

**20 August 2021**

**SUMMARY OF PRODUCT CHARACTERISTICS**

**for**

**Violetta, filmovertrukne tabletter**

**0. D.SP.NO.**

32020

**1. NAME OF THE MEDICINAL PRODUCT**

Violetta

**2. QUALITATIVE AND QUANTITATIVE COMPOSITION**

24 yellow film-coated tablets

Each film-coated tablet contains 60 micrograms of gestodene and 15 micrograms of ethinylestradiol.

*Excipient with known effect:* Each tablet contains 40 mg lactose monohydrate.

4 green placebo (inactive) film-coated tablets

The tablet does not contain active substances.

*Excipients with known effect*: Each tablet contains 37 mg lactose anhydrous and 0.003 mg sunset yellow.

For the full list of excipients, see section 6.1

**3. PHARMACEUTICAL FORM**

Film-coated tablets

The active tablet is a yellow, round, biconvex and film-coated tablet, diameter about 5.5 mm. Engraving on one side: “G43’, the other side is without engraving.

The placebo tablet is a green, round, biconvex film-coated tablet, diameter about 6 mm, without engraving.

**4. CLINICAL PARTICULARS**

**4.1 Therapeutic indications**

Oral hormonal contraception.

The decision to prescribe Violetta should take into consideration the individual woman’s current risk factors, particularly those for venous thromboembolism (VTE), and how the risk of VTE with Violetta compares with other combined hormonal contraceptives (CHCs) (see sections 4.3 and 4.4).

**4.2 Posology and method of administration**

**Posology**

Take regularly and without omission, one tablet daily at the same time of the day, for 28 consecutive days (one yellow, active tablet during the first 24 days, one green, inactive tablet during the 4 following days) with no free interval between each blister pack. A withdrawal bleed usually starts on day 2-3 after the last active tablet and may not have finished before the next pack is started.

How to start Violetta

*No preceding hormonal contraceptive use in the past month*

Take the first tablet on the first day of menstrual bleeding.

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

The woman should start Violetta preferably on the day after the last active tablet of her previous COC, but at the latest on the day following the usual tablet-free or placebo tablet interval of her previous COC. In case a vaginal ring or transdermal patch has been used the woman should start using Violetta preferably on the day of removal, but at the latest when the next application would have been due.

*Changing from a progestogen-only method (progestogen-only pill, injection, implant) or from a progestogen-releasing intrauterine system (IUS)*

The woman may switch any day from the progestogen-only pill and should begin Violetta the next day. She should start Violetta on the day of an implant/IUS removal or, if using an injection, the day the next injection would be due. In all of these situations, the woman should be advised to additionally use a non-hormonal back-up method for the first 7 days of tablet-taking.

*Following first-trimester abortion*

The woman may start Violetta immediately. Additional contraceptive measures are not needed.

*Following delivery or second-trimester abortion*

Since the immediate post-partum period is associated with an increased risk of thromboembolism, COCs should be started no earlier than days 21 to 28 after delivery or second-trimester abortion. The woman should be advised to additionally use a non-hormonal back-up method for the first 7 days of tablet-taking. However, if intercourse has already occurred, pregnancy should be excluded before the actual start of COC use or the woman has to wait for her first menstrual period.

For breastfeeding women, see section 4.6.

**Management of missed tablets**

Placebo tablets from the last row of the blister can be disregarded. However, they should be discarded to avoid unintentionally prolonging the placebo tablet phase. The following advice only refers to missed active tablets:

If the woman is **less than 12 hours** late in taking the active tablet, contraceptive protection is not reduced. The woman should take the tablet as soon as she remembers and should take further tablets at the usual time.

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

1. Tablet-taking must never be discontinued for longer than 4 days

2. 7 days of uninterrupted tablet-taking are required to attain adequate suppression of the hypothalamic-pituitary-ovarian-axis.

Accordingly, the following advice can be given in daily practice:

● Day 1-7

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

● Day 8-14

The woman should take the last missed tablet as soon as she remembers, even if this means taking two tablets at the same time. She then continues to take tablets at her usual time. Provided that the woman has taken her tablets correctly in the 7 days preceding the first missed tablet, there is no need to use extra contraceptive precautions. However, if she has missed more than 1 tablet, the woman should be advised to use extra precautions for 7 days.

● Day 15-24

The risk of reduced reliability is imminent because of the forthcoming placebo tablet phase. However, by adjusting the tablet-intake schedule, reduced contraceptive protection can still be prevented. By adhering to either of the following two options, there is therefore no need to use extra contraceptive precautions, provided that in the 7 days preceding the first missed tablet the woman has taken all tablets correctly. If this is not the case, she should follow the first of these two options and use extra precautions for the next 7 days as well.

1. The woman should take the last missed tablet as soon as she remembers, even if this means taking two tablets at the same time. She then continues to take tablets at her usual time until the active tablets are used up. The 4 placebo tablets from the last row must be discarded. The next blister pack must be started right away. The woman is unlikely to have a withdrawal bleed until the end of the active tablets section of the second pack, but she may experience spotting or breakthrough bleeding on tablet-taking days.

2. The woman may also be advised to discontinue active tablet-taking from the current blister pack. She should then take placebo tablets from the last row for up to 4 days, including the days she missed tablets, and subsequently continue with the next blister pack.

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

**Advice in case of gastro-intestinal disturbances**

In case of severe gastro-intestinal disturbances (e.g., vomiting or diarrhoea), absorption may not be complete and additional contraceptive measures should be taken. If vomiting occurs within 3-4 hours after active tablet-taking, a new (replacement) tablet should be taken as soon as possible. The new tablet should be taken within 12 hours of the usual time of tablet-taking if possible. If more than 12 hours elapse, the advice concerning missed tablets, as given in section 4.2 “Management of missed tablets”, is applicable. If the woman does not want to change her normal tablet-taking schedule, she has to take the extra tablet(s) from another blister pack.

How to postpone a withdrawal bleed

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

To shift her periods to another day of the week than the woman is used to with her current scheme, she can be advised to shorten her forthcoming placebo tablet phase by as many days as she likes. The shorter the interval, the higher the risk that she does not have a withdrawal bleed and will experience breakthrough-bleeding and spotting during the subsequent pack (just as when delaying a period).

Special populations

*Paediatric population*

Safety and efficacy were evaluated in subjects aged 18 years and above. Limited data available for use in adolescents below 18 years.

*Elderly women*

Violetta is not indicated after menopause.

*Hepatic impairment*

Violetta is contraindicated in women with severe hepatic diseases (see also section 4.3).

*Renal impairment*

Violetta has not been specifically studied in renally impaired patients (see also sections 4.3 and 4.4).

**Method of administration**

Oral use.

**4.3 Contraindications**

Combined hormonal contraceptives (CHCs) should not be used in the following conditions. If one of these disorders occurs during the use of Violetta, Violetta must be discontinued immediately.

• Hypersensitivity to the active substances or to any of the excipients listed in section 6.1

• Presence or risk of venous thromboembolism (VTE)

• Venous thromboembolism – current VTE (on anticoagulants) or history of (e.g. deep venous thrombosis [DVT] or pulmonary embolism [PE])

• Known hereditary or acquired predisposition for venous thromboembolism, such as APC-resistance, (including Factor V Leiden), antithrombin-III-deficiency, protein C deficiency, protein S deficiency

• Major surgery with prolonged immobilisation (see section 4.4)

• A high risk of venous thromboembolism due to the presence of multiple risk factors (see section 4.4)

• Presence or risk of arterial thromboembolism (ATE)

• Arterial thromboembolism – current arterial thromboembolism, history of arterial thromboembolism (e.g. myocardial infarction) or prodromal condition (e.g. angina pectoris)

• Cerebrovascular disease – current stroke, history of stroke or prodromal condition (e.g. transient ischaemic attack, TIA)

• Known hereditary or acquired predisposition for arterial thromboembolism, such as hyperhomocysteinaemia and antiphospholipid-antibodies (anticardiolipin-antibodies, lupus anticoagulant).

• History of migraine with focal neurological symptoms.

• A high risk of arterial thromboembolism due to multiple risk factors (see section 4.4) or to the presence of one serious risk factor such as:

• diabetes mellitus with vascular symptoms

• severe hypertension

• severe dyslipoproteinaemia

• Known or suspected carcinoma of the breast

• Carcinoma of the endometrium or other known or suspected oestrogen-dependent neoplasia

• Hepatic adenomas or carcinoma, or active liver disease, as long as liver function tests have not returned to normal

• Undiagnosed genital bleeding

• Serious renal insufficiency or acute renal failure

• Pancreatitis or a history thereof if associated with severe dyslipoproteinaemia

Violetta is contraindicated for concomitant use with medicinal products containing ombitasvir/paritaprevir/ritonavir and dasabuvir or medicinal products containing glecaprevir/pibrentasvir (see sections 4.4 and 4.5).

**4.4 Special warnings and precautions for use**

If any of the conditions or risk factors mentioned below is present, the suitability of Violetta should be discussed with the woman.

In the event of aggravation, or first appearance of any of these conditions or risk factors, the woman should be advised to contact her doctor to determine whether the use of Violetta should be discontinued.

**Risk of venous thromboembolism (VTE)**

The use of any combined hormonal contraceptive (CHC) increases the risk of venous thromboembolism (VTE) compared with no use. **Products that contain levonorgestrel, norgestimate or norethisterone are associated with the lowest risk of VTE. Other products such as Violetta may have up to twice this level of risk. The decision to use any product other than one with the lowest VTE risk should be taken only after a discussion with the woman to ensure she understands the risk of VTE with Violetta, how her current risk factors influence this risk, and that her VTE risk is highest in the first ever year of use. There is also some evidence that the risk is increased when a CHC is re-started after a break in use of 4 weeks or more**.

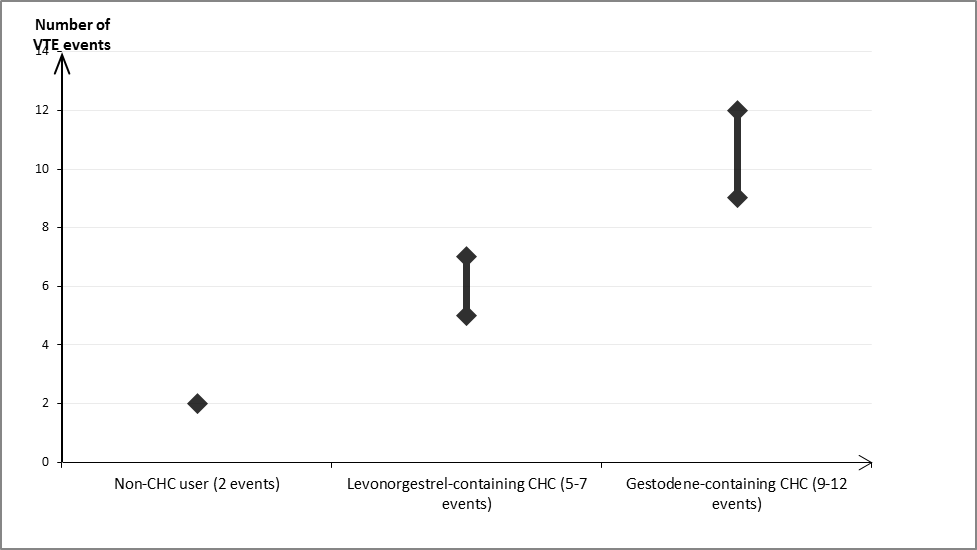
In women who do not use a CHC and are not pregnant about 2 out of 10,000 will develop a VTE over the period of one year. However, in any individual woman the risk may be far higher, depending on her underlying risk factors (see below).

It is estimated[[1]](#footnote-1) that out of 10,000 women who use a CHC containing gestodene between 9 and 12 women will develop a VTE in one year; this compares with about 62 in women who use a levonorgestrel-containing CHC.

In both cases, the number of VTEs per year is fewer than the number expected during pregnancy or in the postpartum period.

VTE may be fatal in 1‑2 % of cases.

**Number of VTE events per 10,000 women in one year**

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Extremely rarely, thrombosis has been reported to occur in CHC users in other blood vessels, e.g. hepatic, mesenteric, renal or retinal veins and arteries.

**Risk factors for VTE**

The risk for venous thromboembolic complications in CHC users may increase substantially in a woman with additional risk factors, particularly if there are multiple risk factors (see table).

Violetta is contraindicated if a woman has multiple risk factors that put her at high risk of venous thrombosis (see section 4.3). If a woman has more than one risk factor, it is possible that the increase in risk is greater than the sum of the individual factors

* in this case her total risk of VTE should be considered. If the balance of benefits and risks is considered to be negative a CHC should not be prescribed (see section 4.3).

**Table: Risk factors for VTE**

|  |  |
| --- | --- |
| **Risk factor** | **Comment** |
| Obesity (body mass index over 30 kg/m²). | Risk increases substantially as BMI rises.  Particularly important to consider if other risk factors also present. |
| Prolonged immobilisation, major surgery, any surgery to the legs or pelvis, neurosurgery, or major trauma.  Note: temporary immobilisation including air travel >4 hours can also be a risk factor for VTE, particularly in women with other risk factors. | In these situations it is advisable to discontinue use of the pill (in the case of elective surgery at least four weeks in advance) and not resume until two weeks after complete remobilisation. Another method of contraception should be used to avoid unintentional pregnancy.  Antithrombotic treatment should be considered if Violetta has not been discontinued in advance. |
| Positive family history (venous thromboembolism ever in a sibling or parent especially at a relatively early age e.g. before 50). | If a hereditary predisposition is suspected, the woman should be referred to a specialist for advice before deciding about any CHC use. |
| Other medical conditions associated with VTE. | Cancer, systemic lupus erythematosus, haemolytic uraemic syndrome, chronic inflammatory bowel disease (Crohn’s disease or ulcerative colitis) and sickle cell disease. |
| Increasing age. | Particularly above 35 years. |

There is no consensus about the possible role of varicose veins or superficial thrombophlebitis in the onset or progression of venous thrombosis.

The increased risk of thromboembolism in pregnancy, and particularly the 6-week period of the puerperium, must be considered (for information see section 4.6).

**Symptoms of VTE (deep vein thrombosis and pulmonary embolism)**

In the event of symptoms women should be advised to seek urgent medical attention and to inform the healthcare professional that she is taking a CHC.

Symptoms of deep vein thrombosis (DVT) can include:

• unilateral swelling of the leg and/or foot or along a vein in the leg;

• pain or tenderness in the leg which may be felt only when standing or walking,

• increased warmth in the affected leg; red or discoloured skin on the leg.

Symptoms of pulmonary embolism (PE) can include:

• sudden onset of unexplained shortness of breath or rapid breathing;

• sudden coughing which may be associated with haemoptysis;

• sharp chest pain;

• severe light headedness or dizziness;

• rapid or irregular heartbeat.

Some of these symptoms (e.g. ‘shortness of breath’, ‘coughing’) are non-specific and might be misinterpreted as more common or less severe events (e.g. respiratory tract infections).

Other signs of vascular occlusion can include: sudden pain, swelling and slight blue discoloration of an extremity.

If the occlusion occurs in the eye symptoms can range from painless blurring of vision which can progress to loss of vision. Sometimes loss of vision can occur almost immediately.

**Risk of arterial thromboembolism (ATE)**

Epidemiological studies have associated the use of CHCs with an increased risk for arterial thromboembolism (myocardial infarction) or for cerebrovascular accident (e.g. transient ischaemic attack, stroke). Arterial thromboembolic events may be fatal.

**Risk factors for ATE**

The risk of arterial thromboembolic complications or of a cerebrovascular accident in CHC users increases in women with risk factors (see table). Violetta is contraindicated if a woman has one serious or multiple risk factors for ATE that puts her at high risk of arterial thrombosis (see section 4.3). If a woman has more than one risk factor, it is possible that the increase in risk is greater than the sum of the individual factors - in this case her total risk should be considered. If the balance of benefits and risks is considered to be negative a CHC should not be prescribed (see section 4.3).

**Table: Risk factors for ATE**

|  |  |
| --- | --- |
| **Risk factor** | **Comment** |
| Increasing age. | Particularly above 35 years. |
| Smoking. | Women should be advised not to smoke if they wish to use a CHC. Women over 35 who continue to smoke should be strongly advised to use a different method of contraception. |
| Hypertension. |  |
| Obesity (body mass index over 30 kg/m2). | Risk increases substantially as BMI increases.  Particularly important in women with additional risk factors. |
| Positive family history (arterial thromboembolism ever in a sibling or parent especially at relatively early age e.g. below 50). | If a hereditary predisposition is suspected, the woman should be referred to a specialist for advice before deciding about any CHC use. |
| Migraine. | An increase in frequency or severity of migraine during CHC use (which may be prodromal of a cerebrovascular event) may be a reason for immediate discontinuation. |
| Other medical conditions associated with adverse vascular events. | Diabetes mellitus, hyperhomocysteinaemia, valvular heart disease and atrial fibrillation, dyslipoproteinaemia, systemic lupus erythematosus. |

**Symptoms of ATE**

In the event of symptoms women should be advised to seek urgent medical attention and to inform the healthcare professional that she is taking a CHC.

Symptoms of a cerebrovascular accident can include:

• sudden numbness or weakness of the face, arm or leg, especially on one side of the body;

• sudden trouble walking, dizziness, loss of balance or coordination;

• sudden confusion, trouble speaking or understanding;

• sudden trouble seeing in one or both eyes;

• sudden, severe or prolonged headache with no known cause;

• loss of consciousness or fainting with or without seizure.

Temporary symptoms suggest the event is a transient ischaemic attack (TIA).

Symptoms of myocardial infarction (MI) can include:

• pain, discomfort, pressure, heaviness, sensation of squeezing or fullness in the chest, arm, or below the breastbone;

• discomfort radiating to the back, jaw, throat, arm, stomach;

• feeling of being full, having indigestion or choking;

• sweating, nausea, vomiting or dizziness;

• extreme weakness, anxiety, or shortness of breath;

• rapid or irregular heartbeats.

Breast cancer and gynaecological cancers

A meta-analysis of data from 54 international studies demonstrated a slightly higher risk (RR=1.24) of breast cancer diagnosis among users of oral contraceptives. This increased risk does not appear to be dependent upon the duration of use. The influence of risk factors such as nulliparity or a family history of breast cancer is not established.

This increased risk is transient and disappears gradually over 10 years after the oral contraceptive is discontinued.

It is possible that the more regular clinical monitoring of women taking oral contraceptives, with increased likelihood of earlier diagnosis, may play an important role in the higher number of breast cancers diagnosed.

Because breast cancer is rare in women under 40 years of age, the excess number of breast cancer diagnoses in current and recent COC users is small in relation to the lifetime risk of breast cancer. Breast cancers diagnosed in ever-users tend to be less advanced clinically than the cancers diagnosed in never-users.

An increased risk of cervical cancer in long-term users of COCs has been reported in some epidemiological studies. However, there continues to be controversy about the extent to which these findings may be due to the confounding effects of sexual behaviour and other factors such as human papilloma virus (HPV).

The published data do not compromise the use of oral contraceptives, as the potential risks appear to be outweighed by the benefits.

In addition, oral contraception with a higher content of ethinylestradiol (50 micrograms) decreases the risk of ovarian and endometrial cancers. Whether this is also the case for oral contraception with a lower content of ethinylestradiol is not known.

Hepatic neoplasia/liver disease

In rare cases benign liver tumours (e.g. focal nodular hyperplasia, hepatic adenomas) and even more rarely, malignant liver tumours have been reported in users of COCs. In isolated cases, these tumours have led to life-threatening intra-abdominal haemorrhage.

Cholestasis has been reported to occur or deteriorate with both pregnancy and COC use, but the evidence of an association with COC use is inconclusive.

Hepatic and hepatobiliary disorders have been reported with COC use. Acute or chronic disturbances of liver function may necessitate the discontinuation of COC use until markers of liver function return to normal.

Headache

The onset or exacerbation of migraine or development of headache with a new pattern that is recurrent, persistent, or severe requires discontinuation of COCs and evaluation of the cause.

Hypertension

Even though slight increases in blood pressure have been reported in many women taking COCs, clinically important increases in blood pressure are rare. If persistent clinical hypertension develops during COC use, intake should be discontinued and the hypertension treated. Use of COCs may be resumed, if appropriate, when normotensive values are reached with antihypertensive therapy.

Other

*Medical examination/consultation*

Prior to the initiation or reinstitution of Violetta a complete medical history (including family history) should be taken and pregnancy must be ruled out. Blood pressure should be measured and a physical examination should be performed, guided by the contra-indications (see section 4.3) and warnings (see section 4.4). It is important to draw a woman's attention to the information on venous and arterial thrombosis, including the risk of Violetta compared with other CHCs, the symptoms of VTE and ATE, the known risk factors and what to do in the event of a suspected thrombosis.

The woman should also be instructed to carefully read the user leaflet and to adhere to the advice given. The frequency and nature of examinations should be based on established practice guidelines and be adapted to the individual woman.

Women should be advised that hormonal contraceptives do not protect against HIV infections (AIDS) and other sexually transmitted diseases.

Caution should be exercised in women with:

• Metabolic disorders such as uncomplicated diabetes.

• Hyperlipidaemia (hypertriglyceridemia, hypercholesterolemia). Women who are being treated for hyperlipidaemias should be followed closely if they elect to use COCs. Persistent hypertriglyceridemia may occur in a small proportion of COC users.

In patients with elevated triglycerides, oestrogen-containing preparations may be associated with rare but large elevations of plasma triglycerides that may lead to pancreatitis.

Obesity (body mass index (BMI) = Weight/Height2 ≥30)

Benign tumours of the breast and uterine dystrophy (hyperplasia, fibroma) Hyperprolactinaemia with or without galactorrhoea.

Close surveillance should also be ensured in the presence of conditions, which have been reported to occur or deteriorate with pregnancy or COC use, respectively in patients presenting or with a history of: epilepsy, migraine, otosclerosis, asthma, family history of vascular disease, varicose veins, herpes gestationis, gallstones, systemic lupus erythematosus, cardiac, renal or hepatic dysfunction, depression, hypertension, chorea, haemolytic uremic syndrome.

Exogenous oestrogens may induce or exacerbate symptoms of angioedema, particularly in women with hereditary angioedema.

In clinical trials, amenorrhea, not linked to pregnancy, was observed in 7 % of cycles (occurring in 24 % of women over the total duration of the clinical trials) and 3.6 % of women experienced consecutive amenorrheic cycles. In the clinical trials, only and 1 % of women discontinued because of amenorrhea.

When Violetta is taken according to directions, in the occurrence of one amenorrheic cycle, there is no reason for discontinuation and performance of a pregnancy test. If Violetta is not taken according to directions or if amenorrhea occurs after a long period of regular menstrual bleeding, pregnancy should be ruled out.

Some women may encounter post-therapeutic amenorrhea (possibly with anovulation) or oligomenorrhoea, especially when such a condition was pre-existing. It usually resolves spontaneously. If prolonged, investigations should be carried out into the possibility of pituitary disorders before any further prescription.

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

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

Depressed mood and depression are well-known undesirable effects of hormonal contraceptive use (see section 4.8). Depression can be serious and is a well-known risk factor for suicidal behaviour and suicide. Women should be advised to contact their physician in case of mood changes and depressive symptoms, including shortly after initiating the treatment.

If melasma/chloasma has appeared during pregnancy or with previous COC use, exposure to sunlight should be avoided to minimize exacerbation of this condition.

Diarrhoea and/or vomiting may reduce COC hormone absorption (see section 4.2).

ALT elevations

During clinical trials with patients treated for hepatitis C virus infections (HCV) with the medicinal products containing ombitasvir/paritaprevir/ritonavir and dasabuvir with or without ribavirin, transaminase (ALT) elevations higher than 5 times the upper limit of normal (ULN) occurred significantly more frequently in women using ethinylestradiol-containing medications such as combined hormonal contraceptives (CHCs). Additionally, also in patients treated with glecaprevir/pibrentasvir, ALT elevations were observed in women using ethinylestradiol-containing medications such as CHCs (see sections 4.3 and 4.5).

Excipients

Each tablet of this medicinal product contains 40 mg lactose monohydrate per active tablet and 37 mg lactose anhydrous per placebo tablet. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency, or glucose-galactose malabsorption should not take this medicine.

The placebo tablet contains the excipient Sunset yellow FCF (E110), which may cause allergic reactions.

**4.5 Interaction with other medicinal products and other forms of interaction**

Interactions between ethinylestradiol or gestodene and other substances may lead to decreased or increased plasma and tissue concentrations of ethinylestradiol or gestodene.

Decreased ethinylestradiol serum concentrations may cause an increased incidence of breakthrough bleeding and menstrual irregularities and may possibly reduce efficacy of the COC.

Enzyme inducers

Interactions can occur with drugs that induce microsomal enzymes (especially cytochrome P450 3A4) which can result in increased clearance of sex hormones and which may lead to breakthrough bleeding and/or contraceptive failure.

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

Women on short term treatment with enzyme inducing drugs should temporarily use a barrier method or another method of contraception in addition to the COC. The barrier method must be used during the whole time of the concomitant drug therapy and for 28 days after its discontinuation.

If the drug therapy runs beyond the end of the active tablets in the COC pack, the placebo tablets must be discarded and the next COC pack should be started right away.

In this situation, a withdrawal bleed should not be expected until the end of the second pack. If the patient does not have a withdrawal bleed during the placebo interval following the end of active tablets from the second pack, the possibility of pregnancy must be ruled out before resuming with the next pack.

For women receiving long-term therapy with enzyme inducers, another reliable, nonhormonal, method of contraception should be used.

Concomitant use not recommended

Enzyme inducing agents such as: anticonvulsants (phenobarbital, phenytoin, primidone, carbamazepine, topiramate); rifabutin; rifampicine; griseofulvine, and possibly St. John's Wort. Reduction in the efficacy of contraception through increased hepatic metabolism during treatment and for one cycle following treatment discontinuation. Preference should be given to a non-hormonal contraceptive method.

When co-administered with COCs many HIV/HCV protease inhibitors and non-nucleoside reverse transcriptase inhibitors can increase or decrease plasma concentrations of oestrogen or progestogen. These changes may be clinically relevant in some cases. Please see the corresponding SmPC of each HIV or HCV protease inhibitors and non-nucleoside reverse transcriptase inhibitors for specific recommendation.

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

Etoricoxib doses of 60 to 120 mg/day have been shown to increase plasma concentrations of ethinylestradiol 1.4 to 1.6-fold, respectively when taken concomitantly with a combined hormonal contraceptive containing 0.035 mg ethinylestradiol.

The clinical relevance of potential interactions with enzyme inhibitors remains unknown.

Modafinil: Risk of a decreased contraceptive efficacy during treatment and for one cycle following treatment discontinuation.

Flunarizine: Risk of galactorrhoea due to increased sensitivity of mammary tissue to prolactin through the action of flunarizine.

Troleandomycin may increase the risk for intrahepatic cholestasis during co-administration with COCs.

Effects of COCs on other medicinal products

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

Clinical data suggests that ethinylestradiol is inhibiting the clearance of CYP1A2 substrates leading to a weak (e.g., theophylline) or to moderate (e.g., tizanidine) increase in their plasma concentration.

The labelling of concomitant medications should be consulted to identify potential interactions.

Pharmacodynamic interactions

Concomitant use with the medicinal products containing ombitasvir/paritaprevir/ritonavir and dasabuvir, with or without ribavirin or glecaprevir/pibrentasvir may increase the risk of ALT elevations (see sections 4.3 and 4.4). Therefore, Violetta users must switch to an alternative method of contraception (e.g., progestagen-only contraception or non-hormonal methods) prior to starting therapy with this combination drug regimen. Violetta can be restarted 2 weeks following completion of treatment with certain anti-viral HCV medicinal products and their combinations.

Other forms of interactions

*Laboratory tests*

The use of oral contraceptives may influence the results of certain laboratory tests including biochemical parameters of liver, thyroid, adrenal and renal function, plasma levels of carrier proteins and lipid/lipoprotein fractions, parameters of carbohydrate metabolism and parameters of coagulation and fibrinolysis. Laboratory staff should therefore be informed about oral contraceptive use when laboratory tests are requested.

**4.6 Fertility, pregnancy and lactation**

Fertility

Violetta is indicated for the prevention of pregnancy.

Women may experience post treatment amenorrhoea following discontinuation of treatment (see section 4.4).

Pregnancy

This medicine is not indicated during pregnancy.

In clinical use to date, and in contrast with diethylstilbestrol, the results of numerous epidemiological studies have made it possible to discount the risk of malformation with oestrogen administered alone or in combination during early pregnancy. In addition, the risks concerning foetal sex differentiation (particularly female) which were described with early, highly androgenomimetic progestogens cannot be extrapolated to more recent progestogens (such as that employed in this proprietary medicinal product) which are markedly less androgenomimetic, if at all.

Consequently, the discovery of pregnancy in a woman receiving an oestrogen-progestogen combination does not justify an abortion.

The increased risk of VTE during the postpartum period should be considered when re-starting Violetta (see sections 4.2 and 4.4).

Breastfeeding

The use of Violetta during lactation may lead to a reduction in the volume of milk produced and to a change in its composition.

The use of this medicine in breast-feeding mothers is not advisable since oestrogen-progestogens can be found in breast milk. During breast-feeding a different method of contraception should be proposed.

**4.7 Effects on ability to drive and use machines**

The impact of Violetta on the ability to drive and use machines has not been systematically evaluated. Violetta is not expected to influence the ability to drive or use machines. Cases of dizziness have been reported. Patients should exercise caution until they know that Violetta does not affect these abilities.

**4.8 Undesirable effects**

Description of selected adverse reactions

An increased risk of arterial and venous thrombotic and thromboembolic events, including myocardial infarction, stroke, transient ischemic attacks, venous thrombosis and pulmonary embolism has been observed in women using CHCs, which are discussed in more detail in section 4.4.

The following undesirable effects have been reported in women of COCs: For serious adverse effects in COC women see also section 4.4.

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **System Organ Class** | **Very common**  **(≥1/10)** | **Common**  **(³≥1/100 to <1/10)** | **Uncommon**  **(³≥1/1,000 to <1/100)** | **Rare**  **(³≥1/10,000 to <1/1,000)** | **Very rare**  **(<1/10,000)** | **Not known**  **(cannot be estimated from the available data)** |
| **Infections and infestations** |  | Vaginitis, including candidiasis |  |  |  |  |
| **Neoplasms benign, malignant and unspecified (incl cysts and polyps)** |  |  |  |  |  | Hepatocellu-lar carcinoma and benign hepatic tumours (e.g. focal nodular hyperplasia, hepatic adenoma) |
| **Immune system disorders** |  |  |  |  |  | Anaphylactic/anaphylac­toid reaction, including very rare cases of angioedema, severe reactions with respiratory and circulatory symptoms and urticaria |
| **Metabolism and nutrition disorders** |  |  | Increased appetite, decreased appetite |  |  | Glucose tolerance impaired |
| **Psychiatric disorders** |  | Mood altered, including depression, nervousness, change in libido |  |  |  |  |
| **Nervous system disorders** | Headache, including migraine | Dizziness, |  |  |  | Optic neuritis, chorea aggravated |
| **Eye disorders** |  |  |  |  | Retinal vascular thrombosis | Contact lens intolerance |
| **Vascular disorders** |  |  | Aggravation of varicose veins | Venous thromboembolism and arterial thromboembolism |  |  |
| **Gastrointestinal disorders** | Abdominal pain | Vomiting, nausea, bloating |  | Pancreatitis |  | Colitis ischaemic, possible aggravation of inflammato­ry bowel disease, abdominal cramps |
| **Hepatobiliary disorders** |  |  |  | Hepatic and hepatobiliary disorders (e.g. hepatitis, hepatic function abnormal), biliary lithiasis1, gallbladder disease2 |  | Jaundice cholestatic, cholestasis1 |
| **Skin and subcutaneous tissue disorders** |  | Acne, rash, alopecia | Chloasma, which may persist, hirsutism |  |  | Erythema multiforme, erythema nodosum |
| **Musculoskele­tal and connective tissue disorders** |  |  |  |  |  | Exacerbation of systemic lupus erythema­tosus |
| **Renal and urinary disorders** |  |  |  |  |  | Haemolytic uraemic syndrome |
| **Reproductive system and breast disorders** | Amenorrho­ea, breast pain, breast tenderness | Break­through bleeding, spotting, dysmenorr­hoea, change in menstrual flow, change in cervical ectropion and secretion, | Breast secretion, breast enlargement |  |  |  |
| **Congenital, familial and genetic disorders** |  |  |  |  |  | Exacerbation of porphyria |
| **General disorders and administration site conditions** |  | Fluid retention/oe­dema |  |  |  |  |
| **Investigations** |  | Weight increased, weight decreased | Blood pressure increased, lipids increased |  |  |  |

1 COCs may worsen existing biliary lithiasis and cholestasis

2 COCs may worsen existing gallbladder disease and may accelerate the development of this disease in previously asymptomatic women.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via:

Lægemiddelstyrelsen

Axel Heides Gade 1

DK-2300 København S

Website: www.meldenbivirkning.dk

**4.9 Overdose**

Symptoms of oral contraceptive overdose in adults and children may include nausea, vomiting, breast tenderness, dizziness, abdominal pain, drowsiness/fatigue; withdrawal bleeding may occur in females. There are no antidotes and further treatment should be symptomatic.

**4.10 Legal status**

B

**5. PHARMACOLOGICAL PROPERTIES**

**5.0 Therapeutic classification**

ATC code: G 03 AA 10. Hormonal contraceptives for systemic use, Progestogens and oestrogens, fixed combinations. Single-phase oestrogen-progestogen combination.

**5.1 Pharmacodynamic properties**

Violetta is a combination oral contraceptive (COC) containing ethinylestradiol (EE) and gestodene. This COC acts by inhibiting ovulation by suppression of the mid-cycle surge of luteinising hormone. Further, the inspissation of cervical mucus so as to constitute a barrier to sperm, and the rendering of the endometrium unreceptive to implantation may play a role as well.

Non-corrected Pearl Index: 0.24 (21,521 cycles).

**5.2 Pharmacokinetic properties**

Ethinylestradiol

*Absorption*

Ethinylestradiol is rapidly and completely absorbed after oral ingestion. After administration of 15 micrograms, peak plasma concentrations of 30 pg/mL are reached after 1‑1.5 hours. Ethinylestradiol undergoes an extensive first pass effect, which displays great interindividual variation. The absolute bioavailability is approximately 45 %.

*Distribution*

Ethinylestradiol has an apparent volume of distribution of 15 L/kg and binding to plasma proteins is approximately 98 %. Ethinylestradiol induces the hepatic synthesis of sex-hormone binding globulins (SHBG) and corticoid-binding globulins (CBG).

During treatment with 15 micrograms ethinylestradiol the plasma concentration of SHBG increases from 86 to about 200 nmol/L.

*Biotransformation*

Ethinylestradiol is metabolised completely (metabolic plasma clearance approximately 10 mL/min/kg). The metabolites formed are excreted in the urine (40 %) and feces (60 %).

*In vitro*, ethinylestradiol is a reversible inhibitor of CYP2C19, CYP1A1 and CYP1A2 as well as a mechanism based inhibitor of CYP3A4/5, CYP2C8, and CYP2J2.

*Elimination*

The elimination half-life of ethinylestradiol is approximately 15 hours. Ethinylestradiol is not excreted in unchanged form to any significant extent. The metabolites of ethinylestradiol are excreted at a urinary to biliary ratio of 4:6.

*Steady state conditions*

Steady state conditions are reached during the second half of the treatment cycle and serum levels of ethinylestradiol accumulate by a factor of about 1.4 to 2.1.

Gestodene

*Absorption*

After oral administration gestodene is rapidly and completely absorbed. The absolute bioavailability is about 100 %. After oral intake of a single 60 micrograms gestodene dose, peak plasma concentrations of 2 ng/mL are reached in about 60 minutes. The plasma concentrations are strongly dependent on the SHBG concentrations.

*Distribution*

Gestodene has an apparent volume of distribution of 1.4 L/kg following a single 60 microgram dose. It is 30 % bound to plasma albumin and 50‑70 % bound to SHBG.

*Biotransformation*

Gestodene is extensively metabolised by the steroid metabolic pathway. The metabolic clearance is about 0.8 mL/min/kg following a single 60 microgram dose. The non-active metabolites formed are excreted in urine (60 %) and faeces (40 %).

*Elimination*

The apparent elimination half-life of gestodene is about 13 hours. The half-life is prolonged to 20 hours after concomitant administration with ethinylestradiol.

*Steady state conditions*

After multiple dosing concomitantly with ethinylestradiol the plasma concentration increases approximately by a factor of 2‑4.

**5.3 Preclinical safety data**

Toxicological studies have been performed on all components individually and on their combination.

Acute toxicity studies in animals showed no evidence of a risk of acute symptoms arising after accidental overdose.

General safety studies with repeated administration have shown no evidence of any effects suggesting any unexpected risks in man.

Long term and repeated dose carcinogenicity studies have not demonstrated any carcinogenic potential; however, it is important to remember that sex steroids are capable of promoting the development of certain tissues into hormone-dependent tumours.

Teratogenicity studies have not indicated any particular risk when oestrogen-progestogen combinations are used correctly; it is however essential to discontinue treatment immediately if taken in error at the beginning of pregnancy.

Mutagenicity studies have not revealed any mutagenic potential for ethinylestradiol or gestodene.

**6. PHARMACEUTICAL PARTICULARS**

**6.1 List of excipients**

Tablet core (active)

Lactose monohydrate

Cellulose, microcrystalline

Polacrilin potassium

Magnesium stearate

Film-coating (active)

Lactose monohydrate

Hypromellose

Titanium dioxide (E171)

Triacetin

Quinoline yellow (E104)

Tablet core (placebo)

Cellulose, microcrystalline

Lactose

Maize starch, pregelatinised

Magnesium stearate

Silica, colloidal anhydrous

Film-coating (placebo)

Polyvinyl alcohol

Titanium dioxide (E171)

Macrogol 3350

Talc

Indigo carmine (E132)

Quinoline yellow (E104)

Iron oxide black (E172)

Sunset yellow FCF (E110)

**6.2 Incompatibilities**

Not applicable.

**6.3 Shelf-life**

2 years.

**6.4 Special precautions for storage**

Do not store above 30 °C.

Store in the original package in order to protect from light and moisture.

**6.5 Nature and contents of container**

Blisters made of transparent PVC-Aluminium foil.

Each blister is placed in a laminated aluminium sachet. The blisters in the sachets are packed into cardboard box with a patient information leaflet, an etui storing bag and weekdays sticker(s) enclosed in each box.

Pack sizes

1×(24+4) film-coated tablets.

3×(24+4) film-coated tablets.

6×(24+4) film-coated tablets.

13×(24+4) film-coated tablets.

Not all pack sizes may be marketed.

**6.6 Special precautions for disposal and other handling**

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

**7. MARKETING AUTHORISATION HOLDER**

Gedeon Richter Plc.

Gyömrői út 19-21

1103 Budapest

Hungary

**8. MARKETING AUTHORISATION NUMBER(S)**

64267

**9. DATE OF FIRST AUTHORISATION**

20 August 2021

**10. DATE OF REVISION OF THE TEXT**

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1. These incidences were estimated from the totality of the epidemiological study data, using relative risks for the different products compared with levonorgestrel-containing CHCs.

   2 Mid-point of range of 5-7 per 10,000 WY, based on a relative risk for CHCs containing levonorgestrel versus non-use of approximately 2.3 to 3.6 [↑](#footnote-ref-1)