SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Serisima 0.03 mg/2.0 mg film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Active ingredient: Ethinylestradiol, Dienogest

1 coated tablet contains:

Ethinylestradiol	30 microgram
Dienogest	2.0 mg

Excipients with known effect: lactose monohydrate (60.90 mg),

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet

White, round film-coated tablets. Approx. 5.0 mm of diameter

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 Serisima should take into consideration the individual woman's current risk factors, particularly those for venous thromboembolism (VTE), and how the risk of VTE with Serisima compares with other CHCs (see sections 4.3 and 4.4).

4.2 Posology and method of administration

Method of administration

Oral use.

Posology

How to take Serisima

One tablet of Serisima daily for 21 consecutive days.

Serisima must be taken both for the hormonal contraception and for the treatment of moderate acne in women according to the following instructions.

The tablets should be taken at approximately the same time of the day each day, if necessary with some liquid.

The first tablet to be taken is the one that corresponds to the day of the week in which the medication is started as written in the blister pack (e.g. “Mo” for Monday).

The rest of the intake is done the in arrow direction, until the blister pack is consumed.

After the first 21 tablets have been taken, a break is made for 7 days. Two to four days after the last tablet, a withdrawal bleed typically begins.

Whether or not a bleed has occurred, the new blister pack is initiated after the 7 treatment-free days.

The contraceptive protection also occurs during the 7-day intake pauses. 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.

How to start of Serisima

• No previous use of hormonal contraception in the past month:

The first day of the cycle (first day of the menstruation) will begin with the intake. When taken correctly, contraception starts on the first day of dosing.

If the intake starts between days 2 and 5, during the first 7 days of the tablet-taking a non-hormonal method of contraception (barrier methods) should be additionally used.

• Switching from another combination compound to hormonal contraception (combined oral contraceptive, vaginal ring, transdermal patch):

Depending on the type of the previously combined oral contraceptive, the intake of Serisima should start either the day after the usual tablet-free interval, following the use of the last active tablet, or the day after the intake of the last placebo tablet of the previously completed combined oral contraceptive. If a transdermal patch or a vaginal ring was used before, then, the intake of Serisima should start the day after the usual ring-free or patch-free interval.

• Switching from a progestogen-only method (mini-pill, implants, injectable forms) or from an intrauterine device:

If the mini-pill has been taken before, the switch can be made any day; the conversion from an implant or an intrauterine device has to happen on the day of the removal; and for an injection compound, at the moment when the next injection is due. In any case, during the first 7 days of the intake of Serisima, it is necessary to use a non-hormonal protection method (barrier method).

• After an abortion in the first trimester, the intake of Serisima can be started immediately. In this case, no additional contraceptive measures are necessary.

• After birth or an abortion in the second trimester (for use during the lactation period, see section 4.6).

Since in the period immediately following childbirth, the risk of thromboembolic events is increased, the intake of oral contraceptives should not be started until 21 to 28 days after childbirth for non-lactating mothers or after an abortion in the second trimester. During the first 7 days of intake, a non-hormonal contraceptive method (barrier method) should be additionally used. If intercourse has already taken place, pregnancy should be excluded or it is necessary to wait until the first spontaneous menstruation before beginning to take the medication.

Management of missed doses

The contraceptive effect of Serisima can be reduced if it is not taken regularly.

If the intake is missed once, but resumed **within 12 hours** from the usual intake time, the contraceptive effect is not affected. All following tablets should be taken again at the usual time.

If the tablet is taken **more than 12 hours** after the usual intake time, the contraceptive effect can no longer be guaranteed. The probability of pregnancy becomes higher the closer the forgotten tablet is to the tablet-free interval.

If the usual withdrawal bleed does not occur following the forgotten dose, pregnancy should be excluded until a new blister pack is started.

The two following rules apply in case of missing to take the tablet:

1. The intake of the tablet should not be interrupted for longer than 7 days.

2. A regular intake of the tablets for at least 7 days is necessary to effectively eliminate the hypothalamus-hypophyseal-ovary axis.

In case of missed tablets, the management is as follows:

- Week 1

The woman should take the last missed tablet as soon as she remembers, even if this means taking two tablets at the same time. She then continues to take tablets at her usual time. However, during the next 7 days an additional barrier method such as a condom should be used. If intercourse took place in the preceding 7 days, the possibility of a pregnancy should be considered. The more tablets are missed and the closer they are to the tablet-free interval the higher the risk of a pregnancy.

- Week 2

The woman should take the last missed tablet as soon as she remembers, even if this means taking two tablets at the same time. She then continues to take the tablets at her usual time. Provided that the woman has taken her tablets correctly in the 7 days preceding the first missed tablet, there is no need to use additional contraceptive precautions. If this is not the case or if she missed more than 1 tablet, the woman should be advised to use additional precautions for 7 days.

- Week 3

A full contraceptive protection cannot be ensured anymore because of the forthcoming 7-days tablet-free interval. However, by adjusting the tablet-intake schedule, reduced contraceptive protection can still be prevented. By adhering to either of the following two options, there is therefore no need for additional contraceptive precautions, provided that in the 7 days preceding the first missed tablet, the woman has taken all tablets correctly. If this is not the case, the woman should follow the instructions described in option 1 and use additional precautions for the next 7 days as well.

1. The woman should take the last missed tablet as soon as she remembers, even if this means taking two tablets at the same time. She then continues to take tablets at her usual time. The next blister pack is to be started right away after finishing of the current blister pack, i.e., there is no tablet-free interval between the two packs. The woman is unlikely to have a withdrawal bleeding until the end of the second pack, but she may experience spotting or breakthrough bleedings during the tablet-taking.

2. The woman can also be advised to discontinue tablet-taking from the current blister pack. She should then have a tablet-free interval of up to 7 days, including the days she missed tablets. She then starts to take tablets from a new blister pack.If the woman missed tablets and subsequently has no withdrawal bleeding in the next regular tablet-free interval, the possibility of a pregnancy should be considered.

<u>Management in case of gastrointestinal disturbances</u>

In case of severe gastrointestinal disturbances, absorption of the active ingredients may not be complete and additional contraceptive measures are necessary. If vomiting occurs in the first 3-4 hours after tablet-taking, the next tablet should be taken as soon as possible. If more than 12 hours elapse, the instructions concerning missed tablets, as given in section 4.2, are applicable. If the woman does not want to change her normal tablet-taking schedule, she has to take the corresponding tablet(s) from another blister pack.

Postponement of the Withdrawal Bleed

To postpone the withdrawal bleed, the user should continue to take the tablets from the next blister pack of Serisima directly, with no tablet-free interval. The withdrawal bleed can be postponed as much as desired, but only until the second blister pack is finished. For that period, breakthrough bleedings or instances of spotting can occur. After the following usual 7-day tablet-free interval, the intake of Serisima can continue as usual.

To change the withdrawal bleeding to a different day of the week as currently, the woman may reduce the forthcoming tablet-free interval by a desired number of days. The shorter is the tablet-free interval, the greater is the possibility that she will has no withdrawal bleeding and that during the intake of the tablets from the next pack breakthrough bleedings or spotting may occur (as in the case of delaying the withdrawal bleeding).

Additional information for particular patient groups

Children and adolescents

Serisima is only indicated after menarche.

Geriatric patients

Not applicable. Serisima is not indicated after menopause.

Patients with hepatic impairment

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

Patients with renal impairment

Serisima has not been specifically studied in renal impaired patients. Available data do not suggest any change in the treatment of this patient group.

4.3 Contraindications

Serisima is contraindicated for concomitant use with the medicinal products containing ombitasvir/paritaprevir/ritonavir, dasabuvir,medicinal products containing glecaprevir/pibrentasvir or sofosbuvir/velpatasvir/voxilaprevir, (see section 4.5).

Combined hormonal contraceptives (CHCs) should not be used in the following conditions. Should any of the below listed conditions appear for the first time during the CHCs 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

- - Presence or history of pancreatitis, if it is associated with severe hypertriglyceridemia.

- - Presence or history of hepatic disease, as long as liver function values have not returned to normal (also Dubin-Johnson and Rotor Syndrome).

- - Presence or history of liver tumors (bening or malignant) .

- - Known or suspected malignant conditions of the genital organs (e.g. in the breast or in the endometrium)

- - Undiagnosed vaginal bleeding.

- - Hypersensitive to any of the active substances or to any of the excipients.

4.4 Special warnings and precautions for use

Warnings

If any of the conditions or risk factors mentioned below is present, the suitability of Serisima 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 Serisima should be discontinued.

In case of suspected or confirmed VTE or ATE, CHC use should be discontinued. In case anti-coagulant therapy is started, adequate alternative contraception should be initiated because of teratogenicity of anticoagulant therapy (coumarins).

Warnings

If any of the conditions or risk factors mentioned below is present, the suitability of Serisima 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 Serisima should be discontinued.

In case of suspected or confirmed VTE or ATE, CHC use should be discontinued. In case anti-coagulant therapy is started, adequate alternative contraception should be initiated because of teratogenicity of anticoagulant therapy (coumarins).

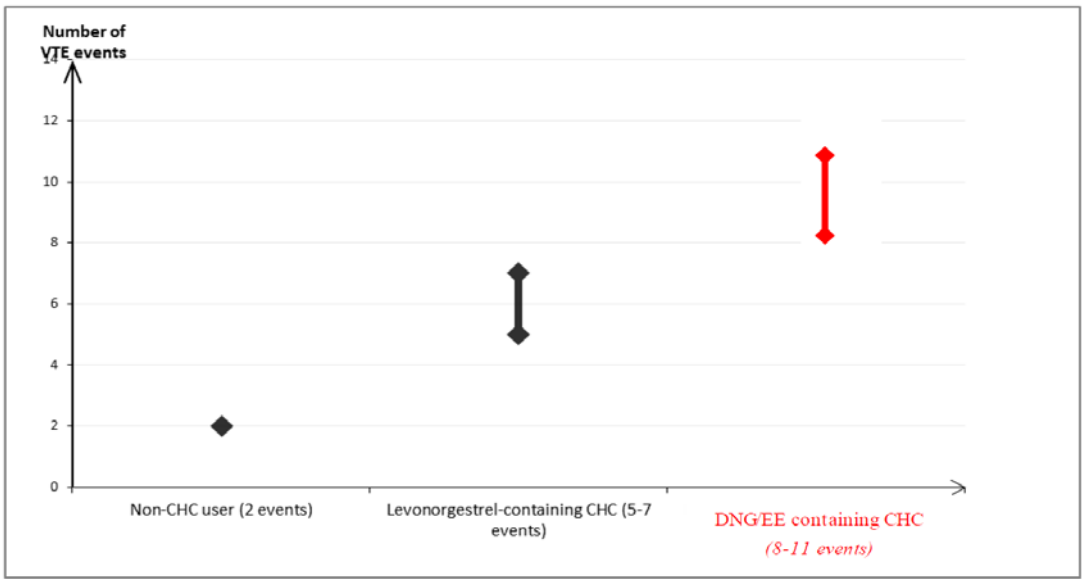
Circulatory Disorders

- **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 Serisima may have up to 1.6 fold this level of risk.The decision to use any product other than one with the lowest VTE risk should be taken only after a discussion with the woman to ensure she understands the risk of VTE with Serisima, 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 (<50 μg 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 levonorgestrel-containing CHC about 6[1] will develop a VTE in one year.
- It is estimated[2] that out of 10,000 women who use a CHC that containing dienogest and ethinylestradiol between 8 and 11[2] women will develop a VTE in one year. ,

Thes number of VTEs per year is fewer than the number expected in women 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



[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 Serisima 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)

- 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).

Serisima 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	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

trauma Note: temporary immobilisation including air travel >4 hours can also be a risk factor for VTE, particularly in women with other risk factors	resume until two weeks after complete remobilisation. Another method of contraception should be used to avoid unintentional pregnancy. Antithrombotic treatment should be considered if Serisima 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 "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). Serisima 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 and 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.

Tumors

Cervix

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).

Breast

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 disappears during the course of the 10 years after cessation of combined COC. 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.

These studies do not provide evidence for causation. 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 breast cancers diagnosed in ever-users tend to be less advanced clinically than the cancers diagnosed in never-users.

Liver
In rare cases, benign liver tumours, and even more rarely, malignant liver tumours have been reported in users of COC. 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 can be life-threatening or fatal.

Other conditions

Hypertension
Although small increases in blood pressure have been reported in many women taking COCs, clinically relevant increases are rare. Only in these rare cases an immediate discontinuation of COC use is justified. If, during the use of a COC in preexisting 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. Where considered appropriate, COC use may be resumed if normotensive values can be achieved with antihypertensive therapy.
Exogenous estrogens may induce or exacerbate symptoms of hereditary and acquired angioedema. Women with hypertriglyceridaemia, or a family history thereof, may be at an increased risk of pancreatitis when using COCs.

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; gallstones; porphyria; systemic lupus erythematosus; haemolytic uraemic syndrome; Sydenham's chorea; herpes gestationis; otosclerosis-related hearing loss.

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 jaundice and/or cholestasis-related 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 diabetics using low-dose COCs (containing <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.

Reduced efficacy
The efficacy of COCs may be reduced in the event of e.g. missed active tablets (see section 4.2), gastro-intestinal disturbances (see section 4.2) or during active tablet taking or concomitant medication (see section 4.5).

Pyschiatric disorders:
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.

Chloasma
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 combined oral contraceptives.

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 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 include curettage.

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, it is unlikely that the woman is pregnant. However, if the COC has not been taken according to these directions prior to the first missed withdrawal bleed or if two withdrawal bleeds are missed, pregnancy must be ruled out before COC use is continued.

Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take Serisima

Medical examination/consultation

Prior the initiation or reinstitution of combined oral contraceptives a complete medical history (including family history) should be taken. Blood pressure should be measured and a physical examination should be performed, guided by the contra-indications (section 4.3) and warnings (section 4.4). It is important to draw a woman's attention to the information on venous and arterial thrombosis, including the risk of Serisima 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.

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.

Effects of other medicinal products on Serisima

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, nonhormonal, 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 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 Serisima 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).

Based on in vitro data, inhibition of CYP enzymes by dienogest appears unlikely when therapeutic doses are administered.

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.

Pharmacodynamic interactions

During clinical trials with patients treated for hepatitis C virus infections (HCV) with the medicinal products containing ombitasvir/paritaprevir/ritonavir and dasabuvir with or without ribavirin, transaminase (ALT) elevations higher than 5 times the upper limit of normal (ULN) occurred significantly more frequent 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 sections 4.3).

Therefore, Serisima 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. Serisima can be restarted 2 weeks following completion of treatment with these combination drug regimens.

Other forms of interactions

Laboratory tests

The use of contraceptive steroids may influence the results of certain laboratory tests, including 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

Serisima is not indicated during pregnancy.

If pregnancy occurs during use, the medication should be discontinued immediately.

Epidemiological studies indicate no increased risk of congenital anomalies in children born to women who used oral contraceptives prior to pregnancy. The majority of recent epidemiological studies also do not indicate a teratogenic effect, when taken inadvertently during early pregnancy. Such studies were not performed with Serisima.

There are too limited data available about the use of Serisima during pregnancy to allow conclusions in terms of negative effects of Serisima on pregnancy and on the health of the fetus or newborn. So far, no relevant epidemiological data are available.

Animal studies have shown undesirable effects during gestation and lactation (see section 5.3). Based on these experimental results in animals, an undesirable hormonal effect of the active substances cannot be ruled out. General experiences with combination compounds for oral contraception during pregnancy, however, did not showed any evidence of adverse effects in humans.

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

Breast-feeding

The lactation can be influenced by the COC, as this can lead to a reduction of the milk production and change composition of the breast milk. Low quantity of steroidal active substances of the contraceptive and/or their matabolites can pass over into breast milk under use of COC and have impact on the child.

Therefore Serisima must not be used until the ablactation of the child.

4.7 Effects on ability to drive and use machines

Serisima has no effect on ability to drive and the ability to drive or operate machines.

4.8 Undesirable effects

The frequencies of adverse events reported n clinical trials (N = 4.942) with Serisima as oral contraception and for the treatment of moderate acne after failure of suitable topical therapies or oral antibiotic treatment in women who elect to use an oral contraceptive are summarized in the following below.

The frequency of possible side effects listed below are defined as:

Common (≥1/100 to <1/10), Uncommon (≥1/1,000 to <1/100), Rare (≥1/10,000 to <1/1,000), Not known (cannot be estimated from the available data)

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

System organ class (MedDRA v.12.0)	**Common**	**Uncommon**	**Rare**	**Not Know**
Infections and infestations		Vaginitis / vulvovaginitis, vaginal candidiasis or other fungal vulvo-vaginal infections	Salpingo-oophoritis, urinary tract infections, cystitis, mastitis, cervicitis, fungal infections candidiasis, oral herpes, influenza, bronchitis, sinusitis, upper respiratory infections, viral infections	
Neoplasms benign, malignant and unspecified (including cysts and polyps)			Uterine leiomyoma, lipoma of breast	
Blood and lymphatic system disorders			Anemia	
Immune system disorders			Hypersensitivity	Exacerbation of symptoms of hereditary and acquired angioedema.
Endocrine disorders			Virilism	
Metabolism and nutrition disorders		Increased appetite	Anorexia	
Psychiatric disorders		Depresse mood	Depression, mental disorders, insomnia, sleep disturbances, aggression	Mood altered libido decresed, libido increased
Nervous system disorders	Headaches	Dizziness, migraines, dizziness	Ischemic stroke, cerebrovascular disorders, dystonia	
Eye disorders			Dry eye, eye irritation, oscillopsia, visual impairment	Contact lens intolerance
Ear and labyrinth disorders			sudden hearing loss, tinnitus, vertigo, hearing impairment	
Cardiac disorders			Cardiovascular disorders, tachycardia [1]	
Vascular disorders		Hypertension, hypotension,	Venous thromboembolism, (VTE) arterial trombiemolism (ATE), pulmonary embolism, thrombophlebitis, diastolic hypertension, orthostatic circulatory dysregulation, hot flush, varicose vein, disorders, veins pain	
Respiratory tract, thoracic and mediastinal disorders			Asthma, hyperventilation	

System organ class (MedDRA v.12.0)	Common	Uncommon	Rare	Not Know
Gastrointestinal disorders		Abdominal pain [2], nausea, vomiting, diarrhea	Gastritis, Enteritis, Dyspepsia	
Skin and subcutaneous tissue disorders		Akne, alopezie, rash[3], pruritus[4]	Dermatitis allergic, dermatitis atopic / neurodermatitis, eczema, psoriasis, hyperhidrosis, chloasma, pigmentation disorder/ hyperpigmentation, seborrhea, dandruff, hirsutism, skin disorders, skin reactions, Peau d'orange , spider naevus	Urticaria, erythema nodosum, erythema multiforme
Musculoskeletal and connective tissue disorders			Back pain, muskoskeletal discomfort, myalgia, pain in the extremity	
Reproductive system and breast disorders	Breast pain[5]	Abnormal withdrawal bleeding[6], intermenstrual bleeding[7], breast enlargement[8], breast oedema, dysmenorrhea, genital/vaginal discharge, ovarian cysts, pelvic pain	Cervical dysplasia, cysts adnexa uteri pain of the adnexa uteri pain, breast cyst, fibrocystic breast disease, dyspareunia, galactorrhea, menstrual disorders	Breast discharge
Congenital, familial and genetic disorders			Manifestation of asymptomatic accessory breast	
General disorders and administration site conditions		Fatigue [9]	Chest pain, oedema peripheral, influenz-like ilness, inflammation, pyrexia, irritability	Fluid retention
Investigations		Weight increased[10]	Blood triglycerides increased, hypercholesterolemia, weight decreased, weight fluctuation	

[1] Including increased heart rate

2 Including te upper and lower adominal pain, abdominal discomfort/distension
[3] Includes rash makulares
[4] Including pruritus generalized
[5] Including breast discomfort and breast tenderness
[6] Including menorrhagia, hypomenorrhoe, oligomenorrhea and amenorrhea
[7] Consists of vaginal hemorrhage and metrorrhagia
[8] Including breast engorgement and breast swelling
[9] Including asthenia and malaise

The most appropriate MedDRA term to describe a certain adverse reaction is 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 women using COCs, which are discussed in section 4.4 'Special warnings and precautions for use'.

Tumors

- The frequency of diagnosis of breast cancer is very slightly increased among OC 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.

- Liver tumors (benign and malignant)
- Cervical Cancer

Other conditions

- Women with hypertriglyceridemia (increased risk of pancreatitis when using COCs)
- Hypertension
- Occurrence or deterioration of conditions for which association with COC use is not conclusive: jaundice and/or pruritus related to cholestasis; gallstone formation; porphyria; systemic lupus erythematosus; hemolytic uremic syndrome; Sydenham's chorea; herpes gestationis; otosclerosis-related hearing loss
- Liver function disturbances
- Changes in glucose tolerance or effect 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 authorization 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 United Kingdom (Northern Ireland) Yellow Card Scheme Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store

4.9 Overdose

The acute oral toxicity of ethinylestradiol and dienogest is very low. If, for example, a child takes several Serisima tablets at the same time, toxic symptoms are unlikely as a result. Symptoms which may occur in such a case are nausea and vomiting and vaginal bleeding. Vaginal bleeding may even occur in girls before their menarche, if they accidentally take the medicinal product. Specific treatment is not normally required. Supportive therapy should be given if necessary

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Progestogens and estrogens, fixed combinations

ATC code: G03AA

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

In clinical trials performed with Serisima the following Pearl index was calculated:
Unadjusted Pearl Index: 0.454 (upper 95% confidence limit: 0.701)
Adjusted Pearl Index: 0.182 (upper 95% confidence limit: 0.358).

Serisima is an effective combined anti-androgenic preparation for oral contraception with ethinylestradiol and the gestagen dienogest.

The contraceptive effect of Serisima is based on the interaction of various factors, the most important of which are seen as the inhibition of ovulation and changes in cervical secretion.

The significant anti-androgenic effect of combinations of ethinylestradiol and dienogest is based, amongst others, on lowering the androgen concentration in serum. In a multicentre study with ethinylestradiol/dienogest a significant improvement in the symptoms of mild to moderate acne and a favourable influence on seborrhoea were observed.

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

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

With the use of the higher-dosed COCs (50 µg 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

Orally administered ethinylestradiol is rapidly and completely absorbed Peak f serum concentrations of about 67 pg/mL, are reached within 1.5 to 4 hours
During absorption and the first-liver passage, ethinylestradiol is metabolized extensively, resulting in a mean oral bioavailability of about 44%.

Distribution

Ethinylestradiol is highly but not-specifically bound to serum albumin (approximately 98%) and induces an increase in the serum concentrations of SHBG (sex hormone-binding globulin). An apparent volume distribution of about 2.8 to

8.6 L/kg was determined

Biotransformation

Ethinylestradiol is subject to presystemic conjugation in small bowel mucosa and the liver. Ethinylestradiol is primarily metabolized by aromatic hydroxylation but a wide variety of different hydroxylated and methylated metabolites are formed, and these are present as free metabolites or and as conjugates with glucuronide and sulphate. The clearance rate was reported to be about 2.3 - 7 mL/min/kg.

Elimination

Ethinylestradiol serum levels decrease in two disposition phases, characterized by half-life of about 1 hour and 10 – 20 hours respectively. Unchanged drug is not excreted. Ethinylestradiol metabolites are excreted at a urinary to biliar ratio of 4: 6. The half-life of metabolite excretion is about 1 day.

Steady-State Conditions

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

- Dienogest

Absorption

Orally administered dienogest is rapidly and almost completely absorbed Peak serum concentrations of 51 ng/mL are reached at about 2.5 hours after single ingestion of Serisima. An absolute bioavailability of about 96% was demostrated in combination with ethinylestradiol.

Distribution

Dienogest is bound to the serum albumin and does not bind to SHBG or corticosteroid-binding globulin (CBG). About 10% of the total serum drug concentration is present as free steroid. 90% is not 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 the range between 37 and 45 L.

Biotransformation

Dienogest is metabolized predominantly through by hydroxylation and conjugation with the formation of endocrinologically largely inactive metabolites. These metabolites are 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 L/h after a single dose.

Elimination

Dienogest serum levels decrease with a half-life in the range of about 9 hours. Only negligible amounts of dienogest are renally excreted in unchanged form. After the

oral administration of 0.1 mg per kg body weight (BW) the ratio of renal to fecal excretion is 3.2. About 86% of the administered dose is eliminated in 6 days, approximately 86% with the major part. 42% being eliminated mainly with the urine in the first 24 hours.

Steady state

Dienogest pharmacokinetics are not influences by the SHBG level. Following daily ingestion drug serum levels increase about 1.5-fold reaching steady-state conditions after about 4 daily administrations.

5.3 Preclinical safety data

Preclinical data with ethinylestradiol and dienogest confirm the expected estrogene and progestine effects.
The preclinical data elevated in scope of conventional studies to toxicity after repeated administration, genotoxicity, carcinogenity and reproductive toxicity did not show any risk for human. However, it must be considered, that sexual hormones can stimulate growth of different hormone-dependent tissues and tumors.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core
Lactose monohydrate
Magnesium stearate
Maize starch
Povidone

Film coating
Hypromellose
Macrogol
Titanium dioxide (E171)

6.2 Incompatibilities

Not applicable

6.3 Shelf life

24 months

6.4 Special precautions for storage

Do not store above 25°C. Store in the original package in order to protect from light

6.5 Nature and contents of container

PVC/PVDC/Aluminum blister, pack sizes: 21 and 3x21 and 6x21 film-coated tablets.
The blister packs may come with a blister holder.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

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

7 MARKETING AUTHORISATION HOLDER

Exeltis Healthcare, S.L.
Avda Miralcampo 7–Polígono Industrial Miralcampo
19200 Azuqueca de Henares – Guadalajara

8 MARKETING AUTHORISATION NUMBER(S)

PL 44081/0007

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

04/02/2022

10 DATE OF REVISION OF THE TEXT

17/03/2023