consciousness or faint with epileptic seizure or without it. Symptoms of myocardial infarction include: 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; cold sweat, nausea, vomiting or dizziness, strong weakness, disturbance or shortbreathing; hurried or irregular heartbeat. The following refers to the risk factors of development of ATE: age above 35 years; smoking, hypertension, obesity (index of body mass is higher than 30 kg/sq.m), burdened familial history (ATE in close relatives at the age less than 50 years), migraine, other diseases: diabetes, hyperhomocisteinemia, cardiac defect and atrial fibrillation, dislipoproteinemia and systemic lupus erythematosis.

It is necessary to consider the increased risk of development of tromboembolism during pregnancy and in puerperal period.

Disorders of peripheral blood circulation can also be observed during diabetes mellitus, systemic lupus erythematosis, hemolytic uraemic syndrome, chronic inflammatory disease of intestinal tract (Crohn's disease or ulcerative colitis) and sickle-cell anaemia.

Increase of the frequency and severity of migraine during administration of CHC (that can precede to cerebrovascular disorders) can be the reason for immediate termination of administration of these medicinal preparations.

The following refers biochemical indicators, indicating genetic or acquired predisposition to venous or arterial thrombosis: resistance to activated protein C, hyperhomocisteinemia, shortcoming antithrombin-III, deficiency of protein C, lack of protein S, antiphospholipidic antibodies (anticardiolipin antibodies, lupus anticoagulant).

During assessment of ratio of risk and benefit, it should be considered that adequate treatment of the corresponding condition can decrease the risk of thrombosis associated with it. Also it should be considered that risk of thromboses and tromboembolism during pregnancy is higher, than during administration of minipills (<0.05 mg of ethinylestradiol). Ivonna Forte medicinal preparation is contraindicated to women with several risk factors of development of VTE and ATE. If woman has more than one risk factors of venous or arterial thrombosis, increase in risk for more than the sum of individual risk factors - in that case the general risk should be estimated. If risk exceeds potential benefit in woman, reception of CHC is contraindicated.

Tumors

In several epidemiological studies it was reported on the increased risk of uterus neck cancer development during a long-term administration of CHC (more than 5 years). However the connection with administration of CHC has not been proved.

Meta-analysis of 54 epidemiological studies has shown that there is a slightly increased relative risk of development of breast cancer, diagnosed in women receiving CHC at the present time (relative risk is 1.24). The increased risk gradually disappears within 10 years after termination of CHC administration. As breast cancer rarely occurs in women under 40 years, increase in the number of breast cancer diagnoses in women receiving CHC at the present time, or those who received it recently, is small in comparison with the general risk of this disease. The connection of developments of breast cancer with CHC administration is not proved. The observed increase of risk can be also a consequence of careful supervision and earlier diagnosis of breast cancer in women receiving CHC. In women who have ever administered CHC, earlier stages of breast cancer have been revealed, than in women, who have never received them.

In rare cases secondary to CHC administration the development benign, and in extremely rare cases - malignant hepatic tumors, which in certain cases led to life-threatening intra-abdominal bleeding. It should be considered in case of emergence of severe pains in stomach, hepatomegalia or signs of intra-abdominal bleeding.

During CHC administration in more high doses (50 μg ethinylestradiol), risk of development of endometrium and ovarian cancer is decreased. Presence of such effect in low-dosed CHC is unknown.

Other conditions

Progestin component of Ivonna Forte - drospirenone - is an antagonist of aldosterone with potassium-sparing properties. In the most of cases an increase in potassium level is not expected. But in clinical trials in some of the women with mild or moderate degree of renal dysfunction, the concomitant reception of potassium-sparing medicinal preparations has slightly increased serum potassium levels during drospirenone administration. Therefore, it is recommended to check the level of serum potassium during the first administration cycle in women with renal failure, in whom serum potassium level prior to CHC administration was on the upper normal level, and who additionally administer potassium-sparing medicinal preparations.

In women with hypertriglyceridemia (or presence of this condition in family history), an increase of pancreatitis development risk is possible at the beginning of CHC administration.

Despite the fact that small increase of arterial pressure was noted in many women receiving CHC, clinically significant increases were rarely noted. Only in these exceptional cases the immediate termination of reception of medicinal preparation is reasonable. If during CHC administration permanent clinically significant increase of arterial pressure develops, it is necessary to withdraw medicinal product and to initiate treatment of arterial hypertension. CHC administration can be renewed after achievement of normal values of arterial pressure by means of hypotensive therapy. The following conditions are developed or aggravated both during pregnancy, and during CHC administration, but their connection with CHC administration is not proved: jaundice and/or pruritus, connected with cholestasis; formation of gallstones; porphyria; systemic lupus erythematosis; hemolytic uraemic syndrome; Sidengam's chorea; herpes gestationis; hearing loss, connected with otosclerosis.

In women with genetic forms of angioedema, exogenous estrogens can cause or worsen symptoms of angioedema. Acute or chronic hepatic dysfunction can demand withdrawal of medicinal preparations until hepatic function values do not return to normal. Recrudescent cholestatic jaundice which is developing for the first time during pregnancy or the history of sex hormones administration, require withdrawal of medicinal preparation.

Although CHC can affect the resistance to insulin and tolerance to glucose, patients with diabetes mellitus who receive low-dose CHC have no need of therapeutic regimen change (<0.05 mg of ethinylestradiol). However, women with diabetes mellitus should be observed carefully during administration of this medicinal product.

Chloasma can be sometimes observed, especially in women with the history of chloasma gravidarum. Women with tendency to chloasma during administration of Ivonna Forte medicinal preparation should avoid a long-term stay in the sunlight and exposure of an ultraviolet radiation.

Ivonna Forte contains 62 mg of lactose in one tablet. Patients with rare genetic intolerance of galactose, Lapp lactase deficiency or glucose-galactose malabsorption who are on a diet with controlled consumption of lactose, should consider this quantity.

Laboratory tests

Administration of CHC could affect the results of some laboratory tests, including biochemical parameters of liver, thyroid gland, adrenal glands and kidneys, content of proteins in plasma, values of carbohydrate metabolism, parameters of fibrillation and fibrinolysis. Alterations usually do exceed normal laboratory values. Drospirenone increases the activity of plasma renin and plasma aldosterone due to moderate antimineralocorticoid effect.

Decrease in effectiveness

Effectiveness of combined hormonal contraceptives can be reduced in the following cases: in case of omission of tablets, during vomiting and diarrhea or as the result of drug interaction.

Poor monitoring of menstrual cycle

Secondary to CHC administration, irregular bleedings can be observed (spotting or breakthrough bleedings), especially within the first months of administration. Therefore, an assessment of any irregular bleedings should be carried out only after adaptation period which is about three cycles.

If irregular bleedings repeat or develop after previous regular cycles, it is necessary to conduct careful examination to exclude malignant neoplasms or pregnancy.

In some women during the break in reception of tablets, withdrawal bleeding may not develop. If CHC are administered according to instructions, it is unlikely that woman is pregnant. Nevertheless, if before that CHC have been received irregularly, or if there are two sequent withdrawal bleedings, pregnancy should be excluded before continuation of medicinal preparation administration.

Additional information for special categories of patients

Children and adolescents: medicinal preparation is indicated only after the beginning of menarche. The available data do not assume dose correction in this group of patients.

Elderly patients: not applicable. Medicinal preparation is not indicated after the beginning of menopause.

Patients with hepatic disorders: Ivonna Forte medicinal preparation is contraindicated to women with serious hepatic diseases until the values of hepatic function return to normal (see the sections "Contraindications", "Pharmacodynamics" and "Pharmacokinetics").

Patients with renal disorders: Ivonna Forte medicinal preparation is contraindicated to women with severe renal failure or with acute renal failure (see the sections "Contraindications", "Pharmacodynamics" and "Pharmacokinetics")

Medical examinations

Prior to the beginning or renewing of Ivonna Forte medicinal preparation administration, it is necessary to study the past medical history, the family anamnesis of woman, to conduct careful general medical and pelvic examination, to exclude pregnancy. The scope of investigations and frequency of control follow-ups should be based on the existing standards of medical practice, considering as required individual peculiarities of each patient. As a rule, blood pressure and heart rate are measured, body mass index is determined, the state mammary glands, abdominal cavity and pelvic organs are checked, including cytological analysis of uterine cervix epithelium (Papanicolaou test). Usually control follow-ups should be conducted at least 1 time in 6 months.

It is important to pay attention of women to information on arterial and venous thromboembolism, including risk of formation of blood clots during Ivonna Forte medicinal preparation administration in comparison with other CHC; symptoms of arterial and venous thromboembolisms; the factors increasing the risk of formation of blood clots and necessary actions in case of suspected thrombosis.

It is necessary to instruct woman about the need to read carefully a package insert and to follow it accurately.

It is necessary to warn woman about the fact that hormonal contraceptives do not protect from HIV infection (AIDS) and other sexually transmissible diseases.

Mode of administration and dosage

Medicinal preparation is administered orally daily, one tablet within 21 days, approximately at the same time, if necessary, washing down with small amount of water. Withdrawal bleeding usually begins on the 2-3 day after administration of the last tablet from package and may not end prior to administration of new package. Each subsequent package is initiated after a seven-day break in administration.

Beginning of administration

In the absence of the history of hormonal contraceptives administration in the previous month, administration of tablets is begun on the first day of menstrual cycle (the first day of menstruation).

Upon switching from other contraceptives (combined oral contraceptives, vaginal ring, contraceptive patch) Ivonna Forte administration should be started on the next day after administration of the last active tablet of CHC used earlier, but not later than the next day after a routine 7-day break or administration of

the last inactive tablet (placebo) used earlier. If earlier vaginal ring or contraceptive patch were used, Ivonna Forte administration should be initiated at the date of their removal, but not later than the day when a new ring should be introduced or a new patch should be pasted.

Upon switching from "only progestagen" method ("mini pills", implants, injection forms) or from progestogen-releasing endometrial system. If earlier "mini-pills" have been administered, switching can be made on any day. Switching 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 Ivonna Forte medicinal preparation, a non-hormonal method of contraception (barrier method) should be used.

After abortion in the first trimester of pregnancy, Ivonna Forte administration can be immediately started. 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. The missed tablet should be taken as soon as possible, subsequent tablets should be administered in usual time.

If from the moment of routine time of administration more than 12 hours passed, contraceptive protection cannot be guaranteed. Medicinal product administration should never be interrupted for more than 7 days. 7 days of continuous administration of tablets are necessary to achieve adequate suppression of pituitary-hypothalamic-ovarian regulation. If routine menstruation does not come after administration of the last tablet from package, pregnancy should be excluded before the beginning of new package. In case of omission of administration of tablets, administration is carried out as follows:

If the tablet is missed from the 1 to the 7 day of administration, then administration of the last missed tablet should be proceed as soon as possible even if it means administration of 2 tablets at the same time. Further administration of tablets takes place in usual time. In addition, it is necessary to use a non-hormonal method of contraception during the next 7 days. If within 7 days before the omission of tablet administration, there was a sexual contact, it is necessary to consider a possibility of pregnancy. The more tablets are missed and the closer the omission of tablet administration is to a 7-day break, the higher the possibility of pregnancy beginning is.

If the tablet is missed from 8 to 14 day of administration, it is necessary to take the missed pill as soon as possible even if it means administration of 2 tablets at the same time. Further administration of tablets happens in routine time. If in the previous 7 days all the pills have been received correctly, there is no need to use the additional methods of contraception. If more than one tablet is missed, before the next withdrawal bleeding, a non-hormonal method of contraception should be used additionally.

If the tablet is missed from the 15 to the 21 day of administration, the risk of decrease in contraceptive effect is inevitable because of the forthcoming break in administration of tablets. In this case, it is necessary to adhere strictly to one of two schemes given below. At the same time, if within 7 days before the omission of pill, all tablets have been received correctly, there is no need to use additional non-hormonal methods of contraception. If not, then it is necessary to adhere to one of two schemes and to use additional methods of contraception in the next 7 days.

Scheme 1. Administration of the last missed tablet should be preceded as soon as possible, even if it means administration of 2 tablets simultaneously. Then the following tablets are administered in usual time. The next package should be started without a seven-day break in administration. Thus, withdrawal bleeding will be absent until the second package ends, however, breakthrough bleeding and spotting can be observed.

Scheme 2. As an alternative, administration of tablets from the current package can be discontinued for 7 days, including the days of tablets omission, Then administration of tablets from the new package should be started.

If tablet administration has been missed, and during the break in administration there is no withdrawal bleeding, pregnancy should be excluded.

Administration during gastrointestinal disorders

In case of vomiting or severe diarrhea during the first 4 hours after administration of Ivonna Forte medicinal preparation, absorption of active components can be not full, and additional contraceptives 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 the other package should be administered. In case of continuous or recrudescent gastrointestinal disorders, methods of contraception should be used additionally.

Delay of the beginning of withdrawal bleeding

To delay the beginning of menstruation, administration of tablets should be continued from a new package immediately after the current one ends. Menstruation can be delayed on the desired term until the end of administration of tablets from the second package. During this time breakthrough bleedings or spotting can be observed. The routine scheme of administration can be renewed after a seven-day break in administration of tablets.

To transfer the beginning of menstruation on the other day of the week, a new package should be started during a seven-day break. The shorter the interval between administration of new and current packages is, the higher the risk of absence of withdrawal bleeding, breakthrough bleeding and spotting is during administration of the next package.

Adverse effects

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

Mental disorders: depression, depressed mood.

Nervous system disorders: headache.

Cardiovascular system disorders: migraine.

Gastrointestinal tract disorders: nausea.

Reproductive system and mammary glands disorders: menstrual disorders, breakthrough bleeding, breast tenderness, increase of mammary glands, vulval discharge, vulvovaginal candidiasis.

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

Mental disorders: decrease or strengthening of libido.

Cardiovascular system disorders: hypertension, hypotension.

Gastrointestinal tract disorders: vomiting, diarrhea.

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

Reproductive system and mammary glands disorders: increase of mammary glands, vaginitis.

General disorders: hypostasis, increase or decrease of body mass.

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

Immune system disorders: hypersensitivity reactions, asthma.

Cardiovascular system disorders: venous or arterial thromboembolism.

Ear disorders: diminished hearing.

Skin and subcutaneous tissue disorders: erythema nodosum, erythema multiforme.

Reproductive system and mammary glands disorders: increase of mammary glands.

During CHC administration the risk of development of venous, thrombotic and thromboembolic events is increased, including myocardial infarction, stroke, transitory ischaemic attack, venous thrombosis and pulmonary embolism.

In the women receiving CHC the following serious adverse reactions were observed (see the section "Precautionary measures"): venous thromboembolic events; arterial thromboembolic events; hypertension; hepatic tumors; conditions, which are developing or aggravated during CHC administration, but their connection with administration of medicinal preparation has not been proved: Crohn's disease, ulcerative colitis, epilepsy, uterine fibroid, porphyria, systemic lupus erythematosis, herpes gestationis, Sydenham's chorea, hemolytic uraemic syndrome, jaundice and/or pruritus, associated with cholestasis; chloasma; during acute or chronic hepatic dysfunction there can be a need to discontinue administration until hepatic function values return to normal. In women with hereditary angioedema administration of estrogen can cause or aggravate its symptoms.

The rate of breast cancer diagnosing in women receiving CHC is slightly increased. As breast cancer is rarely observed in women under 40 years, increase in number of diagnoses of breast cancer in women receiving CHC is insignificant in relation to common risk of this disease.

Overdose

There were no reports on symptoms of medicinal preparation overdose. According to the experience of CHC administration, during overdose the following symptoms can emerge: nausea, vomiting, spotting or metrorrhagia. There is no specific antidote, it is necessary to carry out symptomatic treatment.

Interaction with other medicinal preparations

Interaction between oral contraceptives and other medicinal preparations can lead to breakthrough bleeding and/or decrease in reliability of contraception.

Use of medicinal preparations which induce microsomal hepatic enzymes with Ivonna Forte can lead to increase in clearance of sex hormones (phenytoin, barbiturates, primidone, carbamazepine, rifampicin, ritonavir, bosentan and the drugs for treatment of HIV infection (ritonavir, nevirapine), possibly oxcarbazepine, topiramate, felbamate, griseofulvin, the drugs containing St. John's wort). Maximal enzyme induction is usually observed within 10 days, but can remain for, at least, 4 weeks after the termination of medicinal therapy. According to separate studies, administration of several antibiotics (penicillins, tetracyclines) can reduce contraceptive action. Mechanism of this effect is unknown.

During a short treatment course the abovementioned classes of drugs, except rifampicin, it is necessary to use an additional barrier method of contraception during the concomitant treatment and within 7 days after its termination. During rifampicin administration and within 28 days after its discontinuation, it is necessary to use additional barrier method of contraception.

Patients, receiving the drugs inducing liver enzymes for a long time, should consider a possibility of administration of others reliable non-hormonal methods of contraception.

If administration of concomitant medicinal preparation ends later, than the tablets in current package of Ivonna Forte, then it is necessary to begin administration of tablets from a new package without a seven-day break.

The main metabolites of drospirenone are formed in blood plasma without participation of cytochrome P450 system therefore influence of inhibitors of cytochrome P450 system on drospirenone metabolism is unlikely.

CHC can influence metabolism of other medicinal products which leads to the increase (cyclosporine) or to decrease (lamotrigine) of their concentration in plasma and tissues.

On the basis of the data obtained in the studies in vitro, and the data of in vivo studies with participation of female volunteers receiving omeprazole, simvastatin and midazolam as markers, it was established that drospirenone influence in a 3 mg dose on metabolism of other medicinal products was unlikely.

There is a theoretical possibility of increase of serum potassium level in women receiving Ivonna Forte simultaneously with other medicinal preparations. The concomitant administration of Ivonna Forte and antagonists of aldosterone or potassium-sparing diuretics was not studied. In similar cases it is recommended to determine concentration of potassium in blood serum during the first cycle of administration of Ivonna Forte. Information on each prescribed medicinal product should be checked regarding possible interactions with Ivonna Forte.

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

21 tablets in blister. 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