SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Millinette 20/75 microgram coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 20 micrograms ethinylestradiol and 75 micrograms gestodene.

Excipients with known effect: each tablet contains 35.3068 mg lactose (as lactose monohydrate), 19.6600 mg sucrose.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Coated tablet.

Pale yellow, round, biconvex sugar-coated tablets, both sides are without imprinting.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Contraception.

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

4.2 Posology and method of administration

Do not start or continue with Millinette in case of known or suspected pregnancy.

Posology

How is Millinette taken?
To patients who use a package with 21 active tablets:
The tablets 1-21 contain active substances (active tablets).

The tablets must be taken in the order given on the blister pack, every day at approximately the same point. One tablet is taken daily for 21 consecutive days. Every subsequent blister pack is started after a 7 day tablet-free interval during which time a withdrawal bleeding usually occurs. This bleeding usually starts on the 2nd or 3rd day after taking the last tablet has been taken and it may not have stoped, before the next blister pack is started.

How to start Millinette

No preceding hormonal contraceptive use in the past month
The tablets should be started on day 1 in the woman's normal cycle (i.e. on the first day the woman has a menstrual bleeding). It is acceptable to start the tablets on day 2-5, but during the first cycle the concomitant use of non-hormonal contraception (e.g. condom or spermicide) for the first 7 days is recommended.

Changing from another combined oral pill
The woman should start with Millinette on the day following the usual tablet-free or placebo tablet interval of her previous COC.

Changing from a progestogen-only method (mini pills, injection, implant)
The woman may switch from progestogen-only pills on any day (from an implant on the day the implant is removed or from injection, when the next injection should have been given). In all these cases the woman should be advised to use a concomitant barrier method for the first 7 days of the tablet intake.

After abortion in 1st trimester
The woman may start the tablet intake immediately. In this case, it is not necessary to take further contraceptive precautions.

After delivery or abortion in 2nd trimester
For breastfeeding women - see section 4.6.
The woman should be advised to start on day 21-28 after delivery in non-lactating women or abortion in the 2nd trimester. She should also be advised to use a concomitant contraception method during the first 7 days of tablet intake. However, if she already has had intercourse, pregnancy must be excluded, before she starts the tablets, or she should wait for her first menstrual bleeding.

Missed tablets
The contraceptive effect may be reduced in case of forgotten tablet intake, especially if the forgotten tablets prolong the tablet-free interval-

If the woman has forgotten tablet intake for less than 12 hours, the woman should take the tablet as soon as she remembers this, and the remaining tablets should be taken at the usual time.

If the delay exceeds 12 hours, the contraceptive protection may be reduced.

The woman should take the last missed tablet as soon as she remembers this, even if this means that she has to take 2 tablets at the same time. Hereafter, she continues taking the tablets at the usual time point. She should use a barrier method concomitantly for the next 7 days.

If there are less than 7 days back in the actual package the woman should continue taking the pills in the package until the actual package is empty, there will be no tablet-free interval. This will prevent a prolonged tablet-free interval, which increases the risk of premature ovulation. A withdrawal bleeding is unlikely until the end of the second blister pack, but she may experience spotting or break through bleeding on the days she is taking tablets.

If no bleeding occurs after finishing the second package the possibility of pregnancy must be eliminated before the woman continues with the tablets in the next package.

What to do in case of vomiting/diarrhoea
If vomiting occurs within 3-4 hours after tablet taking, absorption may not be complete. In this case the advice concerning missed tablets, described above should be followed. The woman should take the required extra tablet(s) from another blister pack.
In case of longer lasting or severe gastrointestinal symptoms, the woman should be advised to use another contraceptive method and/or to contact her physician.
How to delay or shift a withdrawal bleeding
In order to delay a withdrawal bleeding, the woman should continue the next blister pack of Millinette without a tablet-free interval. The extension can be carried on for as long as is desired until the end of the second blister pack. During the extension the woman may experience break through bleeding or spotting. Regular intake of Millinette is resumed after the usual 7 days tablet-free interval.

To move menstruation to a weekday other than that on which the woman is used to having it under the current tablet schedule, she can be advised to shorten the next tablet-free period by as many days as she wishes. The shorter the pause, the higher the risk that she will not get her menstruation and will have withdrawal bleeding or spotting while she is taking the next pack (which is also true when menstruation is being delayed).

<u>Special population</u>

Elderly
Not applicable. Millinette is not indicated for use after the menopause.

Hepatic impairment
Millinette is contraindicated in women with hepatic impairment (see section 4.3).

Renal impairment
There are no data available in patients with renal impairment.

Paediatric population
Millinette is recommended only after the first period.

Method of administration

For oral use.

4.3 Contraindications

Combined oral contraceptives (COCs) must not be used in the presence of any of the conditions listed below. Should any of the conditions appear for the first time during COC use, the product must be stopped immediately:

- 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
- Present or previous pancreatitis if associated with serious hypertriglyceridaemia;
- Serious or recent hepatic disorders, as long as liver function tests are not normalised;
- Known or suspected sex-steroid influenced malignant conditions of the breasts or genital organs;
- Present or previous benign or malignant liver tumours
- Undiagnosed vaginal bleeding
- Hypersensitivity to the active substances or to any of the excipients listed in section 6.1.

Millinette is contraindicated for concomitant use with the medicinal products containing

ombitasvir/paritaprevir/ritonavir and dasabuvir, medicinal products containing glecaprevir/pibrentasvir or sofosbuvir/velpatasvir/voxilaprevir (see section 4.5).

4.4 Special warnings and precautions for use

Medical Examination/Consultation
Prior to the initiation or reinstitution of Millinette 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 Millinette 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.

Warnings
If any of the conditions or risk factors mentioned below is present, the suitability of Millinette 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 Millinette 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 Millinette may have up to twice this level of risk. The decision to use any product other than one known to have the lowest VTE risk should be taken only after a discussion with the woman to ensure she understands the risk of VTE with Millinette, 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).

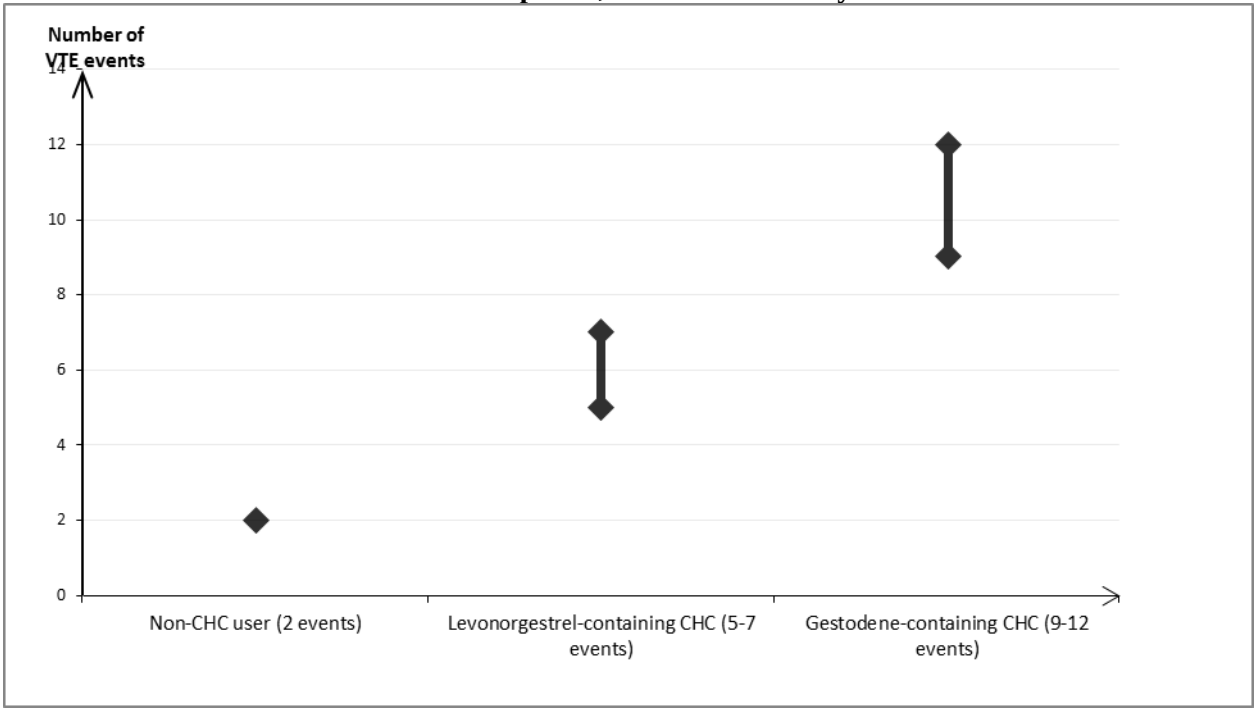
It is estimated[1] that out of 10,000 women who use a CHC containing gestodene between 9 and 12 women will develop a VTE in one year; this compares with about 6[2] in women who use a levonorgestrel-containing CHC.

[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

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



Extremely rarely, thrombosis has been reported to occur in CHC users in other blood vessels, e.g. hepatic, mesenteric, renal, cerebral 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).

Millinette 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.	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.

Note: temporary immobilisation including air travel >4 hours can also be a risk factor for VTE, particularly in women with other risk factors.	Antithrombotic treatment should be considered if Millinette 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 and 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 on "Fertility, pregnancy and lactation" 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). Millinette 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/m^2)	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 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.

Biochemical factors indicating hereditary or acquired predisposition for venous or arterial thrombosis, include activated protein C (APC) resistance, hyperhomocysteinaemia, antithrombin III deficiency, protein C deficiency, protein S deficiency, antiphospholipid antibodies (anticardiolipin antibodies, lupus anticoagulant).

When weighing the advantages/disadvantages the physician should take into consideration that adequate treatment of a given condition may reduce the risk associated with thrombosis and that the risk of developing thrombosis during pregnancy is higher than with low-dose COCs (<50 microgram ethinylestradiol).

Tumours

Cervical cancer
The most important risk factor for cervical cancer is persistent HPV infection. Some epidemi**ological studies have indicated that long-term use of COCs may further contribute to this increased risk but there continues to be controversy about the extent to which this finding is attributable to confounding effects, e.g., cervical screening and sexual behaviour including use of barrier contraceptives.**

Breast cancer
A meta-analysis from 54 epidemiological studies reported that there is a slightly increased relative risk (RR=1.24) of having breast cancer diagnosed in women who are currently using combined oral contraceptives (COCs). The excess risk gradually disappears during the course of the 10 years after stopping COC. As breast cancer is rare among women under 40 years the excess number of breast cancer diagnoses in current and recent COC users is small in relation to the overall risk of breast cancer in their complete life time. The observed pattern of increased risk may be due to an earlier diagnosis of breast cancer in COC users, the biological effects of COCs or a combination of both. The additional breast cancers diagnosed in current users of COCs or in women who have used COCs in the last ten years are more likely to be localised to the breast than those in women who never used COCs.

With the use of the higher-dosed COCs (0.05 mg ethinylestradiol) the risk of endometrial and ovarian cancer is reduced. Whether this also applies to lower-dosed COCs remains to be confirmed.

Hepatic neoplasia/liver disease
In rare cases benign and, in even rarer cases, malignant liver tumours have been reported. In isolated cases these tumours have led to life-threatening intra-abdominal haemorrhage. If severe upper abdominal complaints, liver enlargement or signs of intra-abdominal haemorrhage occur, the possibility of a liver tumour should be included in the differential diagnosis in women taking COCs.

Acute or chronic disturbances of liver function may necessitate the discontinuation of COC use until markers of liver function return to normal.

Other conditions

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.

Women with hypertriglyceridaemia, or a family history thereof, may be at increased risk of pancreatitis when taking COCs.

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.

It has been reported that the following conditions may occur, or worsen both during pregnancy and during use of COCs, but the evidence of a relationship is inconclusive: Jaundice and/or pruritus in connection with cholestasis; development of gallstones; porphyria; systemic lupus erythematosus; haemolytic uraemic syndrome; Sydenham's chorea; herpes gestationis; loss of hearing due to otosclerosis.

Acute or chronic disturbances of liver function may necessitate the discontinuation of COC use until markers of liver function return to normal. Re-emergence of cholestatic jaundice which first occur during pregnancy or previous use of sex hormones requires withdrawal of the use of COCs.

There are reports about liver damage when using CHCs. Early identification of drug related liver damage may reduce the severity of liver toxicity upon withdrawal of the drug. If liver damage is diagnosed the patient must stop using oral contraceptives, use non-hormonal contraception and contact her physician.

Although COCs may have an effect on peripheral insulin resistance and glucose tolerance, there is no evidence for a need to alter the therapeutic regimen in diabetics using low-dose COCs (containing <50 microgram ethinylestradiol). However, diabetic women should be carefully monitored, particularly in the early stage of COC use.

Crohn's disease and colitis ulcerosa have been associated with the use of combined oral contraceptives.

Chloasma may occur, in particular in women with a medical history of chloasma gravidarum. Women with a tendency to chloasma should avoid exposure to sunlight or ultraviolet radiation while taking COCs.

Migraine/headache
Women with migraine (especially migraine with aura) using CHCs may have an increased risk of having a stroke.

The immune system
Angioedema
Exogenous estrogens may induce or exacerbate symptoms of hereditary and acquired angioedema.

Herbal preparations containing St John's wort (*Hypericum perforatum*) should not be used while taking Millinette due to the risk of decreased plasma concentrations and reduced clinical effects of Millinette (see section 4.5).

Reduced efficacy
The efficacy of oral contraceptives may be reduced in the case of missed tablets or vomiting (see section 4.2) or concomitant use of other medicinal product (see section 4.5).

Reduced cycle control
With all combined oral contraceptives, irregular bleeding (spotting or break through bleeding) may occur, especially during the first months. Hence, the evaluation of any irregular bleeding should be considered after a period of adaptation of approximately 3 cycles.

If bleeding irregularities occur after previously regular cycles, then non-hormonal causes should be considered, and adequate diagnostic measures are indicated to exclude malignancy or pregnancy. These may include curettage. If non-hormonal causes are ruled out recommending COC with a higher hormone content may be considered.

In some women withdrawal bleeding may not occur during the tablet-free interval. If the tablets have been taken according to the instructions described in section 4.2, it is unlikely that the woman is pregnant. However, if the tablets have not been taken according to the instructions, before the first absent withdrawal bleeding or if two withdrawal bleeds are missed, pregnancy must be ruled out before COC use is continued.

Excipients
This medicinal product contains lactose and sucrose.
Patients with rare hereditary problems of galactose intolerance, total lactase deficiency, glucose-galactose malabsorption, fructose intolerance or sucrase-isomaltase insufficiency should not take this medicine.

This medicinal product contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

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

Pharmacodynamic interactions
During clinical trials with patients treated for hepatitis C virus infections (HCV) with 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 or sofosbuvir/velpatasvir/voxilaprevir, ALT elevations were observed in women using ethinylestradiol-containing medications such as CHCs (see section 4.3). Therefore, Millinette users must switch to an alternative method of contraception (e.g., progestagen-only contraception or non-hormonal methods) prior to starting therapy with these combination drug regimens. Millinette can be restarted 2 weeks following completion of treatment with these combination drug regimens.

Pharmacokinetic interactions

Effects of other medicinal products on Millinette

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

Management
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.

Short-term treatment
Women on 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 tablets in the COC pack, the next COC pack should be started right after the previous one without the usual tablet-free interval.

Long-term treatment
In women on long-term treatment with enzyme-inducing active substances, another reliable, non-hormonal, method of contraception is recommended.

The following interactions have been reported in the literature.

Substances increasing the clearance of COCs (diminished efficacy of COCs by enzyme-induction), e.g
Barbiturates, bosentan, carbamazepine, phenytoin, primidone, rifampicin and HIV medication ritonavir, nevirapine and efavirenz and possibly also felbamate, griseofulvin, oxcarbazepine, topiramate and products containing the herbal remedy St. John's Wort (*Hypericum perforatum*).

Substances with variable effects on the clearance of COCs
When co-administered with COCs, many combinations of HIV protease inhibitors and non-nucleoside, reverse transcriptase inhibitors, including combinations with HCV inhibitors can increase or decrease, plasma concentrations of estrogen or progestins. The net effect of these changes may be clinically, relevant in some cases.

Therefore, the prescribing information of concomitant HIV/HCV medications should be consulted to identify potential interactions and any related recommendations. In case of any doubt, an additional barrier contraceptive method should be used by women on protease inhibitor or non-nucleoside reverse transcriptase inhibitor therapy.

Substances decreasing the clearance of COCs (enzyme inhibitors):

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

Concomitant administration of strong CYP3A4 inhibitors can increase plasma concentrations of the estrogen or the progestin 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.

Effects of Millinette on other medicinal products

COCs may affect the metabolism of certain other active substances. 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 moderate (e.g. tizanidine) increase in their plasma concentration.

Laboratory tests
The use of contraceptive steroids may influence the results of certain laboratory tests, including the biochemical parameters of liver, thyroid, adrenal, and renal function; plasma levels of (carrier) proteins, e.g. corticosteroid-binding globulin and lipid/lipoprotein fractions; parameters of carbohydrate metabolism and parameters of coagulation and fibrinolysis. Changes generally remain within the normal laboratory range.

4.6 Fertility, pregnancy and lactation

Pregnancy
Millinette is not indicated during pregnancy. If pregnancy occurs during medication with Millinette, the preparation should be withdrawn immediately.
There is no conclusive evidence that the oestrogen and gestagen adversely affects the foetus if conception inadvertently happens during the use of COCs.

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

Breast-feeding
Should not be used.
Lactation may be influenced by COCs as they may reduce the amount and change the composition of human milk. Hence, the use of oral contraceptives cannot generally be recommended until the lactating mother has completely weaned off the child. Small amounts of contraceptive steroids and/or their metabolites can be excreted with the milk, but there is no evidence that this adversely affects infant health.

4.7 Effects on ability to drive and use machines

Millinette has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Description of selected adverse reactions

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

The following serious adverse events have been reported in women using COCs, see sections 4.3 and 4.4.

- Benign liver tumours (e.g. focal nodular hyperplasia, hepatic adenomas).
- Cervical intraepithelial neoplasia and cervical cancer
- Breast cancer.

In the beginning of the treatment period a large part (10-13%) of women may expect adverse events such as headache, breast tenderness, malaise and spot bleeding. These adverse events are usually temporary and disappear after 2-4 months.

The following adverse events were reported by users of COCs but the connection with the use of COCs is neither confirmed or ruled out:

Infections and Infestations Common (≥1/100 to <1/10)	Vaginitis, including candidiasis
Neoplasms benign, malignant and unspecified (including cysts and polyps) Very rare (<1/10,000, including isolated cases)	Hepatocellular carcinomas
Blood and lymphatic system disorders Very rare (<1/10,000, including isolated cases)	Exacerbation of varicose veins
Immune system disorders Rare (≥1/10,000 to <1/1,000) Rare – very rare (<1/1,000) Not known (frequency cannot be estimated from the available data)	Anaphylactic/ anaphylactoid reactions including very rare cases of urticaria, angiooedema and serious reactions with circulatory and respiratory symptoms General disease in the immune system, hypersensitivity. Exacerbation of systemic lupus erythematosus exacerbation of symptoms of hereditary and acquired angioedema
Metabolism and Nutrition disorders Uncommon (≥1/1,000 to <1/100) Rare (≥1/10,000 to <1/1,000) Very rare (<1/10,000, including isolated cases)	Fluid retention. Changed appetite (increased or reduced) Reduced glucose-tolerance Exacerbation of porpfyria

Psychiatric disorders Common (≥1/100 to <1/10) Uncommon (≥1/1,000 to <1/100) Rare – very rare (<1/1,000)	 Depression/ mood swings Reduced libido Increased libido
Nervous system disorders Very common (≥1/10) Uncommon (≥1/1,000 to <1/100) Common (≥1/100 to <1/10) Very rare (<1/10,000, including isolated cases)	 Headache Migraine Nervousness, dizziness Exacerbation of chorea
Eyes Rare – very rare (<1/1,000) Very rare (<1/10,000, including isolated cases)	 Ocular irritation when wearing contact lenses Optical neuritis, retinal vascular thrombosis
Ear and Labyrinth Rare – very rare (<1/1,000)	 General disease in ear and labyrinth
Vascular disorders Uncommon (>1/1,000 to <1/100) Rare (≥1/10,000 to <1/1,000)	 Hypertension Venous or arterial thromboembolism
Gastrointestinal disorders Common (≥1/100 to <1/10) Uncommon (≥1/1,000 to <1/100) Rare – very rare (<1/1,000) Very rare (<1/10,000, including isolated cases)	 Nausea, abdominal pain Vomiting, diarrhoea Other disease in the gastrointestinal tract Pancreatitis, ischaemic colitis Inflammatory intestinal disorder (Crohns disease, ulcerative colitis)
Hepatobiliary Disorders Rare (≥1/10,000 to <1/1,000) Very rare (<1/10,000, including isolated cases) Not known (frequency cannot be estimated from the available data)	 Jaundice Gall bladder disease including gall stones Liver damage (such as hepatitis, abnormal liver function)
Skin and Subcutaneous Tissue	

disorders Common (≥1/100 to <1/10)	Acne
Uncommon (≥1/1,000 to <1/100)	Rash, urticaria, chloasma (melasma) which may be permanent, hirsutism, alopecia
Rare – very rare (<1/1,000)	Various skin diseases (such as erythema multiforme, erythema nodosum)
Renal and Urinary Disorders Very rare (<1/10.000, including isolated cases)	Haemolytic uraemic syndrome
Reproductive system and breast disorders Very common (≥1/10)	Spot bleeding/ break-through bleeding.
Common (≥1/100 to <1/10)	Breast tenderness, pain, swelling, secretion. Dysmenorrhoea, changes in vaginal secretion, amenorrhea
Investigations Common (≥1/100 to <1/10)	Weight increase
Uncommon (≥1/1.000 to <1/100)	Changes in plasma-lipid values including hyper-triglyceridaemia
Rare (≥1/10,000 to <1/1,000)	Reduction of folate level in plasma
Rare – very rare (<1/1,000)	Weight decrease

The following serious adverse events have been reported in women using COCs, see sections 4.3 and 4.4.

- Venous thromboembolism, i.e. deep leg or pelvic venous thrombosis and pulmonary embolism.
- Arterial thromboembolic disorders
- Cervical cancer
- Liver tumours
- Skin and subcutaneous disorders: chloasma; erythema nodosum.

The frequency of diagnosis of breast cancer is very slightly increased among COC-users. As breast cancer is rare in women under 40 years of age the excess number is small in relation to the overall risk of breast cancer. Causation with COC use is unknown. For further information, see sections 4.3 and 4.4.

Interactions

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

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 the Yellow Card Scheme, website: www.mhra.gov.uk/yellowcard.

4.9 Overdose

No serious, harmful effects after overdose have been reported.

Symptoms:
Nausea, vomiting, and in young girls a slight vaginal bleeding.

Treatment:
There is no antidote, and further treatment should be symptomatic.

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Sex hormones and modulators of the genital system; Progestogens and estrogens, fixed combinations; ATC code: G03AA10

The contraceptive effect of contraceptive pills rests on the interaction of various factors, the most important of which are inhibition of ovulation and changes in cervical secretions. Besides protection from pregnancy, contraceptive pills have several positive qualities which, when considered against their negative points, are useful to know when one is making a decision about the prevention of pregnancy. The menstrual cycle becomes more regular, menstruation is often less painful, and bleeding is not as heavy. The latter can contribute to reducing the occurrence of iron deficiency. In addition to this, it has been demonstrated that high-dosage contraceptive pills (50 µg ethinylestradiol) lower the risk of fibrocystic tumours of the breast, ovarian cysts, adnexitis, ectopic pregnancy, as well as endometrial and ovarian cancer. It has not yet been confirmed whether this also applies to low-dosage contraceptive pills.

5.2 Pharmacokinetic properties

Gestodene
Absorption
Gestodene, when taken orally, is absorbed quickly and completely. Following a single dose the maximum serum concentration of 4 ng/mL is reached in approximately one hour. Bioavailability is approximately 99%.

Distribution
Gestodene is bound to serum albumin and to sex hormone binding globulin (SHBG). Only 1-2% of the total amount of gestodene in serum is found as free steroid, while 50-70% is specifically bound to SHBG. The ethinylestradiol-induced increase in SHBG influences the distribution of serum proteins, which causes an increase of the SHBG-bound fraction, and a decrease of the albumin-bound fraction. The apparent distribution volume of gestodene is 0.7 L/kg.

Biotransformation
Gestodene is metabolised completely via the known pathways of steroid metabolism. The metabolic clearance rate from serum is 0.8 mL/min/kg. No interaction occurs when gestodene is taken together with ethinylestradiol.

Elimination
Serum level of gestodene is reduced at 2 rates. The last rate is characterised by a half-life of 12-15 hours. Gestodene is not excreted. Its metabolites are excreted in urine and in bile at a ratio of 6:4.
The half-life of metabolite excretion is approximately 1 day.

Steady-state
Pharmacokinetics of gestodene is influenced by the levels of SHBG in serum, which increase to triple values with ethinylestradiol. Upon daily intake, the level of gestodene in serum increases till approximately four times the single dose value, and reaches steady-state within the second half of the treatment cycle.

Ethinylestradiol
Absorption
Ethinylestradiol, taken orally, is absorbed quickly and completely. Maximal serum concentration of about 80 pg/mL is reached within 1-2 hours. Complete bioavailability, resulting from pre-systemic conjugation and first-pass metabolism, is approximately 60%.

Distribution
Ethinylestradiol is predominantly bound non-specifically to albumin (approx. 98.5), and causes increase in serum concentration of SHBG. The apparent distribution volume is found to be approximately 5 L/kg.

Biotransformation
Ethinylestradiol undergoes pre-systemic conjugation both in the mucosa of the small intestine, and in the liver. Ethinylestradiol is primarily metabolised by aromatic hydroxylation, but many different hydroxylated and methylated metabolites are formed, and found as free metabolites and as glucuronide and sulphate conjugates. The metabolic clearance rate is approximately 5 mL/min/kg.

Elimination
Serum level of ethinylestradiol is reduced at 2 rates, the last one with a half-life of 24 hours. Ethinylestradiol is not excreted, but its metabolites are excreted in urine and in bile at a ratio of 4:6. The half-life of metabolite excretion is approximately 1 day.

Steady-state
Steady-state occurs after 3-4 days, and the serum levels of ethinylestradiol are 30-40% higher than at single dose.

5.3 Preclinical safety data

In order to assess the risk to humans, animal toxicity studies were performed with both ingredients, ethinylestradiol and gestodene, used either separately or in combination.
Systemic tolerance studies did not show any form of undesirable effect, which could indicate an unexpected risk to humans upon repeated intake.

Longer lasting toxicity studies with repeated administration to investigate the risk of tumorigenic activity did not indicate any special risk to humans. It should, however, be pointed out that sex hormones can advance the growth of certain hormone-dependent tissues and tumours.

Studies of toxicity to the embryo and teratogenicity with ethinylestradiol and assessment of the effects of the combination on the fertility of the parent animals, development of the foetus, lactation, and reproductive ability revealed no risk of undesirable effects for humans with the recommended use of the preparation.
In vitro and *in vivo* studies do not indicate a risk of mutagenicity.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:

Sodium calcium edetate

Magnesium stearate

Silica colloidal anhydrous

Povidone K-30

Maize starch

Lactose monohydrate

Tablet coat:

Quinoline yellow (E 104)

Povidone K-90

Titanium dioxide (E 171)

Macrogol 6000

Talc

Calcium carbonate (E170)

Sucrose

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Store below 25°C. Store in the original package in order to protect from light and moisture.

6.5 Nature and contents of container

Blister: PVC/PVDC/aluminium.

Blister: PVC/PVDC/aluminium in PETP/aluminium/PE bag.

Pack sizes: 1 x 21 tablets; 3 x 21 tablets, 6 x 21 tablets, 13 x 21 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements for disposal.

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

7 MARKETING AUTHORISATION HOLDER

Gedeon Richter Plc.
19-21 Gyömrői út
1103 Budapest
Hungary

8 MARKETING AUTHORISATION NUMBER(S)

PL 04854/0122

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10 DATE OF REVISION OF THE TEXT

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