Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Mistra 2mg/0.03mg Film-Coated Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 2 mg dienogest and 0.03 mg ethinylestradiol.

Excipient with known effect:
Each film-coated tablet contains 47.66 mg lactose monohydrate.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet.

White or almost white, round, biconvex film-coated tablets, diameter about 5.5 mm. Engraving on one side: "G53"; other side: without engraving.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Oral contraception.

Treatment of moderate acne after failure of suitable topical therapies or oral antibiotic treatment in women who elect to use an oral contraceptive.

The decision to prescribe Mistra 2 mg/0.03 mg film-coated tablets should take into consideration the individual woman's current risk factors, particularly those for venous thromboembolism (VTE), and how the risk of VTE with Mistra 2 mg/0.03 mg film-coated tablets compares with other combined hormonal contraceptives (CHCs) (see sections 4.3 and 4.4).

4.2 Posology and method of administration

Method of administration
Oral use.

Posology
How to take Mistra 2 mg/0.03 mg film-coated tablets

Mistra 2 mg/0.03 mg film-coated tablets must be taken as described in the following for hormonal contraception as well as for the treatment of women with moderately severe acne. For maintenance of contraceptive efficacy, the advice in section "Management of missed tablets" is to be observed.

One tablet is to be taken daily for 21 consecutive days.The tablets must be taken every day at about the same time, if necessary with a little liquid, in the order shown on the blister pack. Intake of tablets from the next blister pack is started after a 7-day tablet-free interval, during which time usually a withdrawal bleed occurs. This usually starts 2-3 days after taking the last tablet and may not have finished before the next pack is started.

Apparent improvement of acne usually takes at least three months and further improvement has been reported after six months of treatment. Women should be assessed 3-6 months after treatment initiation and periodically thereafter to review the need for continuation of treatment.

Beginning of the intake of Mistra 2 mg/0.03 mg film-coated tablets

No preceding hormonal contraceptive use (in the past month)
Tablet taking is to be started on the first day of the natural cycle (i.e. the first day of the menstrual bleeding).

Changing from another combined oral contraceptive (COC)
The intake of Mistra 2 mg/0.03 mg film-coated tablets should preferably start on the day after intake of the last active tablet (the last tablet containing active substances) of the previously used COC, but at the latest on the day following the usual tablet-free or placebo tablet interval of the previous COC.

Changing from a vaginal ring or transdermal patch
The intake of Mistra 2 mg/0.03 mg film-coated tablets should preferably start on the day of removal of the last ring or patch of one cycle pack, but at the latest when the next application would be due.

Changing from a progestogen-only method (mini pill, injection, implant) or from a progestogen-releasing intrauterine system (IUS)
If the mini-pill has been taken previously, the change can be made on any day (the switch from an implant or an IUS must be made on the day of removal and the switch from an injectable must be made at the time the next injection would be due). In each case, during the first 7 days of tablet taking, the additional use of a barrier method is necessary.

After an abortion in the first-trimester
Intake of Mistra 2 mg/0.03 mg film-coated tablets may start immediately. In this case, no additional contraceptive measures are necessary.

After birth or an abortion in the second-trimester
The woman should be advised to start intake 21 to 28 days after childbirth or an abortion in the second trimester. When starting later, the woman should additionally use a barrier method for the first 7 days. However, if intercourse has already occurred, pregnancy must be excluded before the start of COC intake, or the first menstrual bleed should be awaited.

For breastfeeding women see section 4.6.

Management of missed tablets

If the missed intake is noticed **within 12 hours** after the usual intake time, the tablet must be taken immediately. All following tablets should be taken again at the usual time. Contraceptive protection is not reduced in this case.

If the intake time is exceeded by **more than 12 hours**, contraceptive protection is no longer fully guaranteed. The following two basic rules should be considered in case of missed tablet intake:
- The intake of the tablets must never be interrupted for longer than 7 days;
- 7 days of uninterrupted tablet-taking are required to attain adequate contraceptive protection, i.e. suppression of the hypothalamic-pituitary-ovarian-axis.

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

Week 1
The intake of the last missed tablet should be resumed as soon as possible, even if this means taking two tablets at the same time. Then, the further tablet intakes take place at the usual time. In addition, a barrier method such as a condom should be used for the next 7 days. If intercourse has taken 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 regular tablet-free interval, the higher the risk of a pregnancy.

Week 2
The intake of the last missed tablet should be resumed as soon as possible, even if this means taking two tablets at the same time. Then, the further tablet intakes take place at the usual time.
Provided that the tablets were taken correctly in the 7 days preceding the first missed tablet, there is no need to use additional contraceptive precautions. However, if this is not the case or if more than 1 tablet was missed, additional protective measures should be recommended for 7 days.

Week 3
Because of the forthcoming 7-day tablet-free interval, full contraceptive protection is no longer guaranteed. By adjusting the 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 additional contraceptive measures, provided that in the 7 days preceding the first missed tablet the tablets were taken correctly. If this is not the case, the woman should follow the first option and should use additional precautions for the next 7 days as well.

1. The user should take the last missed tablet as soon as possible, even if this means taking two tablets at the same time. The rest of the tablets are then taken at the usual time. Intake from the next blister pack is started right after finishing the current blister pack, i.e. there should be no tablet-free interval between the two packs. It is unlikely that the user will have a withdrawal bleed until the end of the second pack, but she may experience spotting or break-through bleeding during the intake.

2. Also, discontinuing the intake from the current blister pack can be recommended, followed by a tablet-free interval of up to 7 days, including the days when tablets were missed. Tablet intake is then continued with the next blister pack.

If tablets are missed and subsequently no withdrawal bleeding takes place in the next tablet-free interval, the possibility of a pregnancy should be considered.

Advice in case of gastro-intestinal disturbances
In case of severe gastrointestinal disturbances, absorption of the active substances may not be complete and additional contraceptive measures are necessary. If vomiting occurs within 3-4 hours after intake of the tablet(s), an additional tablet should be taken as soon as possible. If more than 12 hours have elapsed, the advice concerning missed tablets as given in section 4.2 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.

Postponement of the withdrawal bleed
To postpone the withdrawal bleed, intake from the next blister pack should be started directly after finishing a Mistra 2 mg/0.03 mg film-coated tablets blister pack, without a tablet-free interval. Intake can be continued for as long as desired, but only until the second blister pack is finished. During the intake from the second blister pack, break-through bleeding or spotting may occur. After the regular 7 day tablet-free interval, intake of Mistra 2 mg/0.03 mg film-coated tablets can be resumed as usual.

To shift the withdrawal bleed to another day of the week than with the current tablet-taking schedule, the tablet-free interval can be shortened by the desired number of days. The shorter the tablet-free interval, the higher is the probability that a withdrawal bleed will not occur and that break-through bleeding and spotting will occur during intake from the next blister pack (just as when postponing a withdrawal bleed).

Additional information for special patient populations

Paediatric population
Mistra 2 mg/0.03 mg film-coated tablets is only indicated after the menarche.

Elderly
Not applicable. Mistra 2 mg/0.03 mg film-coated tablets is not indicated after the menopause.

Hepatic impairment
Mistra 2 mg/0.03 mg film-coated tablets is contraindicated in women with severe liver disorders (see section 4.3).

Renal impairment
Mistra 2 mg/0.03 mg film-coated tablets has not been investigated in patients with impaired renal function. Available data do not suggest a change of treatment in this patient population.

4.3 Contraindications

Combined hormonal contraceptives (CHCs) should not be used in the following conditions. Should any of the conditions appear for the first time during CHC intake, intake must be discontinued 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
- Pancreatitis or a history thereof if associated with severe hypertriglyceridemia
- Presence or history of severe hepatic disease as long as liver function values have not returned to normal
- Presence or history of liver tumours (benign or malignant)
- Known or suspected sex-steroid influenced malignancies (e.g. of the genital organs or the breasts)
- Undiagnosed vaginal bleeding
- Hypersensitivity to the active substances or to any of the excipients listed in section 6.1.

Mistra 2 mg/0.03 mg film-coated tablet 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

Warnings
If any of the conditions or risk factors mentioned below is present, the suitability of Mistra 2 mg/0.03 mg film-coated tablets 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 Mistra 2 mg/0.03 mg film-coated tablets should be discontinued.

In case of suspected or confirmed thrombosis, CHC use must be discontinued. Due to the teratogenicity of anticoagulant therapy (coumarins), an adequate alternative contraception should be initiated.

Circulatory disorders

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 Mistra 2 mg/0.03 mg film-coated tablets may have up to 1.6 fold this level of risk. The decision to use any product other than one known with the lowest VTE risk should be taken only after a discussion with the woman to ensure she understands**
- the risk of VTE with Mistra 2 mg/0.03 mg film-coated tablets,
- 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).

Epidemiological studies in women who use low dose combined oral contraceptives (<0.05 mg ethinylestradiol) have found that out of 10,000 women between about 6 to 12 will develop a VTE in one year.

It is estimated that out of 10 000 women who use a low dose CHC that contains levonorgestrel, about 6[1] will develop a VTE in a year.

It is estimatedthat out of 10 000 women who use a CHC containing dienogest and ethinylestradiol between 8 and 11[2] women will develop a VTE in one year.

The number of VTEs per year is fewer than the number expected during pregnancy or in the postpartum period.

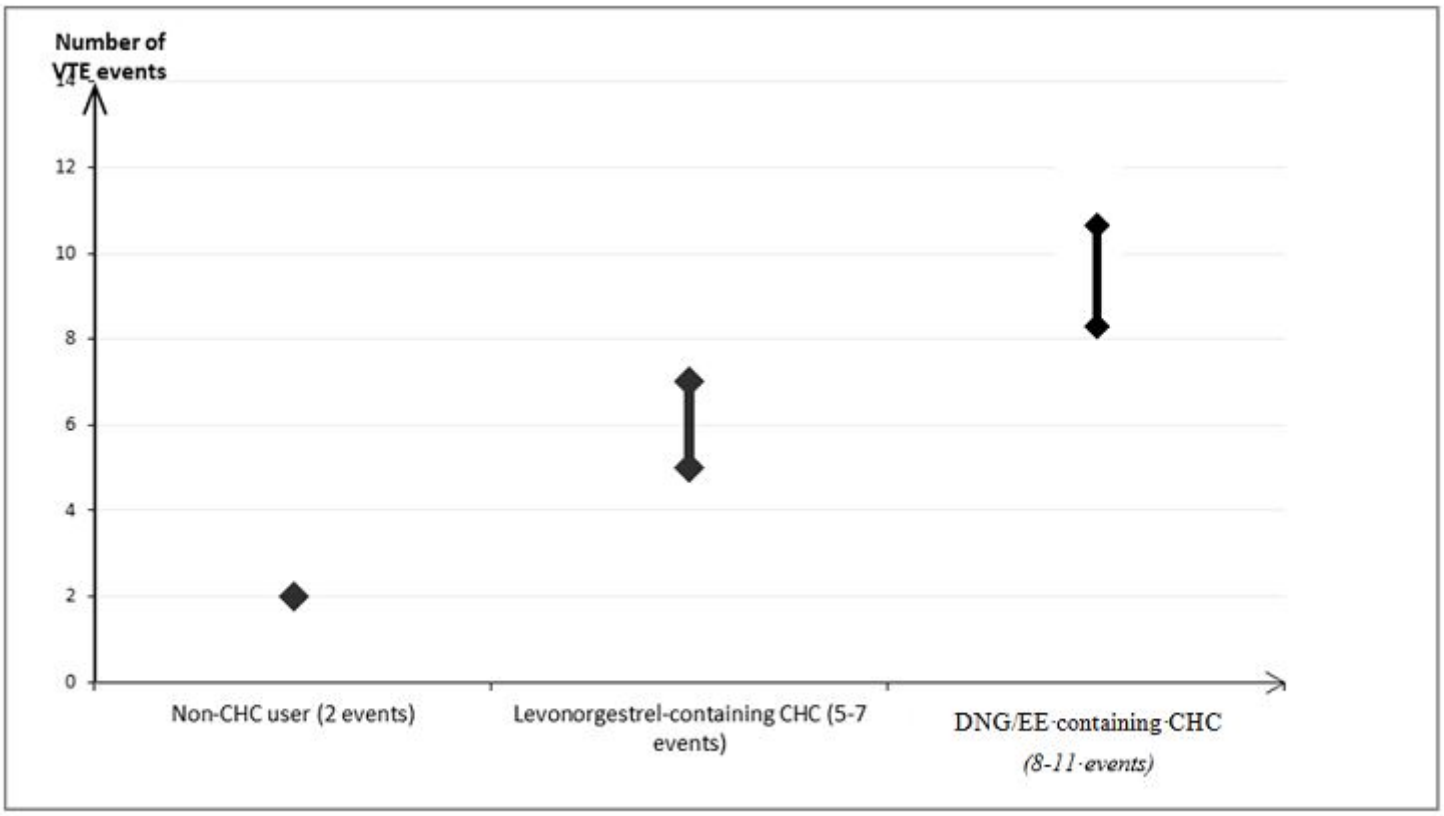
VTE may be fatal in 1-2% of cases.

[1] 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

[2] Data from a meta-analysis estimate that the VTE risk in dienogest and EE users is slightly higher compared to users of COCs containing levonorgestrel (Hazard Ratio of 1.57 with the risk ranging from 1.07 to 2.30)

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 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).

Mistra 2 mg/0.03 mg film-coated tablets 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/m^2)	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 patch/pill/ring (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 Mistra 2 mg/0.03 mg film-coated tablets 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 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). Mistra 2 mg/0.03 mg film-coated tablets 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 (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.

Tumours

An increased risk of cervical cancer in long-term users of COCs (> 5 years) has been reported in some epidemiological studies, but there continues to be controversy about the extent to which this finding is attributable to the confounding effects of sexual behaviour and other factors such as human papilloma virus (HPV).

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 COCs. The excess risk gradually returns to the age related risk during the course of the 10 years after cessation of COC use. 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 overall risk of breast cancer.

In rare cases, benign liver tumours, 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 haemorrhages. A hepatic tumour should be considered in the differential diagnosis when severe upper abdominal pain, liver enlargement or signs of intra-abdominal haemorrhage occur in women taking COCs.

Malignant tumours may be life-threatening or fatal.

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 an increased risk of pancreatitis when using COCs.

Although small increases in blood pressure have been reported in many women taking COCs, clinically relevant increases are rare. However, if, during the use of a COC, constantly elevated blood pressure develops, the doctor should consider discontinuation of the COC and treatment of the hypertension. Where considered appropriate, COC use may be resumed if normotensive values can be achieved with antihypertensive therapy. If, however, during the use of a COC in pre-existing hypertension, constantly elevated blood pressure values or a significant increase in blood pressure do not respond adequately to antihypertensive treatment, the COC must be withdrawn.

The following conditions have been reported to occur or deteriorate with both pregnancy and COC use, but the evidence of an association with COC use is inconclusive: jaundice and/or pruritus related to cholestasis; cholelithiasis; porphyria; systemic lupus erythematosus; haemolytic uraemic syndrome; Sydenham's chorea; herpes gestationis; otosclerosis-related hearing loss.

Exogenous estrogens mayinduce or exacerbate symptoms of hereditary and acquired angioedema.

Acute or chronic disturbances of liver function may necessitate the discontinuation of COC use until markers of liver function return to normal. Recurrence of cholestatic icterus and/or cholestatic pruritus which previously occurred during pregnancy or during previous use of sex steroids necessitates the discontinuation of COCs.

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 diabetic women using low dose COCs (< 0.05 mg ethinylestradiol). However, diabetic women should be carefully observed, particularly in the early stage of COC use.

Worsening of endogenous depression, of epilepsy, of Crohn's disease and of ulcerative colitis has been reported during COC use.

Chloasma may occasionally occur, especially in women with a history of chloasma gravidarum. Women with a tendency to chloasma should avoid exposure to the sun or ultraviolet radiation whilst taking COCs.

Medical examination

Prior to the initiation or reinstitution of Mistra 2 mg/0.03 mg film-coated tablets 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 Mistra 2 mg/0.03 mg film-coated tablets 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 oral contraceptives do not protect against HIV infections (AIDS) and other sexually transmitted diseases.

Reduced efficacy

The efficacy of COCs may be reduced in the event of e.g. missed tablets (see section 4.2), gastrointestinal disturbances (see section 4.2) or when certain other medicinal products are taken concomitantly (see section 4.5).

Irregular bleeding

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 or 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. These may also include curettage.

It is possible that in some women, withdrawal bleeding may not occur during the tablet-free interval. If the COC has been taken according to the directions described in section 4.2, a pregnancy is unlikely. However, if intake has not taken place according to these directions prior to the first missed withdrawal bleed or if two withdrawal bleeds are missed, pregnancy must be ruled out with certainty before COC use is continued.

Excipient
This medicinal product contains 47.66 mg lactose monohydrate per tablet. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

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, Mistra 2 mg/0.03 mg film-coated tablets 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. Mistra 2 mg/0.03 mg film-coated tablets can be restarted 2 weeks following completion of treatment with these combination drug regimens.

Pharmacokinetic interactions
Effects of other medicinal products on Mistra 2 mg/0.03 mg film-coated tablets

Interactions can occur with medicinal products that induce microsomal enzymes. This can result in increased clearance of sex hormones and may lead to break-through bleeding and/or loss of contraceptive efficacy.

Management
Enzyme induction can already be observed after a few days of treatment. Maximal enzyme induction is usually observed within a few weeks. After the cessation of therapy enzyme induction may be sustained for up to 4 weeks.

Short-term treatment
Women on treatment with liver enzyme-inducing medicines 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 duration of the concomitant intake of the medicinal product and for 28 days after its discontinuation.

If any of these medicinal products runs beyond the end of the tablets in the COC blister pack, the next COC blister 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 liver enzyme-inducing medicines, another reliable, non-hormonal method of contraception is recommended.

Substances increasing the clearance of COCs (reduced efficacy of COCs by enzyme-induction), such as:
Barbiturates, carbamazepine, phenytoin, primidone, rifampicin and possibly also oxcarbazepine, topiramate felbamate, griseofulvin and medicinal products containing St. John's Wort (*Hypericum perforatum*).

Substances with variable effects on the clearance of COCs
Many HIV/HCV protease inhibitors and non-nucleoside reverse transcriptase inhibitors as well as combinations thereof can increase or decrease plasma concentrations of estrogens and progestins when administered concomitantly with COCs. 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 doubt, an additional contraceptive barrier method should be used by women during protease inhibitor or non-nucleoside reverse transcriptase inhibitor therapy.

Substances (enzyme inhibitors) reducing the clearance of COCs
The clinical relevance of potential interactions with enzyme inhibitors remains unclear. Concomitant use of strong CYP3A4 enzyme inhibitors may increase plasma concentration of estrogen or progestin or both. It was shown for etoricoxib in doses of 60 to 120 mg/day to increase plasma concentration of ethinylestradiol 1.4- or 1.6-fold, if COCs containing 35 microgram ethinylestradiol are taken concomitantly.

Effects of Mistra 2 mg/0.03 mg film-coated tablets on other medicinal products
COCs may affect the metabolism of other active substances. Accordingly, plasma and tissue concentrations may either be increased (e.g. ciclosporin) or decreased (e.g. lamotrigine).

Based on in vitro data, an inhibition of CYP enzymes by dienogest is unlikely when used in therapeutic doses.

Clinical data suggest that ethinylestradiol inhibits the clearance of CYP1A2 substrates and leads to a slight (e.g. theophylline) or moderate (e.g. tizanidine) increase of plasma concentrations.

Laboratory tests
The use of steroid contraceptives may influence the results of certain laboratory tests, including biochemical parameters of liver, thyroid, adrenal and renal function, as well as 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 range.

4.6 Fertility, pregnancy and lactation

Pregnancy
Mistra 2 mg/0.03 mg film-coated tablets is not indicated during pregnancy.

If pregnancy occurs during intake of Mistra 2 mg/0.03 mg film-coated tablets, the medicinal product must be discontinued immediately. Extensive epidemiological studies have revealed neither an increased risk of birth defects in children born to women who used COCs prior to pregnancy, nor a teratogenic effect when combined oral contraceptives were taken inadvertently during pregnancy.

Animal studies have shown undesirable effects during pregnancy and lactation (see section 5.3). Based on these study results in animals, an undesired hormonal effect of the active substances cannot be excluded. However, general experience with COCs during pregnancy did not provide evidence for an undesirable effect in humans.

The increased risk of VTE during the postpartum period should be considered when re-starting Mistra 2 mg/0.03 mg film-coated tablets (see sections 4.2 and 4.4).

Breast-feeding
Breast-feeding may be influenced by COCs as they may reduce the quantity and change the composition of breast milk. Small amounts of the contraceptive steroids and/or their metabolites may be excreted with the milk during COC use. These amounts may affect the child. Therefore, Mistra 2 mg/0.03 mg film-coated tablets should not be used until complete weaning of the child.

4.7 Effects on ability to drive and use machines

No studies to evaluate the effect on the ability to drive and use machines have been performed. No effects on the ability to drive and use machines have been observed in COC users.

4.8 Undesirable effects

The frequencies of undesirable effects in clinical studies (n = 4,942) during the use of {dienogest 2 mg and ethinylestradiol 0.03 mg} tablets for oral contraception and for the treatment of women with moderate acne that do not show contraindications for oral contraceptives and after failure of suitable topical treatments are summarized in the following table. Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

The frequency rates are defined as “common” (≥ 1/100 to < 1/10), “uncommon” (≥ 1/1,000 to < 1/100) and “rare” (≥ 1/10,000 to < 1/1,000). Additional undesirable effects that only occurred during post-marketing studies and whose frequency cannot be estimated are listed under “not known”.

System Organ Class (MedDRA)	**Common**	**Uncommon**	**Rare**	**Not known**
Infections and infestations		vaginitis/vulvovagi-nitis, vaginal candidiasis or vulvovaginal fungal infections	salpingo-oophoritis, urinary tract infections, cystitis, mastitis, cervicitis, fungal infections, candidiasis, oral herpes, influenza, bronchitis, sinusitis, infections of the upper respiratory tract, viral infections	
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)			uterine leiomyoma, lipoma of breast	

Blood and lymphatic system disorders			anaemia	
Immune system disorders			hypersensitivity	exacerbation of symptomsof hereditary and acquired angioedema
Endocrine disorders			virilism	
Metabolism and nutrition disorders		increased appetite	anorexia	
Psychiatric disorders		depressed mood	depression, mental disorders, insomnia, sleep disorders, aggression	mood changes, libido increased, libido decreased
Nervous system disorders	headache	dizziness migraine	ischaemic stroke, cerebrovascular disorders, dystonia	
Eye disorders			dry eye, eye irritations, oscillopsia, vision decreased	contact lens intolerance
Ear and labyrinth disorders			sudden hearing loss, tinnitus, vertigo, deterioration of hearing	
Cardiac disorders			cardiovascular disorders, tachycardia[3]	
Vascular disorders		hypertension, hypotension	venous thromboembolism (VTE), arterial thromboembolism (ATE), pulmonary embolism, thrombophlebitis diastolic hypertension, orthostatic dysregulation, hot flushes, varicose veins, vein discomfort, vein pain	

Respiratory, thoracic and mediastinal disorders			asthma, hyperventilation	
Gastrointestinal disorders		abdominal pain[4], nausea, vomiting, diarrhoea	gastritis, enteritis, dyspepsia	
Skin and subcutaneous tissue disorders		acne, alopecia, skin rash[5], pruritus[6]	allergic dermatitis, atopic dermatitis/neuroder-matitis, eczema, psoriasis, hyperhidrosis, chloasma, pigmentation, disorders/hyperpig-mentation, seborrhoea, dandruff, hirsutism, skin changes, skin reactions, orange peel skin, spider naevus	urticaria, erythema nodosum, erythema multiforme
Musculoskeletal and connective tissue disorders			back pain, musculoskeletal disorders, myalgia, pain in the extremities	

Reproductive system and breast disorders	breast pain[7]	irregular withdrawal bleeding[8], intermenstrual bleedings[9], breast enlargement[10], breast oedema, dysmenorrhoea, vaginal discharge, ovarian cyst, pelvic pain	cervical dysplasia, cysts in the adnexa uteri, pain in the adnexa uteri, breast cysts, fibrocystic mastopathy, dyspareunia, galactorrhoea, menstruation disorders	breast discharge
Congenital, familial and genetic disorders			manifestation of an accessory breast	
General disorders and administration site condition		fatigue[11]	chest pain, peripheral edema, influenza-like symptoms, inflammations, pyrexia, irritability	fluid retention
Investigations		weight increased	increase of blood triglycerides, hypercholesterolemia, weight decreased, weight fluctuation	

[3] Including accelerated heart rate
[4]: Including pain in upper and lower abdomen, abdominal discomfort, bloating,
[5]: Including macular exanthema
[6]: Including generalised pruritus
[7]: Including breast discomfort and breast tension
[8]: Including menorrhagia, hypomenorrhoea, oligomenorrhoea and amenorrhoea
[9]: Consisting of vaginal haemorrhage and metrorrhagia
[10]: Including swelling of breast/swelling
[11]: Including asthenia and malaise

In order to describe a certain undesirable effect, the most appropriate MedDRA terms (version 12.0) are listed. Synonyms or related conditions are not listed, but should be taken into account as well.

Description of selected adverse reactions
The following serious adverse events have been reported in COC users, which are discussed in section 4.4 "Special warnings and precautions for use":
Tumours
- The frequency of diagnosis of breast cancer is slightly increased among COC users. As breast cancer is rare in women under 40 years of age, the additional risk is small in relation to the overall risk of developing breast cancer. The causality with COC use is unknown.
- Liver tumours.
- Cervix carcinoma.

Other conditions
- Women with hypertriglyceridemia (increased risk of pancreatitis during COC use);
- Hypertension;
- Occurrence or deterioration of conditions for which association with COC use is not conclusive: cholestatic icterus, formation of gallstones, porphyria, systemic lupus erythematosus, haemolytic uraemic syndrome, Sydenham's chorea, herpes gestationis, otosclerosis-related hearing loss;
- Exogenous estrogens mayinduce or exacerbate symptoms of hereditary and acquired angioedema;
- Liver dysfunction;
- Change in glucose tolerance or influence on peripheral insulin resistance;
- Crohn's disease, ulcerative colitis;
- Chloasma.

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

HPRA Pharmacovigilance
Earlsfort Terrace
IRL - Dublin 2
Tel: +353 1 6764971
Fax: +353 1 6762517
Website: www.hpra.ie
e-mail: medsafety@hpra.ie.

4.9 Overdose

The acute oral toxicity of ethinylestradiol and dienogest is very low. If, for example, a child takes several {dienogest 2 mg and ethinylestradiol 0.03 mg} tablets at the same time, toxic symptoms are therefore unlikely. Symptoms that may possibly occur in this case are nausea and vomiting and, in young girls, slight vaginal bleeding. In general there is no need of special treatment; if necessary, treatment should be supportive.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Sex hormones and modulators of the genital system; Progestogens andestrogens, fixed combinations.
ATC code: G03AA16

All hormonal contraceptives have a very low failure rate if taken according to instructions. The failure rate may be higher if they are not taken according to instructions (e.g. missed pill).

In clinical trials performed with {dienogest 2 mg and ethinylestradiol 0.03 mg} tablets, the following Pearl Index was calculated:
Unadjusted Pearl Index: 0.454 (upper 95% confidence interval: 0.701).
Adjusted Pearl Index: 0.182 (upper 95% confidence interval: 0.358).

Mistra 2 mg/0.03 mg film-coated tablets is an antiandrogenic combination medicinal product for oral contraception containing ethinylestradiol and the progestin dienogest.

The contraceptive effect of Mistra 2 mg/0.03 mg film-coated tablets is based on the interaction of various factors, of which the most important are the inhibition of ovulation and changes in cervical secretion.

The pronounced antiandrogenic effect of the combination of ethinylestradiol and dienogest is, among others, based on the reduction of the androgen concentration in serum. In a multicentre study with {dienogest 2 mg and ethinylestradiol 0.03 mg} tablets, an essential improvement of the symptoms of mild to moderate acne as well as a favourable effect on seborrhoea could be shown.

Dienogest is a 19-nortestosterone derivative, with a 10-30 times lower *in vitro* affinity for the progesterone receptor compared to other synthetic progestogens. *In vivo* data in animals demonstrated a strong progestogenic and antiandrogenic effect. Dienogest has no significant androgenic, mineralocorticoid, or glucocorticoid effect *in vivo*.

The ovulation inhibition dose of dienogest alone was determined to be 1 mg/day.

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.

5.2 Pharmacokinetic properties

Ethinylestradiol

Absorption
Ethinylestradiol is rapidly and completely absorbed after oral administration. Maximum serum concentrations of about 67 pg/ml are reached within 1.5-4 hours. During absorption and first liver passage, ethinylestradiol is extensively metabolized, resulting in a mean oral bioavailability of approximately 44%.

Distribution
Ethinylestradiol is highly but non-specifically bound to serum albumin (approximately 98%), and induces an increase in the serum concentrations of SHBG (sex hormone-binding globulin). The apparent volume of distribution was determined to be 2.8-8.6 1/kg.

Biotransformation
Ethinylestradiol is subject to pre-systemic conjugation in both small bowel mucosa and liver.
It is primarily metabolized by aromatic hydroxylation, but a wide variety of hydroxylated and methylated metabolites are formed. These are present as free metabolites and as conjugates with glucuronides and sulphate.
The clearance rate is approximately 2.3-7 ml/min/kg.

Elimination
Ethinylestradiol serum levels decrease in 2 phases characterized by half-lives of about 1 hour and 10-20 hours. Ethinylestradiol is not excreted in unchanged form. The ethinylestradiol metabolites are excreted at a urinary to biliary ratio of 4:6. The elimination half-life of metabolites is approximately one day.

Steady-state conditions
Steady-state conditions are reached during the second half of the treatment cycle when serum levels are about twofold higher than compared to a single dose.

Dienogest

Absorption
Dienogest is rapidly and almost completely absorbed after oral administration. Maximum serum concentrations of 51 ng/ml are reached at approximately 2.5 hours after single intake of tablet. An absolute bioavailability of approximately 96% was demonstrated in combination with ethinylestradiol.

Distribution
Dienogest is bound to serum albumin and does not bind to SHBG or corticosteroid binding globulin (CBG). About 10% of the total serum drug concentrations are present as free steroid, 90% are non-specifically bound to albumin. The ethinylestradiol-induced increase in SHBG does not influence the serum protein binding of dienogest. The apparent volume of distribution of dienogest is in a range between 37 and 45 l.

Biotransformation
Dienogest is predominantly metabolized through hydroxylation and conjugation, with the formation of endocrinologically largely inactive metabolites. These metabolites are very quickly cleared from plasma so that in human plasma no important metabolite is observed besides unchanged dienogest. The total clearance (Cl/F) is 3.6 1/h after single administration.

Elimination
Dienogest serum levels decrease with a half-life of approximately 9 hours. Only negligible amounts of dienogest are renally excreted in unchanged form. After oral administration of 0.1 mg per kg body weight, the ratio of renal to faecal excretion is 3.2. About 86% of the administered dose is eliminated within 6 days, with the major part, i.e. 42%, being eliminated mainly with the urine in the first 24 hours.

Steady-state conditions
Dienogest pharmacokinetics are not influenced by SHBG levels. Following daily intake drug serum levels increase about 1.5-fold reaching steady-state conditions after 4 days of administration.

5.3 Preclinical safety data

Preclinical studies with ethinylestradiol and dienogest confirmed the expected estrogenic and progestogenic effects.

Preclinical data showed no specific risk for humans based on conventional studies of repeated dose toxicity, genotoxicity, carcinogenic potential and toxicity to reproduction. However, it should be considered that sex steroids can promote the growth of certain hormone-dependent tissues and tumours.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:
Lactose monohydrate
Maize starch
Hypromellose type 2910
Talc
Polacrilin potassium
Magnesium stearate

Film-coating:
Polyvinyl alcohol
Titanium dioxide (E 171)
Macrogol 3350
Talc

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Store below 25ºC. Store in the original packaging in order to protect from light.

6.5 Nature and contents of container

Mistra 2 mg/0.03 mg film-coated tablets are packaged in white PVC/PE/PVDC// Aluminium blisters. The blisters are packed into folding box with package leaflet and etui storage bag is enclosed in each box.

Pack sizes:

21 film-coated tablets
3x21 film-coated tablets

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

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

7 MARKETING AUTHORISATION HOLDER

Gedeon Richter Plc
Gyömroi út 19-21
H-1103, Budapest
Hungary

8 MARKETING AUTHORISATION NUMBER

PA1330/018/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 6th October 2017
Date of last renewal: 3rd March 2021

10 DATE OF REVISION OF THE TEXT

December 2022