Ministry of Health of the Republic of Belarus

Package leaflet

Ivonna
film-coated tablets, 3 mg/0.02 mg

Stamp:
AGREED BY
Ministry of Health of the Republic of Belarus
Order of the Ministry of Health of the Republic of Belarus
dated 19.11.2015, No. 1158

cl. No.11 dated 12.11.2015
Stamp:
JLLC "TriplePharm",
Development, Registration and Standardization Department
Controlled Copy

Trade name Ivonna
International nonproprietary name Drospirenone/Ethinylestradiol
Pharmaceutical form Film-coated tablets, 3 mg/0.02 mg
Description
Active tablet: Round biconvex pink coated tablets.
Placebo tablet: Round biconvex white coated tablets.
Composition per 1 tablet
Active substances:
Drospirenone – 3 mg
Ethinylestradiol – 0.02 mg
Excipients: lactose monohydrate, corn starch, peptized corn starch, povidone K-30 (E1201), croscarmellose sodium, polysorbate 80 (E433), magnesium stearate (E470b).
Coat composition: polyvinyl alcohol, titan dioxide (E171), macrogol 3350, talc (E553b), iron (III) oxide yellow (E172).
Composition per 1 placebo tablet
Active substances: absent
Excipients: lactose anhydrous, povidone K-30 (E1201), magnesium stearate (E470b).
Coat composition: polyvinyl alcohol, titan dioxide (E171), macrogol 3350, talc (E553b).
Pharmacotherapeutic group. Hormonal contraceptives for systemic use. Combinations of progestagens and estrogens.
ATC-code G03AA12
Pharmacological properties
Pharmacodynamics
Ivonna is an oral contraceptive containing ethinylestradiol and progestagen drospirenone.
Contraceptive action of Ivonna 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, the pharmacological profile of drospirenone is close to the properties of natural hormone progesterone.
During correct administration Pearl Index (number of pregnancies for 100 women per year) is 0.41 (the highest bilateral 95% confidence interval 0.85). General Pearl Index is 0.80 (the highest bilateral 95% confidence interval 1.30). In the study of ovulation suppression during 3 cycles, comparison of a 24-day and a 21-day dosage regimen of 3 mg drospirenona/0.20 mg ethinylestradiol as a result of which a 24-day regimen had a greater influence on suppression of follicular development. After the intended mistakes in administration of a drug dose on the third cycle of therapy, in most part of women who were on a 21-day dosage regimen, activity of ovaries was observed, including ovulation ("ovulation run"), in comparison with women who were on a 24-day dosage regimen. Activity of ovaries after the end of therapy returned to the values which had been before therapy in 91.8% of the women who were on a 24-day dosage regimen.

Two multicenter, double blind, randomized placebo-controlled studies were carried out for assessment of effectiveness and safety of administration of combination of ethinylestradiol 0.02 mg / drospirenone 3 mg in women with moderate acne. After 6 months of therapy, in comparison with placebo, ethinylestradiol / drospirenone demonstrated statistically relevant higher reduction by 15.6% of inflammatory foci (49.3% versus 33.7%), by 18.5% of the noninflammatory centers (40.6% versus 22.1%) and by 16.5% of total number of foci (44.6% versus 28.1%). Besides, more subjects, by 11.8%, reached level "clear" or "almost clear" according to Investigator Static Global Assessment scale (ISGA) (18.6% versus 6.8%). The combination of ethinylestradiol and drospirenone leads to increase in concentration of globulin linking sex hormones, and to decrease in quantity of free testosterone. The relationship between the specified changes and decrease in severity of acne eruption in women who are healthy in all other aspects, but who have the same problem with skin, was not established. Impact of antiandrogenic activity of drospirenone on acne is not established.

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 35 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 in two phases with the final half-life period 1.6±0.7 hours and 27.0±7.5 hours. Drospirenone binds to serumal albumine and doesn't bind to sex hormone binding globulin (SHBG), or corticosteroid-binding globulin (CBG). Only 3-5% of general concentration of drospirenone in serum are present as free steroid. The increase of SHBG 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.

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 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

Maximum equilibrium concentrations of drospirenone in serum are achieved between the 7^{th} and the 14^{th} day of administration and are about 60 ng/ml. The increase in concentration of drospirenone in blood serum approximately by 2-3 times was noted owing to accumulation which resulted from the rate of half-life period in terminal phase and dosing interval. Hereafter the increase in concentration of drospirenone in blood serum was observed between the 1^{st} and the 6^{th} cycles of administration, after which concentration increase was not observed.

Pharmacokinetics in special clinical cases

Equilibrium concentration of drospirenone in blood serum in women with mild renal failure (clearance of creatinine (CC) 50-80 ml/min.) is comparable with the corresponding indicators in women with normal function of kidneys. In women with moderate renal failure (CC 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). Pharmacokinetics during severe hepatic failure was not studied.

Ethinylestradiol

Absorption

After oral administration ethinylestradiol is quickly and almost completely absorbed. The highest concentration in blood serum is reached in 1-2 hours after oral administration and is about 88-100 pg/ml. Absolute bioavailability of ethinylestradiol in the result of presystemic conjugation and metabolism of the first passage is about 60%. Concomitant food intake decreases bioavailability of ethinylestradiol approximately in 25% of the subjects, however in the rest of the subjects it was not observed.

Distribution

Concentration of ethinylestradiol in serum is decreased in two phases, final phase is characterized by the half-life period which is approximately 24 h. Ethinylestradiol to a great degree is not specifically linked to serum albumin (approximately 98.5%), and induces increase of SHBG and CBG in blood serum. Apparent volume of ethinylestradiol distribution is 5 l/kg.

Metabolism

Ethinylestradiol undergoes presystemic conjugation in small intestine mucous membrane and liver. Ethinylestradiol is primarily metabolized by aromatic hydroxylation, however various hydroxylated and methylated metabolites both as free, and as conjugates with glucuronides and sulphates. The rate of methabolic clearance of ethinylestradiol is approximately 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 24 hours.

Equilibrium concentration

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

Indications

- Contraception;
- Treatment of moderate form of acne in women over 14 years, if patient intends to administer oral contraceptives to prevent pregnancy;
- Treatment of symptoms of premenstrual dysphoric disorder (PDD), if patient intends to administer oral contraceptives to prevent pregnancy.

Contraindications

CHC shouldn't be used, in case of presence of any conditions listed below. In case of development of any conditions for the first time secondary to Ivonna administration, administration of medicinal preparation should be discontinued:

- hypersensitivity to any of components of Ivonna medicinal product;
- thrombosis (venous and arterial) and thromboembolism (including deep venous thrombosis, pulmonary artery thromboembolism, myocardial infarction), cerebrovascular disorders;
- conditions preceding thrombosis (including transient ischaemic attack, angina pectoris);
- high risk of arterial and venous thrombosis;

- migraine with focal neurologic symptoms;
- diabetes mellitus with vascular complications;
- pancreatitis with expressed hypertriglyceridemia;
- hepatic failure and serious hepatic diseases (until hepatic tests are not normalized);
- hepatic tumors (benign and malignant);
- severe and acute renal failure;
- adrenal failure;
- revealed hormonedependent malignant diseases (including genitals or mammary glands) or suspicion of them;
- vaginal bleeding of unclear genesis;
- pregnancy or suspicion of it, breastfeeding period.

Administration with care

If any of conditions/risk factors provided below exist at the present time, then it is necessary to weigh carefully potential risk and expected advantage of administration of the combined oral contraceptives in each individual case:

- risk factors of development of thrombosis and thromboembolism (smoking, thromboses, myocardial infarction or cerebrovascular diseases at young age in close relatives, obesity, dislipoproteinemia, arterial hypertension, migraine, valvular diseases of the heart, heart rhythm disorder, long-term immobilization, serious surgical interventions, extensive trauma);
- other diseases in case of which disorders of peripheral blood circulation can be noted (diabetes; systemic lupus erythematosus; hemolytic uraemic syndrome; Crohn's disease and nonspecific ulcerative colitis; sickle-cell anaemia; phlebitis of superficial veins);
- hereditary angioedema;
- 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, cholestasis, cholelithiasis, otosclerosis with impairment of hearing, porphyria, herpes gestationis, Sydenham's chorea);
- presence of hereditary angioedema. It is necessary to consult a doctor in the presence the following symptoms: swelling face, throat or tongue, and/or breathing difficulty. Products containing estrogen can aggravate these symptoms;
- postpartum period.

Precautionary measures

Administration during pregnancy and breastfeeding

Administration of Ivonna during pregnancy is contraindicated.

In case of pregnancy detection during Ivonna administration, medicinal product should be immediately cancelled.

Administration of oral contraceptives 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.

Special instructions

With care

Medicinal preparation should be administered only on doctor’s prescription.

Hormonal contraceptives don’t protect from HIV-infection (AIDS) and other sexually transmissible diseases!

Ivonna medicinal preparation can be indicated in women to treat the symptoms of *premenstrual dysphoric disorder* (PMDD) during administration of medicinal preparation for contraception. Effectiveness of Ivonna used for the treatment of PMDD during more than three menstrual cycles has been not studied.

The main manifestations of PMDD according to the 4th edition of the "Guidance on diagnostics and statistics" (DSM-IV) are the following: expressed suppressed condition, anxiety or tension, affective lability, constant anger. Decrease in interest in daily activity, difficulty with concentration of attention, lack of energy, change of appetite or sleep, feeling of loss of control belong to other manifestations. Physical symptoms of PMDD are the following: sensitivity of mammary gland, headache, joint and muscle pain, meteorism and increase in body weight. The listed symptoms regularly appear in the specified order during lutein cycle and resolve in several days after the beginning of menstruation; this disorder considerably influences educational or production activity, complicates routine public activity and relations with other people. The diagnosis is made by the attending physician on the basis of DSM-IV criteria, symptomatology is assessed prospectively during at least two menstrual cycles. When establishing diagnosis, it is extremely important to exclude other cyclic affective disorders. Effectiveness of medicinal preparation in treatment of premenstrual syndrome (PMS) has not been studied.

Ivonna can be indicated for the treatment of moderate form of common acne (acne vulgaris) in women under 14 years who do not have contraindications to therapy by means of oral contraception, who had the first menstruation. Medicinal preparation should be used for treatment of acne only in case when patient wishes to administer oral contraceptives to prevent pregnancy. If any of conditions and/or risk factors provided below exist at the present time, then it is necessary to weigh carefully potential risk and expected advantage of administration of combined oral contraceptives (CPC) in each individual case and to discuss it with the woman before she decides to begin administration of medicinal preparation. In case of aggravation, enhancement or the first manifestation of any of these conditions or risk factors, woman should consult with the doctor who can make a decision on the need of discontinuation of treatment.

Cardiovascular system disorders

The results of epidemiological studies indicate the presence of relationship between CPC administration and increase of frequency of development of venous and arterial thromboses and thromboembolisms (such as a deep vein thrombosis, pulmonary artery thromboembolism, myocardial infarction, cerebrovascular disorders) during administration of combined oral contraceptives. The data on the diseases are noted rarely. The risk of development of venous thromboembolism (VTE) is maximum in the first year of administration of such medicinal preparations. The increased risk is present after primary use of combined oral contraceptives or renewing of administration of the same or different combined oral contraceptives (after a break between administrations of medicinal preparations in 4 weeks and more). Data of large prospective study with participation of 3 groups of patients show that this increased risk is present mainly within the first 3 months. Common risk of venous thromboembolism (VTE) in the patients receiving low-dosed combined oral contraceptives (<50 μg of ethinylestradiol) is two-three times higher, than in nonpregnant patients who don't administer CPC, however, this risk remains lower in comparison with the risk of VTE during pregnancy and childbirth.

VTE can threaten life or lead to lethal outcome (in 1-2% of cases). Venous thromboembolism which is demonstrated as deep vein thrombosis, or pulmonary embolism can occur when using any combined oral contraceptive. Extremely rarely during administration of combined oral contraceptive there is thrombosis of other blood vessels, for example, hepatic, mesenteric, renal, cerebral veins and arteries or retinal vessels. The agreement of opinion concerning relation between emergence of these events and administration of combined oral contraceptives is absent.

Symptoms of deep venous thrombosis (DVT) include: 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).

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 the 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. Other signs of vascular occlusion: sudden pain, edema and mild blue discoloration of extremities. 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. Arterial thromboembolism can threaten life or lead to lethal outcome.

A possibility of the increased synergetic risk of thrombosis should be considered in women who have a combination of risk factors or show higher severity to individual risk factors. This increased risk can be more, than simple set of risk factors. Oral contraceptives should not be indicated in case of negative assessment of risk-benefit ratio.

The risk of development of thrombosis (venous and/or arterial) and thromboembolisms increases in the following cases: with advancing age; in smokers (with increase in quantity of cigarettes or with advancing age risk increases, especially in women over 35); during obesity (body weight index more than 30 kg/m^2); family anamnesis (for example, venous or arterial thromboembolism ever in close relatives or parents at relatively young age). In case of genetic or acquired predisposition, woman should be examined by the corresponding specialist to make a decision on a possibility of administration of combined oral contraceptives; long-term immobilization, serious surgical intervention, any surgery on legs or extensive trauma. In the following situations it is desirable to stop use of combined oral contraceptives: in case of planned surgery, at least, in four weeks prior to it and not to proceed to administration within two weeks after termination of immobilization; dislipoproteinemia; arterial hypertension; migraine; valvular disease of the heart; thrombogenic heart rhythm disorders (e.g., atrial fibrillation).

The question of possible role of varicosity and superficial thrombophlebitis in the development of venous thromboembolism remains disputable.

It is necessary to consider the increased risk of development of thromboembolism in postpartum period. Peripheral circulation disorders can be also observed during diabetes mellitus, dystemic lupus erythematosus, hemolytic uremic syndrome, chronic inflammatory bowel disease (Crohn's disease or nonspecific ulcerative colitis) and sickle-cell anaemia.

Increase in frequency and severity of migraine during administration of combined oral contraceptives (that can precede cerebrovascular disorders) can be the basis for immediate termination of medicinal preparation administration; The following belongs to biochemical measurements indicating genetic or acquired predisposition to venous or arterial thrombosis: resistance to activated protein C, hyperhomocisteinemia, lack of antitrombin-III, lack of protein C, lack of protein S, antiphospholipid antibodies (anticardiolipin antibodies, lupus anticoagulant).

During assessment of risk and benefit ratio, it is necessary to consider that adequate treatment of corresponding condition can reduce the associated risk of thrombosis. Also it should be considered that the risk of thrombosis and thromboembolism during pregnancy is higher, than during administration of the low-dose oral contraceptives (< 0.05 mg ethinylestradiol).

Tumors

The most essential risk factor of development of cervical cancer is persistent papilloma viral infection. There are reports on a slight increase of the risk of development of cervical cancer during the prolonged use of combined oral contraceptives. Connection with administration of combined oral contraceptives is not proved. Contradictions concerning the degree in which these findings are connected with screening regarding pathology of uterine cervix or with peculiarities of sexual behavior (more rare administration of barrier methods of contraception) remain. Meta-analysis of 54 epidemiological studies show that there is a slightly increased relative risk of development of breast cancer diagnosed in the women receiving combined oral contraceptives at the present time (relative risk is 1.24). The increased risk gradually disappears within 10 years after withdrawal of medicinal product administration. As cancer of mammary glands is rarely observed in women under 40 years, increase in the number of diagnoses of breast cancer in the women receiving combined oral contraceptives at the present time, or those who have been receiving it recently, is insignificant in relation to general risk of this disease. The observed increase of risk can be a consequence of earlier diagnosis of breast cancer in the women receiving combined oral contraceptives, biological effect of oral contraceptives or a combination of both factors. In the women using the combined oral contraceptives clinically less expressed breast cancer is detected, than in the women, who have never received it.

In rare cases secondary to administration of combined oral contraceptives the development of benign, and in extremely rare cases - of malignant hepatic tumors were observed which in some cases brought to life-threatening intra-abdominal bleeding. It should be considered during execution of differential diagnosis in case of emergence of severe pains in stomach, hepatomegalia or signs of intra-abdominal bleeding. Tumors can threaten life or lead to lethal outcome.

If any of conditions/risk factors provided below exist at the present time, then it is necessary to weigh carefully potential risk and expected advantage of administration of the combined oral contraceptives in each individual case and to discuss it with the woman before she decides to begin administration of medicinal preparation. In case of aggravation, enhancement or the first manifestation of any of these conditions or risk factors, woman should consult with the doctor who can make a decision on the need of discontinuation of treatment.

Other conditions

Clinical trials showed lack of influence of drospirenone on concentration of potassium in blood serum in patients with mild to moderate renal failure. There is a theoretical risk of development of hyperkalemia in patients with impaired renal function with initial concentration of potassium on the standard top, who concomitantly receive medicinal preparations leading to potassium retention in the body. However, in

women with an increased risk of hyperkalemia development it is recommended to determine serum potassium concentration during the first cycle of medicinal preparation administration.

In women with hypertriglyceridemia (or presence of this condition in the familial history), the increase of risk of pancreatitis development is possible during administration of combined oral contraceptives.

Although a slight increase of arterial pressure was described in many women receiving combined oral contraceptives, clinically significant increase was noted rarely. Nevertheless, if during administration of combined oral contraceptives permanent, clinically significant increase of arterial pressure develops, it is necessary to discontinue medicinal preparation and to begin treatment of arterial hypertension. Administration of combined oral contraceptives can be continued if normal values of arterial pressure have been reached via hypotensive therapy.

The following conditions as were reported to be developed or aggravated both during pregnancy, and during administration of combined oral contraceptives, but their connection with administration of combined oral contraceptives was 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. Cases of Crohn's disease and nonspecific ulcerative colitis secondary to administration of combined oral contraceptives are also described.

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 combined oral contraceptives.

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

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

Laboratory tests

Administration of combined oral contraceptives can influence the results the several laboratory tests, including indicators of function of liver, kidneys, thyroid gland, adrenal glands, level of transport proteins in plasma, indicators of carbohydrate metabolism, parameters of coagulation and fibrinolysis. Changes usually do not exceed the limits of normal values. Drospirenone increases activity of plasma renin and aldosterone, that is connected with its antimineralocorticoid effect.

Decrease in effectiveness

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

Secondary to administration of combined oral contraceptives, 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 active tablets (pink), withdrawal bleeding may not develop. If combined oral contraceptives are administered according to instructions, it is unlikely that woman is pregnant. Nevertheless, if before that, combined oral contraceptives have been received irregularly, or if there are two sequent withdrawal bleeding, pregnancy should be excluded before continuation of medicinal preparation administration.

Medical examinations

Prior to the beginning or renewing of Ivonna medicinal preparation administration, it is necessary to study the past medical history, the family anamnesis of woman, to conduct careful general medical (including blood pressure measurement, heart rate, determination of body mass index) and pelvic examination (including analysis of mammary glands and cytological examination of cervical mucus), to exclude pregnancy. The scope of additional investigations and frequency of control follow-ups is determined individually. As a rule, control follow-ups should be conducted at least 1 time in a year.

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: Administration of medicinal product s not recommended in postclimacteric period. Medicine is not indicated in this group of patients.

Patients with hepatic disorders: Ivonna 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: medicinal preparation is contraindicated to women with severe renal failure or with acute renal failure. See the sections "Contraindications", "Pharmacodynamics" and "Pharmacokinetics".

Mode of administration

Medicinal preparation is administered orally. Medicinal product should be administered every day, approximately at the same time, if necessary washing down with small amount of water, as on the label. One active tablet should be administered daily during 24 days, then one placebo-tablet daily within 4 days. Administration of tablets from the next package should be initiated after ending of administration of tablets from the previous package, without break between the packages. As a rule, menstruation begins on the 2-3 day after administration of placebo-tablets (white tablets from the last row of the package), and may continue during administration of tablets from the next 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, i.e. on the first day of menstrual bleeding beginning.

Upon switching from other combined oral hormonal contraceptives, combined oral contraceptives, vaginal ring or contraceptive patch

It is preferable to begin drug administration on the next day after administration of the last active tablet from the previous package, but under no circumstances later than the next day after a scheduled 7-day break (for medicinal preparations containing 21 tablets) or after administration of the last placebo tablet

(for medicinal preparations containing 28 tablets in a package). Administration of medicinal preparations should be started on the day of removal of vaginal ring or plaster, but not later than the day when the 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.

Ivonna administration may be started on any day after administration of "mini-pills", on the day of implant or intrauterine contraceptive removal, or on the day when the next injection of contraceptive should be made. Anyway, during the first 7 days of administration of tablets, additional barrier method of contraception should be used.

After abortion in the I trimester of pregnancy

Administration of medicinal product can be immediately started. In this case, there is no need in additional measures of contraception.

After the act of delivery or abortion in the II trimester of pregnancy

Administration of medicinal product is recommended to be initiated on the 21-28 day or abortion in the II trimester of pregnancy. In case of later administration of tablets, an additional barrier method of contraception should be used during the first 7 days of administration of tablets. However if woman has already had sexual intercourse, prior to administration of Ivonna a possibility of pregnancy should be excluded or menstruation should be waited for.

Administration of missed tablets

Omission of placebo tablets (the last 4 tablets of the last row of packing) can be ignored, however they need to be thrown out, in order to avoid incidental prolongation of the period of administration of placebo tablets.

If delay in reception of active tablets is less than 24 hours, contraceptive protection is not decreased. In this case it is necessary to take the missed tablet as soon as possible, the following tablet should be taken in usual time. If delay in reception of active tablets is more than 24 hours, contraceptive protection can be reduced. It is necessary to continue administration of tablets according to the recommendations provided below:

The tablet is missed from the 1 to the 7 day. The missed tablet should be taken immediately (even if it means administration of 2 tablets at the same time). The next tablet needs to be taken in usual time. Additional barrier method of contraception should be used during the next 7 days. In case of sexual contact within 7 days before the first omission of tablet, a possibility of pregnancy should be considered.

The tablet is missed from the 8 to the 14 day. The missed tablet should be taken immediately (even if it means administration of 2 tablets at the same time). The next tablet needs to be taken in usual time. Provided that woman has been taken tablets correctly within 7 days before the first omission of tablet, additional measures of contraception are not required. Otherwise or in the case of omission of two or more tablets, additional measures of contraception should be used during the next 7 days.

One tablet is missed from the 15 to the 24 day. The risk of decrease in reliability of contraception is inevitable. It is necessary to adhere strictly to one of two following schemes. Provided that woman has been taken tablets correctly within 7 days before the first omission of tablet, additional measures of contraception are not required. Otherwise the 1st scheme and additional barrier method of contraception should be used during the next 7 days.

Scheme 1. The missed tablet should be taken as soon as possible (even if it means administration of 2 tablets simultaneously). The following tablets are administered at the usual time, until active tablets in package end. 4 placebo tablets should be thrown out, and administration of tablets from the following package should be started immediately. Withdrawal bleeding is unlikely until active tablets of the

following package end. Spotting and breakthrough bleedings can be observed during administration of tablets.

Scheme 2. Administration of tablets from the current package can be discontinued. A 4-day break should be made, including days of omission of tablets and administration of medicinal preparation from a new package should be started.

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

Administration during gastrointestinal disorders

In case of severe gastrointestinal disorders absorption can be incomplete; additional measures of contraception should be taken.

In a case vomiting or diarrhea within 4 hours after administration of active tablet, recommendation on the case of tablet omission should be followed. If woman doesn't want to change her usual dosage regimen and shift menstruation beginning on the other day of the week, an additional active tablet should be taken from the other package.

Delay of menstruation beginning

To delay the beginning of menstruation, administration of tablets should be continued from a new package of Ivonna, missing placebo tablets from the current package. Cycle can be prolonged on any desired term until the end of active tablets from the second package. During administration of tablets from the second package, spotting or breakthrough bleedings can be observed. The routine administration of medicinal preparation is renewed the end of administration of placebo-tablets.

To transfer the beginning of menstruation on the other day of the week, the next phase of administration of placebo tablets should be shortened on the desired number of days. The shorter the interval is, the higher the risk of absence of withdrawal bleeding, breakthrough bleeding and spotting is during administration of the second package.

Adverse effects

During Ivonna administration the following adverse effects can be observed (common: ≥1/100 - <1/10; uncommon: ≥1/1000 - <1/100; rare ≥1/10000 - <1/1000; unknown frequency: cannot be established, on this basis of the available data).

Gastrointestinal tract disorders: common: nausea; uncommon: pain in stomach, vomiting, dyspepsia, flatulence, gastritis, diarrhea; rare: enlargement of abdomen, feeling of fullness of gastrointestinal tract, hernia of oesophagus, oral cavity candidiasis, constipation, dry mouth.

Blood and the lymphatic system disorders: uncommon: migraine, varicose vein disease, hypertension; rare: anemia, thrombocytopenia, tachycardia, phlebitis, vascular disease, nasal bleeding, syncope.

Eye disorders: rare: conjunctivitis, eye dryness, eye disorders.

Central nervous system disorders: common: headache; uncommon: dizziness, paresthesia; rare: vertigo, tremor.

Mental disorders: common: mood swings; uncommon: depression, nervousness, somnolence; rare: anorgasmia, insomnia.

Hepatobiliary disorders: rare: gall bladder pain, cholecystitis.

Metabolism disorders: rare: hyperorexia, anorexia, hyperkalemia, hyponatremia.

Skin and subcutaneous tissue disorders: uncommon: acne, pruritus, skin rash; rare: chloasma, eczema, alopecia, acneiform dermatitis, skin dryness, erythema nodosum, hypertrichosis, skin disease, skin striae, contact dermatitis, photosensitive dermatitis, skin papules; frequency unknown: erythema multiforme.

Musculoskeletal and connective tissue disorders: uncommon: backache, extremity pain, muscle spasms.

Reproductive system and mammary glands disorders: common: mastodynia, metrorrhagia, amenorrhea; uncommon: vaginal candidiasis, pelvic pain, increase of mammary glands, fibrocystic breast disease, uterine/vaginal bleeding, genital discharge, hot flashes, menstrual disorder, vaginitis, dysmenorrhea,

hypomenorrhea, menorrhagia, vaginal dryness, deviations in Papanicolaou test, decreased libido; rare: dyspareunia, vulvovaginitis, post-coital bleeding, withdrawal bleedings, lacteal cysts, hyperplasia of mammary gland, mammary neoplasms, uterine cervix polyp, atrophy of endometrium, ovarian cyst, enlarged uterus.

Infections and infestations: rare: candidiasis.

Other: uncommon: increase of body mass, asthenia, excessive sweating, edema; rare: allergic reactions, endocrine disorders, decrease of body mass, fever, hypersensitivity reactions.

Adverse reactions with very rare frequency of emergence or with delayed symptoms which can be connected with administration of peroral combined contraceptives:

- venous thromboembolism;
- arterial thromboembolism;
- hypertension;
- hepatic tumors;
- emergence or aggravation of diseases for which relationship with administration of combined oral contraceptive has not been finally demonstrated: Crohn's disease, ulcerative colitis, epilepsy, uterine fibroid, porphyria, systemic lupus erythematosus, herpes gestationis, Sydenham's chorea, hemolytic uraemic syndrome, cholestatic jaundice;
- chloasma;
- acute or chronic hepatic dysfunction can require termination of administration of combined oral contraceptive until liver function tests return to normal;
- in women with hereditary angioedema, exogenously introduced estrogen can cause or strengthen angioedema symptoms.

The rate of breast cancer diagnosing in women receiving combined oral contraceptives is slightly increased. As breast cancer is rarely observed in women under 40 years, additional risk is low in comparison with the general risk of breast cancer development. Causal relationship with administration of combined oral contraceptives is unknown. For additional information see the section “Contraindications” and “Precautionary measures”.

Overdose

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

Drug interaction

Use of medicinal preparations which induce microsomal hepatic enzymes with Ivonna can lead to increase in clearance of sex hormones, that can provoke breakthrough bleeding and/or decrease of reliability of contraception (phenytoin, barbiturates, primidone, carbamazepine, rifampicin, ritonavir, nevirapine, possibly oxcarbazepine, topiramate, felbamate, griseofulvin, the drugs containing St. John's wort). During administration of these medicinal preparations additional barrier method of contraception should be used, as well as within 28 days after its withdrawal.

According to separate studies, administration of several antibiotics (penicillins, tetracyclines) can reduce enterohepatic cycle of estrogens, decreasing concentration of ethinylestradiol. During administration of antibiotics and within 7 days after their withdrawal, an additional barrier method of contraception should be used. If within 7 days of additional barrier method of contraception use, active tablets end,

administration of placebo-tablets from current package should be missed and administration of tablets from the following package of Ivonna should be started.

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

There is a theoretical possibility of increase of serum potassium level in women receiving Ivonna simultaneously with other medicinal preparations, which can increase potassium serum level (ACE inhibitors, angiotensin-2 receptor antagonists, several anti-inflammatory medicinal preparations, potassium-sparing diuretics and aldosterone antagonists). In such cases, it is recommended to determine concentration of potassium in blood serum during the first cycle of Ivonna administration.

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 (24 pink tablets with active substance and 4 white placebo tablets) in blister pack made of polyvinylchloride/ polyvinylidene chloride film and flexible package on the basis of aluminum foil. 1, 2, or 3 blisters with a package insert in cardboard package.

Information on manufacturer

Manufactured by Laboratorios Leon Farma, S.A, Spain

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